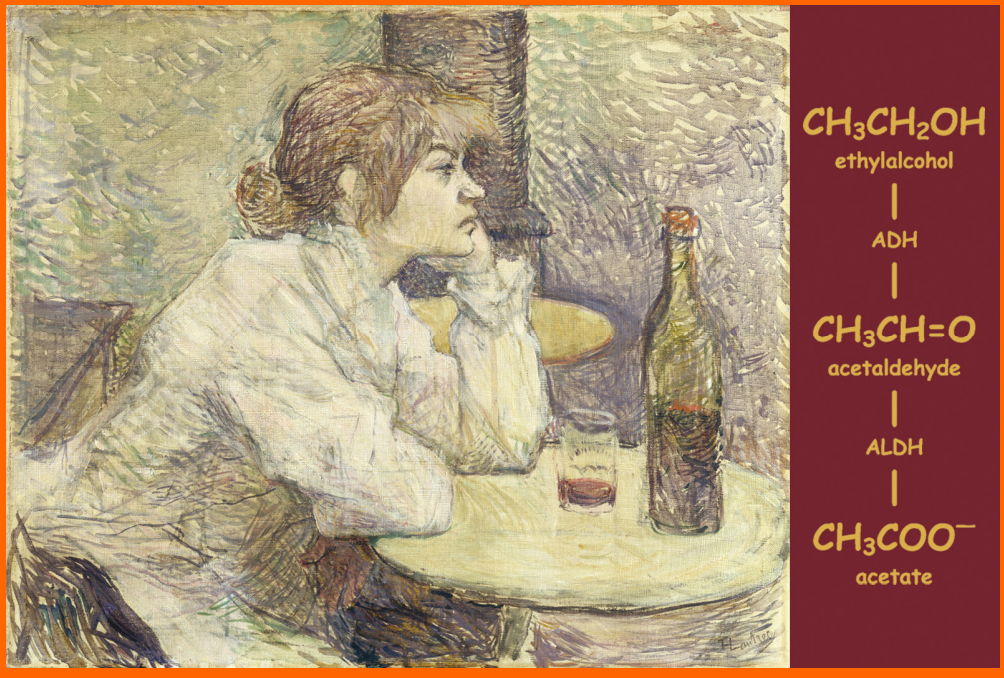
WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 96

Alcohol Consumption and Ethyl Carbamate



LYON, FRANCE
2010

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 96

Alcohol Consumption and Ethyl Carbamate

This publication represents the views and expert opinions
of an IARC Working Group on the
Evaluation of Carcinogenic Risks to Humans,
which met in Lyon,

6–13 February 2007

2010

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at http://monographs.iarc.fr/.

This programme has been supported since 1982 by Cooperative Agreement U01 CA33193 with the United States National Cancer Institute, Department of Health and Human Services. Additional support has been provided since 1986 by the Health, Safety and Hygiene at Work Unit of the European Commission Directorate-General for Employment, Social Affairs and Equal Opportunities, and since 1992 by the United States National Institute of Environmental Health Sciences, Department of Health and Human Services. The contents of this volume are solely the responsibility of the Working Group and do not necessarily represent the official views of the U.S. National Cancer Institute, the U.S. National Institute of Environmental Health Sciences, the U.S. Department of Health and Human Services, or the European Commission Directorate-General for Employment, Social Affairs and Equal Opportunities.

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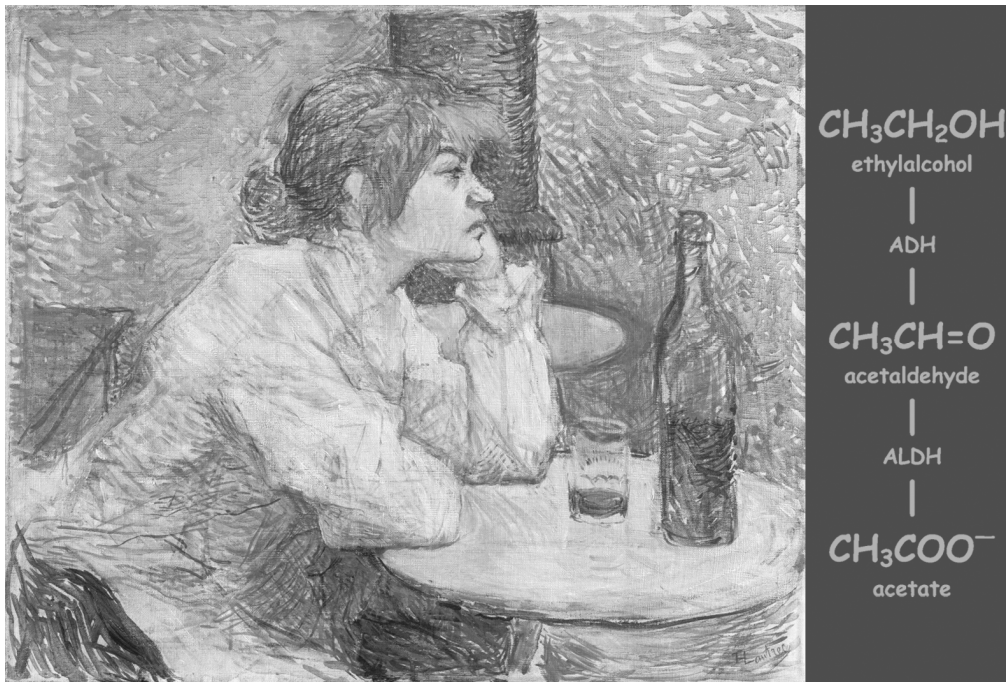

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Photo: Imaging Department © President and Fellows of Harvard College, reproduced with permission.
The chemical formulae show the two-step metabolism of ethyl alcohol, mediated by the key enzymes ADH and ALDH.

Cover design: Roland Dray (IARC)

CONTENTS

NOTE TO THE READER

The term ‘carcinogenic risk’ in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer under some circumstances. The *Monographs* evaluate cancer hazards, despite the historical presence of the word ‘risks’ in the title.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a *Monograph* does not mean that it is not carcinogenic.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Section of IARC Monographs, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Section of IARC Monographs, so that corrections can be reported in future volumes.

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

VOLUME 96
ALCOHOL CONSUMPTION

Lyon, 6–13 February 2007

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2 Each participant was asked to disclose pertinent research, employment, and financial interests. Current financial interests and research and employment interests during the past 3 years or anticipated in the future are identified here. Minor pertinent interests are not listed and include stock valued at no more than US$10 000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are listed as significant pertinent interests.

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a *Monograph* or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended '...that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.' The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase 'of chemicals' was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics

and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad-hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term 'agent' refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms 'neoplasm'

and 'tumour' are used interchangeably.

The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006; see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues

and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad-hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme website (http://monographs.iarc.fr). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph,* or participate in the evaluations.

(d) Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at http://monographs.iarc.fr).

(e) The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests,

employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano *et al.*, 2004).

The names and principal affiliations of participants are available on the *Monographs* programme website (http://monographs.iarc.fr) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano *et al.*, 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme website (http://monographs.iarc.fr) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

For most chemicals and some complex mixtures, the major collection of data and the preparation of working papers for the sections on chemical and physical properties, on analysis, on production and use, and on occurrence are carried out under a separate contract funded by the US National Cancer Institute. Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and

sent, prior to the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme website soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

1. Exposure data
2. Studies of cancer in humans
3. Studies of cancer in experimental animals
4. Mechanistic and other relevant data
5. Summary
6. Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(*a*) *General information on the agent*

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(*b*) *Analysis and detection*

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(*c*) *Production and use*

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production, which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(*d*) *Occurrence and exposure*

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

(*e*) *Regulations and guidelines*

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(*a*) *Types of study considered*

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(*b*) *Quality of studies considered*

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study

design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to a number of aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

Firstly, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Secondly, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than those with national rates. Internal comparisons of frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since they minimize the potential for confounding related to the difference in risk factors between an external reference group and the study population.

Thirdly, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(*c*) *Meta-analyses and pooled analyses*

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well-conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland, 1998).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well-conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad-hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(*d*) *Temporal effects*

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although, at best, they allow only indirect inferences about mechanisms of carcinogenesis.

(*e*) *Use of biomarkers in epidemiological studies*

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio *et al.*, 1992; Toniolo *et al.*, 1997; Vineis *et al.*, 1999; Buffler *et al.*, 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b).

This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(*f*) *Criteria for causality*

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

A number of scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires firstly that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn *et al.*, 1986; Tomatis *et al.*, 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio *et al.*, 1995). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where

applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate (e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(*a*) *Qualitative aspects*

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi)

whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo transition to malignancy, the agent should nevertheless be suspected of being carcinogenic and requires further investigation.

(*b*) *Quantitative aspects*

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce non-linearity in the dose–response relationship (Hoel *et al.*, 1983; Gart *et al.*, 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(*c*) *Statistical analyses*

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980; Gart *et al.*, 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the

time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman *et al.*, 1994; Dunson *et al.*, 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls, particularly when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals (Haseman *et al.*, 1984; Fung *et al.*, 1996; Greim *et al.*, 2003).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(*a*) *Toxicokinetic data*

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(*b*) *Data on mechanisms of carcinogenesis*

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

(i) *Changes in physiology*

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) *Functional changes at the cellular level*

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related

to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) *Changes at the molecular level*

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio *et al*., 1992; McGregor *et al*., 1999). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system *in vitro* affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour promotion, cell transformation and gap–junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published (Montesano *et al*., 1986; McGregor *et al*., 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals *in vivo* indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated *in vivo* provide less weight,

partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio *et al*., 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al*., 1986; McGregor *et al*., 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. Capen *et al.*, 1999).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(*c*) *Other data relevant to mechanisms*

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the

number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(*d*) *Susceptibility data*

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(*e*) *Data on other adverse effects*

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme website (http://monographs.iarc.fr).

(*a*) *Exposure data*

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(*b*) *Cancer in humans*

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(*c*) *Cancer in experimental animals*

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(*d*) *Mechanistic and other relevant data*

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(*a*) *Carcinogenicity in humans*

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

***Limited evidence of carcinogenicity*:** A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

***Inadequate evidence of carcinogenicity*:** The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

***Evidence suggesting lack of carcinogenicity*:** There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(*b*) *Carcinogenicity in experimental animals*

Carcinogenicity in experimental animals can be evaluated using conventional

bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

***Limited evidence of carcinogenicity*:** The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

***Inadequate evidence of carcinogenicity*:** The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

***Evidence suggesting lack of carcinogenicity*:** Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(*c*) *Mechanistic and other relevant data*

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–

activity relationships, metabolism and toxicokinetics, physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak', 'moderate' or 'strong'. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(*d*) *Overall evaluation*

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories,

and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is *carcinogenic to humans*.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is *probably carcinogenic to humans*.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is *possibly carcinogenic to humans*.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in

this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans*.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is *probably not carcinogenic to humans*.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(*e*) *Rationale*

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

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GENERAL REMARKS

This ninety-sixth volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of alcohol consumption and ethyl carbamate (sometimes called urethane), a frequent contaminant of yeast-fermented foods and beverages. Alcohol drinking was reviewed in Volume 44 (IARC, 1988), and ethyl carbamate in Volume 7 (IARC, 1974) of the *IARC Monographs*. A large number of epidemiological and experimental studies have been published since then, and these are reviewed in this Volume. A summary of the findings was published in *The Lancet Oncology* (Baan *et al*., 2007).

Although moderate alcohol consumption has some health benefits, in particular with respect to cardiovascular problems (WHO, 2004), the consumption of alcohol has been identified as one of the top-10 risks contributing to the worldwide burden of disease (Ezzati *et al.*, 2004). In 2002, more than 1900 million people (≥15 years of age) around the world were estimated to be regular consumers of alcoholic beverages, with an average daily consumption of 13 g of ethanol (about one drink). In general, men drink alcohol more often and in larger quantities than women do. On the basis of production data, *per-capita* consumption is highest in Eastern Europe and the Russian Federation. In Africa, South America, and Asia, alcohol consumption is comparatively lower, but in those regions a large proportion of alcohol is produced locally and remains unrecorded. Over the past four decades, alcohol consumption has remained stable in most regions of the world except in the Western Pacific region — predominantly China — where it has increased about five times during that period. In addition to ethanol and water, alcoholic beverages can contain many different substances derived from fermentation — e.g., ethyl carbamate —, from contamination, and from the use of additives or flavours.

The Working Group reviewed the epidemiological evidence on the possible association between alcoholic beverage consumption and cancer at 27 anatomical sites, and re-affirmed the previous conclusion (IARC, 1988) that cancers of the upper digestive tract (*oral cavity*, *pharynx*, *larynx*, *oesophagus*) and the *liver* are causally related to the consumption of alcoholic beverages. In addition, the Working Group considered that there is *sufficient evidence* to conclude that cancer of the *colorectum* and the female *breast* also belong in this list.

Regular consumption of alcoholic beverages is associated with an increased risk for cancers at different sites along the upper digestive tract (see above): daily intake of around 50 g of ethanol increases the risk for these cancers two- to three-fold, compared with the risk in non-drinkers. For these cancer types the effects of drinking and smoking seem to be multiplicative, which demonstrates the harmful effect of the combination of these two habits.

Consumption of alcoholic beverages was confirmed as an independent risk factor for primary liver cancer. Cirrhosis and other liver diseases often occur before the cancer becomes manifest and patients with these disorders generally reduce their alcohol intake.

Therefore, the effect of alcohol consumption on the risk for liver cancer is difficult to quantify.

The Working Group reviewed more than 100 epidemiological studies that assessed the association between alcoholic beverage consumption and female breast cancer. A pooled analysis of studies on more than 58 000 women with breast cancer showed that daily consumption of about 50 g of alcohol is associated with a relative risk of approximately 1.5 (95% confidence interval 1.3–1.6), compared with that in non-drinkers. Due to the very large size of this study population, a statistically significant relative risk could even be established for regular consumption of about 18 g of alcohol, about 1–2 drinks daily.

Pooled results from eight cohort studies on the association between alcoholic beverage consumption and colorectal cancer, and data from a number of meta-analyses provided evidence of an increased relative risk of about 1.4 for colorectal cancer resulting from regular consumption of about 50 g of alcohol per day, compared with that in non-drinkers. This association seems to be similar for colon cancer and for rectal cancer.

For non-Hodgkin lymphoma and cancer of the kidney the results of the available studies led the Working Group to conclude that there is evidence of the absence of an increased risk with increasing alcohol consumption. For kidney cancer this inverse trend was seen in both men and women.

The epidemiological studies on the risk for stomach cancer and those on lung cancer in association with alcoholic beverage consumption showed inconsistent results, in both cases due to confounding factors. In the case of *lung* cancer, tobacco smoking is an obvious confounder, and although some studies presented data on the risk for lung cancer in non-smokers the results were inconsistent. Likewise, the epidemiological studies on the risk for *stomach* cancer showed variable results, probably because alcohol drinking may have been accompanied by dietary deficiencies and other unfavourable lifestyle factors that impact on stomach-cancer incidence.

For other cancers, the evidence of an association between alcoholic beverage consumption and cancer risk was generally sparse or inconsistent.

With regard to cancer in experimental animals, the Working Group reviewed a large number of bio-assays, including those that had become available since the previous evaluation (IARC 1988). For ethanol, the evidence of carcinogenicity in experimental animals is now considered *sufficient*, where it had been judged *inadequate* before. For acetaldehyde, the primary metabolite of ethanol, the *sufficient evidence* of carcinogenicity in experimental animals, already indicated in Volume 36 (IARC, 1985), was re-affirmed.

The metabolism of ethanol, the key component in alcoholic beverages, is surprisingly simple and proceeds in two dehydrogenation steps. In humans, the major enzymes involved are the alcohol dehydrogenases (ADH), which oxidize ethanol to acetaldehyde, and the aldehyde dehydrogenases (ALDH), which detoxify acetaldehyde to acetate. In contrast, the genetic variations within the two groups of dehydrogenases are very complex, showing wide differences in enzyme kinetics and substrate specificities.

A striking example of a genetic polymorphism that strongly influences the response to alcoholic beverage consumption is the variant allele *ALDH2*2*, which encodes an

inactive subunit of the enzyme ALDH2. This allele is dominant and highly prevalent in certain eastern-Asian populations (28–45%), but rare in other ethnic groups. Most homozygous carriers of this allele (*ALDH2*2/*2*) are abstainers or infrequent drinkers, because – when they consume alcohol – the enzyme deficiency would cause a strong facial flushing response, physical discomfort, and severe toxic reactions. In heterozygous carriers (*ALDH2*1/*2*, with about 10% residual ALDH2 activity) these acute adverse effects are less severe, but compared with those with fully active enzyme (*ALDH2*1/*1* genotype), these persons have higher levels of acetaldehyde in their blood and saliva after alcohol drinking, and higher levels of acetaldehyde-related DNA adducts in their lymphocytes. In addition, when they consume alcohol these individuals are at highly elevated risk for several alcohol-related aerodigestive cancers.

In recent years, a number of epidemiological studies have focused on the functional effect of this and other genetic polymorphisms in ADH and ALDH iso-enzymes in different human populations, and analyzed the ensuing risks for cancers associated with consumption of alcoholic beverages. Because of their obvious relevance for the mechanistic considerations regarding the role of ethanol and its metabolite acetaldehyde in carcinogenesis, these genetic epidemiological studies are reviewed and discussed in the subsection 'Genetic susceptibility' of Section 4 in this Volume.

On the basis of the epidemiological evidence, which showed little indication that the carcinogenic effects of alcoholic beverage consumption depend on the type of alcoholic beverage, and given the *sufficient evidence* that ethanol causes cancer in experimental animals, the Working Group evaluated "Ethanol in alcoholic beverages" as *carcinogenic to humans*. In addition, the Working Group acknowledged the important role of acetaldehyde in the development of alcohol-related cancer, especially of the oesophagus, but refrained from making a formal evaluation.

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CONSUMPTION OF ALCOHOLIC BEVERAGES

1. Exposure Data

1.1 Types and ethanol contents of alcoholic beverages

1.1.1 *Types of alcoholic beverage*

Most cultures throughout the world have traditionally consumed some form of alcoholic beverages for thousands of years, and local specialty alcoholic beverages still account for the majority of all those that exist. Only a small number have evolved into commodities that are produced commercially on a large scale. In world trade, beer from barley, wine from grapes and certain distilled beverages are sold as commodities. Other alcoholic beverages are not sold on the international market. In many developing countries, however, various types of home-made or locally produced alcoholic beverages such as sorghum beer, palm wine or sugarcane spirits continue to be the main available beverage types (WHO, 2004).

It is difficult to measure the global production or consumption of locally available beverages, and few data exist on their specific chemical composition (see Section 1.6). A discussion of unrecorded alcohol production, which includes these traditional or home-made beverages, is given in Section 1.3. Although these types of alcoholic beverage can be important in several countries at the national level, their impact is fairly small on a global scale.

This monograph focuses on the main beverage categories of beer, wine and spirits unless there is a specific reason to examine some subcategory, e.g. alcopops or flavoured alcoholic beverages. These categories are, however, not as clear-cut as they may seem. There are several beverages that are a combination of two types (e.g. fortified wines, in which spirits are added to wine). The categorization above is based on production methods and raw materials, and not on the ethanol content of the beverages (see Section 1.2).

Another classification of beverages is the Standard International Trade Classification (SITC) that has four categories: wine from fresh grapes, cider and other fermented

beverages, beer and distilled alcoholic beverages (for further details, see SITC Rev 3 at United Nations Statistics Division (2007; http://unstats.un.org/unsd/cr)).

1.1.2 *Alcohol content of different beverages*

In this monograph, percentage by volume (% vol) is used to indicate the ethanol content of beverages; this is also called the French or Gay-Lussac system. The American proof system is double the percentage by volume; a vodka which is 40% by volume is thus 80 proof in the USA (IARC, 1988).

The standard approach to measuring the amount of ethanol contained in a specific drink is as follows. The amount of alcoholic beverage typically consumed for each type of beverage (e.g. a 330-mL bottle of beer or a 200-mL glass of wine) is multiplied by the ethanol conversion factor, i.e. the proportion of the total volume of the beverage that is alcohol. Ethanol conversion factors differ by country, but are generally about 4–5% vol for beer, about 12% vol for wine and about 40% vol for distilled spirits. Thus, the ethanol content of a bottle of beer is calculated as (330 mL) × (0.04) = 13.2 mL ethanol. In many countries, ethanol conversion factors are used to convert the volume of beverage directly into grams of ethanol. In other countries, volumes of alcohol may be recorded in 'ounces'. Relevant alcohol conversion factors for these different measures are (WHO, 2000): 1 mL ethanol = 0.79 g; 1 United Kingdom fluid oz = 2.84 cL = 28.4 mL = 22.3 g; 1 US fluid oz = 2.96 cL = 29.6 mL = 23.2 g.

The ethanol content in beer usually varies from 2.3% to over 10% vol, and is mostly 5–5.5% vol. In some countries, low-alcohol beer, i.e. below 2.3% vol, has obtained a considerable share of the market. In general, beer refers to barley beer, although sorghum beer is consumed in large quantities in Africa.

The ethanol content of wine usually varies from 8 to 15% vol, but light wines and even non-alcoholic wines also exist.

The ethanol content of spirits is approximately 40% vol, but may be considerably higher in some national specialty spirits. Also within the spirits category are aperitifs, which contain around 20% vol of alcohol. Alcopops, flavoured alcoholic beverages or ready-to-drink beverages usually contain 4–7% vol of alcohol, and are often pre-mixed beverages that contain vodka or rum.

1.2 Production and trade of alcoholic beverages

1.2.1 *Production*

(a) Production methods

Most yeasts cannot grow when the concentration of alcohol is higher than 18%. This is therefore the practical limit for the strength of fermented beverages, such as wine, beer and sake (rice wine). In distillation, neutral alcohol can be produced at strengths in excess of 96% vol of alcohol.

(i) *Beer production*

The process of producing beer has remained unchanged for hundreds of years. The basic ingredients for most beers are malted barley, water, hops and yeast. Barley starch supplies most of the sugars from which the alcohol is derived in the majority of beers throughout the world. Other grains used are wheat and sorghum. The starch in barley is enclosed in a cell wall, and these wrappings are stripped away in the first step of the brewing process, which is called malting. Removal of the wall softens the grain and makes it more readily milled. The malted grain is milled to produce relatively fine particles and these are then mixed with hot water in a process that is called mashing. The water must process the right mix of salts. Typically, mashes contain approximately three parts of water to one part of malt and are maintained at a temperature of ~65 °C. Some brewers add starch from other sources such as maize (corn) or rice to supplement the malt. After ~1 h of mashing, the liquid portion is recovered by either straining or filtering. The liquid (the wort) is then boiled for ~1 h. Boiling serves various functions, including sterilization and the removal of unpleasant grainy contents that cause cloudiness. Many brewers add sugar or at least hops at this stage. The hopped wort is then cooled and pitched with yeast. There are many strains of brewing yeast and brewers tend their strains carefully because of their importance to the identity of the brand. Fundamentally, yeasts can be divided into lager and ale strains. Both types need a little oxygen to trigger off their metabolism. Ale fermentations are usually complete within a few days at temperatures as high as 20 °C, whereas lager fermentations, at temperatures which are as low as 6 °C, can take several weeks. Fermentation is complete when the desired alcohol content has been reached and when an unpleasant butterscotch flavour, which develops during all fermentation, has been removed by the yeast. The yeast is then harvested for use in the next fermentation. Nowadays, the majority of beers receive a relatively short conditioning period after fermentation and before filtration. This is performed at –1 °C or lower (but not so low as to freeze the beer) for a minimum of 3 days. This eliminates more proteins and ensures that the beer is less likely to cloud in the packaging or glass. The filtered beer is adjusted to the required degree of carbonation before being packed into cans, kegs, or glass or plastic bottles (Bamforth, 2004).

(ii) *Wine production*

A great majority of wine is produced from grapes, but it can also be produced from other fruits and berries. The main steps in the process of wine making are picking the grapes, crushing them and possibly adding sulfur dioxide to produce a wine must. After addition of *Saccharomyces*, a primary/secondary fermentation then takes place. This newly fermented wine is then stabilized and left to mature, after which the stabilized wine is bottled (and possibly left to mature further in the bottle).

Red grapes are fermented with the skin, and yield ~20% more alcohol than white grapes. Ripe fruit should be picked immediately before it is to be crushed. Harvesting is becoming increasingly mechanical although it causes more physical damage to the

grapes, and sulfur dioxide may be added during the mechanical harvesting. The grapes are then stemmed and crushed. The stems are not usually left in contact with crushed grapes to avoid off-flavours. An initial crushing separates grapes from stems with the aim of achieving an even breakage of grapes. It is not necessary to separate the juice from the skins immediately for red wine, but it is for white, rosé or blushwines. The juice is settled at a low temperature (< 12 °C), after which it is drained and pressed. To accelerate juice settling and obtain a clearer product, pectic enzyme is frequently added at the crushing stage. Once the juice is separated from the skins, it is held overnight in a closed container. Thereafter, it is centrifuged before the addition of yeast. In locations where the grapes do not ripen well because of a short growing season, it may be necessary to add sugar (sucrose). Dried yeast is usually used in wine making (contrary to beer brewing). Oxygen is introduced to satisfy the demand of the yeast. White wines are fermented at 10–15 °C, whereas red wines are fermented at 20–30 °C. Fermentation is complete within 20–30 days. Wine is usually racked off the yeast when the fermentation is complete, although some winemakers leave the yeast for several months to improve the flavour. After fermentation, the wine is clarified with different compounds depending on the type of wine (bentonite, gelatine, silica gels). Maintaining them in an anaerobic state then stabilizes the wines and prevents spoilage by most bacteria and yeast. Wines tend to benefit from ageing, which is performed in either a tank, barrel or bottle. The extent of ageing is usually less for white than for red wines. During ageing, the colour, aroma, taste and level of sulfur dioxide are monitored. If wine is aged in oak barrels, some characteristics are derived from the barrel.

Residual oxygen is removed during packaging and some winemakers add sorbic acid as a preservative to sweet table wines. To avoid the use of additives, attention must be paid to cold filling and sterility, and to avoid taints, corks should be kept at a very low moisture content. The shelf life of wine is enhanced by low-temperature storage (Bamforth, 2005).

(iii) *Production of spirits*

The neutral alcohol base used for several different spirits is frequently produced from cereals (e.g. corn, wheat), beet or molasses, grapes or other fruit, cane sugar or potatoes. These basic substances are first fermented and then purified and distilled. Distillation entails heating the base liquid so that all volatile substances evaporate, collecting these vapours and cooling them. This liquid may be distilled several times to increase purity. The process leads to a colourless, neutral spirit, which may then be flavoured in a multitude of ways. For some spirits, such as cognac and whisky, the original flavouring of the base liquid is retained throughout the distilling process, to give the distinct flavour. After distillation, water is added to give the desired strength of the beverage.

Vodka is a pure unaged spirit distilled from agricultural products and is usually filtered through charcoal. Neutral alcohol is the base for vodka, although many flavourings can be found in modern vodkas, such as fruit and spices. Other beverages based

on neutral distilled alcohol are gin, genever, aquavit, anis and ouzo. For example, the distinct flavour of gin comes from distillation in the presence of plants such as juniper, coriander and angelica, and the peel of oranges and lemons.

Rum is produced from molasses or cane sugar; whisky is produced from a mash of cereals and is matured for a minimum of 3 years. Brandy comes from distilled wine and needs to mature in oak. Fruit spirits may be produced by fermentation and distillation of a large number of fruit and berries, such as cherries, plums, peaches, apples, pears, apricots, figs, citrus fruit, grapes, raspberries or blackberries (Bamforth, 2005).

(b) Production and trade volumes

According to the SITC (SITC Rev. 3.1, code 155; United Nations Statistic Division 2007), the activity of manufacture of alcoholic beverages is divided into three categories:

1551 **- Distilling, rectifying and blending of spirits; ethyl alcohol production from fermented materials**. This class includes: the manufacture of distilled, potable, alcoholic beverages: whisky, brandy, gin, liqueurs and 'mixed drinks'; the blending of distilled spirits; the production of ethyl alcohol from fermented materials; and the production of neutral spirits.

1552 – **Manufacture of wine**. This class includes: the manufacture of wine from grapes not grown by the same unit; the manufacture of sparkling wine; the manufacture of wine from concentrated grape must; the manufacture of fermented but not distilled alcoholic beverages: sake, cider, perry, mead, other fruit wines and mixed beverages containing alcohol; the manufacture of vermouth and similar fortified wines; the blending of wine; and the manufacture of low-alcohol or non-alcoholic wine.

1553 – **Manufacture of malt liquors and malt**. This class includes: the manufacture of malt liquors, such as beer, ale, porter and stout; the manufacture of malt; and the manufacture of low-alcohol or non-alcoholic beer.

According to the alcoholic beverage industry, the global market for alcoholic drinks reached a volume of 160.2 billion litres of alcohol in 2006. The market is forecasted to grow further in the coming years. The compound annual average growth rate in volume has been around 2% per year from 2000 to 2006. A similar growth rate is expected in the coming 5 years. The value of the global drinks market in 2006 was 812.4 billion US $ (Market is valued according to retail selling price including any applicable taxes). Both volume and value grow at a steady rate of around 1–2% per year.

The sales of beer, cider and flavoured alcoholic beverages dominate the market with a 48.7% share of the global value. Wine is the second highest in value at 28.3% and is followed by spirits at 22.9%.

Europe continues to be the largest alcoholic drinks market and accounts for 59% of the global market value. Europe is followed by the USA (23.7%) and the Asia-Pacific region (17.2%).

On-trade (on-premises) sales distribute alcoholic products worth 38.7% of the total market revenue, followed by supermarkets/hypermarkets (20.8%) and specialist

Table 1.1 Top 10 beer producers

Rank	Country	Production in 1000 hectolitres (2002 estimate)
1	USA	231 500
2	China	231 200
3	Germany	109 000
4	Brazil	85 000
5	Japan	70 500
6	Russia	70 000
7	Mexico	65 000
8	United Kingdom	56 800
9	Spain	28 000
10	Netherlands	25 300

From Modern Brewery Age (2002)

retailers (12.1%) (Datamonitor, 2006, Datamonitor does not cover all countries as it is more focused on developed countries; for e.g. Africa, the data are almost non-existent).

The market for alcoholic beverages shows considerable variation in growth. In most developed economies, the market is mature, i.e. stable but not growing. In these countries, most people have reached an economic status where they can buy alcoholic beverages if they wish to do so. However, Brazil, the Russian Federation, China, India and some transitional economies in Europe have a market that is greatly increasing in value. In general, low- and middle-income countries tend to move from locally produced alcoholic beverages to commercial brands as their economic status improves. Simultaneously, they also show a shift from other beverages to beer. In developed markets, sales volumes for beer are static or declining, with intensified competition from wine and spirits (ICAP, 2006). Regarding beverage-specific production, Table 1.1 presents the 10 largest beer-producing countries in 2002. Of these, Germany, Mexico and the Netherlands are especially prominent exporters of beer (see Section 1.2.2). In Brazil, China, Japan and the Russian Federation, most of the beer produced is consumed in the domestic market.

The largest wine producers (Table 1.2) are the traditional European wine-producing countries such as France, Spain and Italy, but also include those from the New World such as South Africa. It is clear that the major wine-producing countries are also the greatest wine-exporting countries.

With regard to the production of spirits, China and India are the largest producers (Table 1.3). All of the developing countries listed (plus Japan and the Russian Federation) are large producers of spirits but are not prominent exporters of their products; they are all predominantly spirit-drinking countries.

Table 1.2 Top 10 wine (including all fermented) producers

Rank	Country	Production in 1000 hectolitres (2001)
1	France	53 389
2	Italy	50 093
3	Spain	30 500
4	USA	19 200
5	Argentina	15 835
6	China	10 800
7	Australia	10 163
8	Germany	8 891
9	Portugal	7 789
10	South Africa	6 471

From WHO Global Alcohol Database (undated)

An overall observation is that developing countries, such as Brazil, China and India are prominent among the largest producers of beer and/or spirits.

1.2.2 *Trade in alcoholic beverages*

(a) Trends in trade

Overall, trade in alcoholic beverages has increased almost 10-fold over the past 30 years. The increase is, however, proportional to the overall increase in world trade of all goods. Alcoholic beverages hold a stable 0.5% of the total value of global trade. This

Table 1.3 Top 10 spirits producers

Rank	Country	Production in 1000 hectolitres (2003)
1	China	577 490
2	India	154 860
3	Russian Federation	138 500
4	Japan	102 360
5	USA	98 000
6	United Kingdom	82 195
7	Thailand	71 340
8	Brazil	70 000
9	Germany	39 100
10	France	36 345

From WHO Global Alcohol Database (undated)

Table 1.4 Principal importers and exporters of beer in 2005[a]

Country	Share of world total (%)
Imports	
USA	42.5
United Kingdom	8.4
Italy	6.7
France	5.9
Canada	4.6
Germany	3.8
Ireland	2.7
Netherlands	2.6
Spain	2.5
Belgium	1.4
Exports	
Netherlands	19.4
Mexico	18.8
Germany	13.1
Belgium	8.4
United Kingdom	7.5
Ireland	4.1
Denmark	4.0
Canada	3.0
USA	2.5
France	2.4

From United Nations Statistics Division (2007) [a] Based on value of trade

would mean that for every 200 US $ in global trade, 1 US $ involves alcoholic beverages. The trends in trade do not correlate to trends in consumption.

(b) Countries with highest imports or exports

Over the past 30 years, France, Italy, the United Kingdom and the USA have been the largest importers of beer. The major change is that the USA have increased their share of the world trade from 29% in 1992 to 42% in 2005. For beer exports, Mexico features prominently, and has had an increase in trade share from 5.8% in 1992 to 18.8% in 2005 (see Table 1.4).

Regarding wine imports, two new countries have emerged as principal traders—Japan and the Russian Federation. Global export is still dominated by the traditional large wine-producing countries, such as France, although the share of French wines has decreased from nearly 50% in 1992 to 33% in 2005. Two more recent wine-producing

Table 1.5 Principal importers and exporters of wine in 2005[a]

Country	Share of world total (%)
Imports	
United Kingdom	20.0
USA	18.5
Germany	11.3
Belgium	5.0
Canada	4.9
Japan	4.9
Netherlands	4.0
Switzerland	3.6
Russian Federation	3.1
France	3.0
Exports	
France	33.3
Italy	18.9
Australia	10.0
Spain	9.4
Chile	4.2
Germany	3.4
Portugal	3.1
USA	3.0
South Africa	2.8
New Zealand	1.6

From United Nations Statistics Division (2007) [a] Based on value of trade

countries—South Africa and New Zealand— have entered the list of large wine traders (see Table 1.5).

The Russian Federation is now a major importer of spirits. For the principal exporting countries, there has been more fluctuation over the past 30 years than for other beverages. For example, Mexico and Spain have been on and off the list of major exporters, and Germany and Sweden became major exporters in 2005 (see Table 1.6).

Overall, the ranking of countries for both imports and exports of all beverages has been fairly stable over the years. Almost no low-income countries are among the top 10. Only a small minority of countries worldwide are involved in any significant trade at the global level and mostly the same countries are implicated for all beverages.

Table 1.6 Principal importers and exporters of distilled alcoholic beverages in 2005[a]

Country	Share of world total (%)
Imports	
USA	27.8
Spain	7.9
Germany	6.6
France	5.1
United Kingdom	5.0
Russian Federation	4.1
Japan	3.8
Canada	2.8
Singapore	2.7
Italy	2.2
Exports	
United Kingdom	32.6
France	17.8
USA	4.9
Germany	4.8
Ireland	4.5
Mexico	4.3
Sweden	3.8
Italy	3.4
Singapore	2.9
Spain	2.5

From United Nations Statistics Division (2007) [a] Based on value of trade

1.3 Trends in consumption

1.3.1 *Indicators of alcoholic beverage consumption*

Three methods exist to measure consumption of alcoholic beverages in a population: surveys of a representative sample of a country or a large region of a country; determination of consumption from available statistics, such as production and sales/taxation records; and determination of consumption based on indirect indicators such as availability of raw materials to produce alcohol (e.g. sugar, fruit).

Overall, surveys have been shown in general to underestimate consumption compared with estimates from production and sales records (Gmel & Rehm, 2004), at least in developed countries. One reason for this underestimation is that surveys do not usually include people who live outside a household and who drink heavily, such as institutionalized people or the homeless. The degree of underestimation varies, and can range from 70% in some cases up to almost full coverage in others. For this reason,

international comparisons of total consumption between developed countries mostly use production and sales-based statistics (Rehm *et al.*, 2003). Whenever possible, recorded consumption should be supplemented by estimates of unrecorded consumption. This is especially important in developing countries, where unrecorded consumption is on average more common and, in some regions of the world, constitutes more than 50% of the overall consumption.

1.3.2 *Assessment of total consumption per head (per-capita consumption)*

(a) Measurement of adult per-capita consumption of recorded alcoholic beverages

Data on per-capita alcoholic beverage consumption provide the consumption in litres of pure alcohol per inhabitant in a given year. They are available for the majority of countries, often given over time, and avoid the underestimation of total volume of consumption that is commonly inherent in survey data (e.g. Midanik, 1982; Rehm, 1998; Gmel & Rehm, 2004). Adult per-capita consumption, i.e. consumption by all persons aged 15 years and above, is preferable to per-capita consumption *per se* since alcoholic beverages are largely consumed in adulthood. The age pyramid varies in different countries; therefore, per-capita consumption figures based on the total population tend to underestimate consumption in countries where a large proportion of the population is under the age of 15 years, as is the case in many developing countries. For more information and guidance on estimating per-capita consumption, see WHO (2000).

Three principal sources for per-capita estimates are national government data, information from the Food and Agriculture Organization of the United Nations (FAO) and data from the alcoholic beverage industry (Rehm *et al.*, 2003). Where available, the best and most reliable information stems from national governments, usually based on sales figures, tax revenue and/or production data. Generally, sales figures are considered to be the most accurate, provided that sales of alcoholic beverages are separated from those of any other possible items sold at a given location, and that they are beverage-specific. One of the drawbacks of production figures is that they are always dependent on accurate export and import data; if these are not available, the production figures will yield an under- or an overestimation.

The most complete and comprehensive international data set on per-capita consumption was published by FAO (until 2003). FAOSTAT, the database of the FAO, publishes production and trade information for different types of alcoholic beverage for almost 200 countries. The estimates are based on official reports of production by national governments, mainly by the Ministries of Agriculture in response to an annual FAO questionnaire. The statistics on imports and exports derive mainly from Customs Departments. If these sources are not available, other government data such as statistical yearbooks are consulted. The accuracy of the FAO data relies on reporting by member nations. The information from member nations probably underestimates informal,

home and illegal production, but these sources are still covered more accurately by the FAO than by estimates based solely on production or sales figures.

The third main source of information is the alcoholic beverage industry. In this category the most widely used is World Drinks Trends (WDT), published by the Commission for Distilled Spirits (World Advertising Research Centre Ltd, 2005). The WDT estimates are based on total sales in litres divided by the total mid-year population and use conversion rates that are not published. WDT also tries to calculate the consumption of both incoming and outgoing tourists. Currently, at least partial data are available for 58 countries. Other sources from the alcoholic beverage industry, as well as market research companies, are less systematic, entail fewer countries and are more limited in providing information over time.

The WHO Global Alcohol Database (undated) systematically collects and compares per-capita data from different sources on a regular basis (for procedures and further information, see Rehm *et al.*, 2003; WHO, 2004) using data from the United Nations for population estimates. The information in this section derives from this database, which has explicit rules for selecting and processing data to ensure their comparability.

The main limitations of adult per-capita estimates are twofold: they do not incorporate most unrecorded consumption (see below); and they are only aggregate statistics that cannot easily be disaggregated into sex and age groups. Thus, surveys have to play a crucial role in any analysis of the effect of consumption of alcoholic beverages on the burden of disease (see below).

(b) Assessment of adult per-capita consumption of unrecorded alcoholic beverages

Most countries have at least a low level of so-called unrecorded alcoholic beverage consumption. Unrecorded alcoholic beverages simply means that the alcoholic beverages produced and/or consumed are not recorded in official statistics of sales, production or trade. In some countries, unrecorded alcoholic beverages are the major source of such commodities (see Table 1.7). Unrecorded consumption stems from a variety of sources (Giesbrecht *et al.*, 2000): home production, illegal production and sales, illegal (smuggling) and legal imports (cross-border shopping) and other production and use of alcoholic beverages that are not taxed and/or are not included in official production and sales statistics.

A portion of the unrecorded alcoholic beverages derives from different local or traditional beverages that are produced and consumed in villages or homes. The production may be legal or illegal, depending on the strength of the beverage. Worldwide, information on these alcoholic beverages and their production or consumption volumes is scarce. Local production consists mostly of the fermentation of seeds, grains, fruit, vegetables or parts of palm trees, and is a fairly simple process. The alcohol content is quite low and the shelf life is usually short—1 or 2 days before the beverage is spoilt.

Table 1.7 Characteristics of alcoholic beverage consumption by country 2002 (average of available data 2001–03)[a]

WHO Region Country	Adult population[b]	Alcohol consumption[c]	Unrecorded consumption[d]	Abstainers[e]		Recorded beverages consumed		
				Men (%)	Women (%)	Beer (%)	Wine (%), inc. other fermented beverages	Spirits (%)
Africa D								
Algeria	21 300	0.5	0.3	80	98	70.1	51.4	0.0
Angola	7 777	5.1	1.6	NA	NA	63.5	21.1	15.4
Benin	4 214	1.7	0.5	NA	NA	91.0	7.2	1.8
Burkina Faso[f]	6 255	7.9	3.3	63	64	93.2	0.7	6.1
Cameroon	8 926	6.4	2.6	59	74	63.8	35.6	0.6
Cape Verde	277	6.1	1.9	NA	NA	55.9	37.1	7.0
Chad	4 665	6.6	6.3	72	82	84.0	2.4	13.7
Comoros	424	0.2	0.0	97	100	22.5	25.8	51.7
Equatorial Guinea	263	2.5	0.8	NA	NA	100.0	0.0	0.0
Gabon	776	12.2	3.7	NA	NA	64.1	15.9	19.9
Gambia	827	3.2	1.0	NA	NA	99.6	0.0	0.4
Ghana	12 390	5.2	3.6	47	62	83.5	5.2	11.4
Guinea N. A. Bissau	767	3.6	1.1	NA	NA	51.4	26.7	21.9
Guinea	4 939	0.2	0.1	NA	NA	73.5	24.2	2.4
Liberia	1 703	5.2	1.6	NA	NA	5.8	0.1	94.1
Madagascar	9 509	2.0	0.6	NA	NA	11.7	10.7	77.6
Mali[f]	6 381	0.5	0.0	95	97	85.5	10.4	4.1
Mauritania[f]	1 596	0.0	0.0	97	98	20.6	16.9	62.5
Mauritius[f]	904	3.9	1.0	26	56	75.8	7.9	16.4
Niger	6 433	0.1	0.0	NA	NA	68.0	31.9	0.1
Nigeria	67 835	14.1	3.5	46	55	12.1	87.9	0.0
Sao Tome and Principe	87	9.5	2.9	NA	NA	18.9	71.1	10.0

Table 1.7 (continued)

WHO Region Country	Adult population[b]	Alcohol consumption[c]	Unrecorded consumption[d]	Abstainers[e]		Recorded beverages consumed		
				Men (%)	Women (%)	Beer (%)	Wine (%), inc. other fermented beverages	Spirits (%)
Senegal[f]	6 094	1.3	0.8	91	98	51.6	39.6	8.8
Seychelles[f]	NA	8.5	5.2	14	46	66.2	20.6	13.2
Sierra Leone	2 800	9.0	2.4	57	65	4.7	95.0	0.3
Togo	3 174	1.5	0.5	NA	NA	85.8	10.0	4.2
Africa E								
Botswana	1 090	7.9	3.0	37	70	45.2	26.9	27.9
Burundi	3 619	14.0	4.7	NA	NA	24.8	75.1	0.0
Central Africa Republic	2 208	3.3	1.7	NA	NA	58.8	39.7	1.5
Congo (Democratic Republic of the)	27 875	3.2	1.3	NA	NA	63.0	36.3	0.6
Congo (Republic of) [f]	1 946	4.5	2.2	48	61	62.4	12.2	25.4
Cote d'Ivoire[f]	9 940	2.4	0.5	57	76	79.8	19.0	1.1
Eritrea	2 134	1.4	0.6	NA	NA	97.9	0.0	2.1
Ethiopia[f]	39 460	5.5	4.6	57	64	88.6	1.0	10.4
Kenya	18 137	5.6	4.0	NA	NA	59.9	1.8	38.4
Lesotho	1 084	5.6	3.7	47	81	86.1	0.0	13.9
Malawi	6 416	1.9	0.5	58	91	80.3	1.1	18.6
Mozambique	10 430	2.1	0.8	NA	NA	25.0	10.5	64.5
Namibia[f]	1 118	7.5	3.8	39	53	68.0	9.5	22.5
Rwanda	4 678	11.3	4.3	NA	NA	14.6	85.2	0.2
South Africa	31 159	9.1	2.2	57	82	58.5	21.1	18.9
Swaziland	592	11.0	4.1	79	92	93.3	0.7	6.0
Tanzania (United Republic of)	20 452	7.5	2.0	NA	NA	92.5	5.6	2.0
Uganda	12 884	18.6	0.0	48	60	31.6	67.3	1.1

Table 1.7 (continued)

WHO Region Country	Adult population[b]	Alcohol consumption[c]	Unrecorded consumption[d]	Abstainers[e]		Recorded beverages consumed		
				Men (%)	Women (%)	Beer (%)	Wine (%), inc. other fermented beverages	Spirits (%)
Zambia	5 966	5.8	3.2	57	81	84.6	0.4	15.0
Zimbabwe	7 473	13.5	9.0	52	90	30.0	1.2	68.8
America A								
Canada	25 516	9.8	2.0	18	26	55.1	18.6	26.9
Cuba	8 915	4.5	2.0	29	70	17.1	9.4	71.4
USA	228 220	9.6	1.0	34	54	61.2	14.4	28.7
America B								
Antigua and Barbuda	NA	6.3	0.8	NA	NA	14.7	21.6	63.7
Argentina	27 331	10.5	2.0	9	26	26.7	62.8	4.7
Bahamas	220	11.1	1.3	NA	NA	8.9	9.7	81.4
Barbados	214	7.0	–0.5	29	70	28.5	8.3	63.3
Belize	156	8.6	2.0	24	44	51.9	1.3	46.8
Brazil	127 411	8.8	3.0	13	31	58.5	5.0	35.7
Chile	11 569	8.8	2.0	22	29	26.5	35.2	34.7
Colombia	29 554	7.7	2.0	5	21	54.9	1.1	43.6
Costa Rica	2 852	7.7	2.0	33	66	15.2	3.9	80.9
Dominica	NA	9.2	1.1	NA	NA	9.7	13.7	76.6
Dominican Republic	5 617	7.5	1.0	12	35	43.8	1.7	54.6
El Salvador	4 243	5.6	2.0	NA	NA	30.6	1.4	68.0
Grenada	NA	7.2	0.9	NA	NA	24.0	10.9	65.1
Guyana	523	5.9	2.0	20	40	34.5	0.0	62.1
Honduras	3 992	4.7	2.0	72	84	46.3	1.5	52.2
Jamaica	1 767	3.9	2.0	38	61	88.2	4.7	7.0
Mexico	69 336	7.6	3.0	36	65	76.8	0.7	22.6

Table 1.7 (continued)

WHO Region Country	Adult population[b]	Alcohol consumption[c]	Unrecorded consumption[d]	Abstainers[e]		Recorded beverages consumed		
				Men (%)	Women (%)	Beer (%)	Wine (%), inc. other fermented beverages	Spirits (%)
Panama	2 106	6.6	0.8	NA	NA	60.2	2.7	37.1
Paraguay[f]	3 512	5.2	1.5	9	33	92.4	6.7	0.0
St Kitts and Nevis	NA	7.6	0.9	NA	NA	45.9	9.3	44.9
St Lucia	109	9.7	–1.0	24	52	19.7	4.5	75.8
St Vincent and the Grenadines	81	7.9	1.0	NA	NA	14.1	3.2	82.7
Suriname	302	6.2	0.0	30	55	47.2	0.8	52.1
Trinidad and Tobago	991	4.3	0.0	29	70	56.3	2.1	41.6
Uruguay[f]	2 557	9.8	2.0	25	43	15.3	61.2	17.6
Venezuela	17 072	9.0	2.0	19	39	84.6	0.0	14.6
America D								
Bolivia	5 276	6.3	3.0	24	45	59.2	2.0	38.8
Ecuador	8 407	7.2	5.4	41	67	76.9	3.2	19.9
Guatemala[f]	6 582	3.8	2.0	49	84	40.5	1.7	57.8
Haiti	4 967	7.5	0.0	58	62	0.4	0.4	99.2
Nicaragua	3 057	3.6	1.0	12	50	32.4	1.6	65.9
Peru	17 761	9.9	5.9	20	29	NA	NA	NA
Eastern Mediterranean B								
Bahrain	503	6.8	0.0	NA	NA	32.5	5.2	62.3
Iran	45 725	1.0	1.0	90	95	0.0	1.8	98.2
Jordan	3 236	0.5	0.3	NA	NA	71.8	2.0	26.1
Kuwait	1 823	0.1	0.0	NA	NA	63.2	0.0	36.8
Lebanon	2 431	4.0	0.5	67	87	10.3	18.4	71.4
Libyan Arab Jamahiriya	3 789	0.0	0.0	NA	NA	76.4	10.3	13.3
Oman	1 606	0.6	0.3	NA	NA	100.0	0.0	0.0

Table 1.7 (continued)

WHO Region Country	Adult population[b]	Alcohol consumption[c]	Unrecorded consumption[d]	Abstainers[e]		Recorded beverages consumed		
				Men (%)	Women (%)	Beer (%)	Wine (%), inc. other fermented beverages	Spirits (%)
Qatar	521	4.3	0.5	NA	NA	7.0	0.0	93.0
Saudi Arabia	13 917	0.6	0.6	NA	NA	100.0	0.0	0.0
Syrian Arab Republic	10 838	0.9	0.4	NA	NA	10.4	73.3	16.3
Tunisia[f]	7 001	1.6	0.5	77	100	62.5	38.5	0.0
United Arab Emirates[f]	2 879	1.0	1.0	86	94	0.0	100.0	0.0
Eastern Mediterranean D								
Afghanistan	13 802	0.0	0.0	NA	NA	36.9	6.4	56.8
Djibouti	432	2.1	0.5	NA	NA	30.2	4.4	65.4
Egypt	45 581	0.6	0.5	99	100	70.2	10.9	18.9
Iraq	15 378	0.2	0.0	NA	NA	79.0	0.0	20.9
Morocco[f]	20 375	1.5	1.0	77	99	60.0	51.3	0.0
Pakistan	89 157	0.3	0.3	90	99	34.4	65.6	0.0
Somalia	4 172	0.5	0.5	NA	NA	100.0	0.0	0.0
Sudan	20 536	1.3	1.0	NA	NA	0.0	0.0	100.0
Yemen	10 024	0.3	0.2	NA	NA	88.1	0.0	11.9
Europe A								
Austria	6 813	11.6	0.7	6	16	59.0	35.6	15.2
Belgium	8 577	10.7	0.2	12	26	54.5	30.0	14.1
Croatia	3 768	17.0	4.5	12	29	38.7	52.0	9.3
Cyprus	633	12.2	1.0	10	15	30.2	20.4	47.3
Czech Republic	8 642	13.9	1.0	9	20	71.8	16.8	34.3
Denmark	4 370	13.7	2.0	2	4	50.9	37.1	11.6
Finland	4 278	11.2	1.9	7	8	47.9	24.8	27.4
France	48 750	13.3	1.0	4	9	16.9	59.8	23.3

Table 1.7 (continued)

WHO Region Country	Adult population[b]	Alcohol consumption[c]	Unrecorded consumption[d]	Abstainers[e]		Recorded beverages consumed		
				Men (%)	Women (%)	Beer (%)	Wine (%), inc. other fermented beverages	Spirits (%)
Germany	70 042	13.2	1.0	7	9	58.4	25.6	19.2
Greece	9 415	10.9	1.8	NA	NA	25.0	47.8	23.1
Iceland	221	7.6	1.0	11	12	50.7	24.2	24.2
Ireland	3 112	14.7	1.0	17	26	68.1	14.5	23.1
Israel	4 565	3.3	1.0	26	45	41.8	10.6	47.6
Italy	49 689	9.9	1.5	19	49	19.1	75.8	5.4
Luxembourg	362	14.2	–1.0	NA	NA	45.5	54.6	13.4
Malta	321	6.4	0.3	NA	NA	41.1	46.0	16.3
Netherlands	13 106	10.3	0.5	9	22	49.5	26.1	20.8
Norway	3 644	7.5	2.0	6	6	59.8	27.5	18.2
Portugal	8 678	12.9	1.0	NA	NA	30.2	48.8	14.4
Slovenia	1 674	9.9	3.0	6	26	55.9	33.8	10.3
Spain[f]	35 646	12.5	1.0	25	50	38.2	33.9	25.0
Sweden	7 315	9.0	3.0	10	16	57.0	35.9	20.4
Switzerland	5 969	11.4	0.5	14	30	30.8	51.1	17.8
United Kingdom	48 042	13.3	2.0	9	14	52.4	22.5	17.7
Europe B								
Albania	2 188	5.2	3.0	NA	NA	41.8	17.4	40.9
Armenia	2 323	3.3	1.9	16	56	8.7	18.0	73.4
Azerbaijan	5 860	7.0	1.9	39	62	22.8	2.3	74.9
Bosnia and Herzegovina	3 218	13.5	3.0	45	87	18.4	2.4	79.1
Bulgaria	6 717	9.4	3.0	26	57	13.4	43.4	39.3
Georgia[f]	3 666	4.1	2.5	11	51	23.1	71.4	5.5
Kyrgyzstan	3 383	4.9	2.0	34	61	9.0	7.6	83.4

Table 1.7 (continued)

WHO Region Country	Adult population[b]	Alcohol consumption[c]	Unrecorded consumption[d]	Abstainers[e]		Recorded beverages consumed		
				Men (%)	Women (%)	Beer (%)	Wine (%), inc. other fermented beverages	Spirits (%)
Macedonia (Former Yugoslav Republic of)	1 596	7.0	2.9	NA	NA	46.8	33.9	19.3
Poland	31 693	10.9	3.0	16	34	53.6	18.7	25.8
Romania	18 192	14.7	4.0	23	53	34.7	32.7	29.4
Slovakia[f]	4 412	14.6	4.0	5	9	52.4	17.4	39.8
Tajikistan	3 705	4.6	4.0	NA	NA	3.4	38.5	58.1
Turkey	49 177	4.1	2.7	66	92	55.0	8.8	40.0
Turkmenistan	3 035	2.1	1.0	NA	NA	8.4	90.3	1.3
Uzbekistan	16 380	3.4	1.9	NA	NA	17.7	16.6	65.7
Europe C								
Belarus	8 215	11.0	4.9	11	29	16.7	12.4	70.9
Estonia	1 122	11.0	1.0	10	32	57.3	4.8	22.6
Hungary[f]	8 498	17.4	4.0	4	8	31.9	35.7	30.6
Kazakhstan[f]	11 043	8.1	4.9	26	44	27.1	8.2	64.6
Latvia	1 955	11.6	2.3	15	32	23.4	5.7	74.0
Lithuania	2 820	14.2	4.9	10	28	48.0	11.2	40.9
Moldova (Republic of)	3 353	25.0	12.0	13	30	5.7	7.9	86.4
Russian Federation[f]	120 831	15.2	4.9	12	26	18.1	10.2	72.1
Ukraine[f]	40 054	15.6	10.5	15	28	20.0	11.0	80.0
South East Asia B								
Indonesia	151 683	0.6	0.5	90	99	46.5	0.8	52.8
Sri Lanka	15 117	2.4	2.1	67	98	49.9	1.6	48.4
Thailand	47 053	7.7	2.0	44	90	23.3	0.3	79.5
South East Asia D								

Table 1.7 (continued)

WHO Region Country	Adult population[b]	Alcohol consumption[c]	Unrecorded consumption[d]	Abstainers[e]		Recorded beverages consumed		
				Men (%)	Women (%)	Beer (%)	Wine (%), inc. other fermented beverages	Spirits (%)
Bangladesh	84 829	0.2	0.2	87	100	36.4	3.8	59.7
Bhutan	1 215	0.7	0.3	NA	NA	100.0	0.0	0.0
India	703 046	2.2	1.9	80	98	17.5	0.0	100.0
Korea (Democratic People's Republic of)	16 377	3.5	0.5	NA	NA	6.6	0.0	93.4
Maldives	175	2.3	0.5	NA	NA	20.6	23.5	55.9
Myanmar	33 574	0.7	0.4	52	91	10.4	0.2	89.4
Nepal	15 234	2.4	2.2	51	73	36.3	1.5	62.2
Western Pacific A								
Australia	15 488	9.2	0.0	14	21	63.3	31.0	16.2
Brunei Darussalem	242	0.5	0.3	NA	NA	70.6	5.9	23.5
Japan	109 266	9.6	2.0	11	29	25.1	4.7	50.8
New Zealand	3 029	9.8	0.5	12	17	49.5	26.1	20.8
Singapore	3 283	3.1	1.0	67	82	62.2	6.7	27.8
Western Pacific B								
Cambodia	8 099	2.1	0.5	NA	NA	18.2	0.6	81.2
China	988 456	5.9	0.8	25	61	23.5	0.6	76.9
Cook Islands	NA	2.0	0.4	NA	NA	0.0	39.8	60.2
Fiji	557	2.9	1.0	79	98	79.3	7.9	12.7
Kiribati	NA	2.8	2.0	51	93	90.8	0.6	8.6
Korea (Republic of)	37 833	14.8	7.0	12	39	29.6	38.0	32.4
Lao People's Democratic Republic	3 205	7.9	1.0	30	67	12.3	0.4	87.3
Malaysia	16 002	2.1	1.0	83	97	85.7	0.0	14.3

Table 1.7 (continued)

WHO Region Country	Adult population[b]	Alcohol consumption[c]	Unrecorded consumption[d]	Abstainers[e]		Recorded beverages consumed		
				Men (%)	Women (%)	Beer (%)	Wine (%), inc. other fermented beverages	Spirits (%)
Micronesia (Federated States of)	65	2.2	1.1	45	91	100.0	0.0	0.0
Mongolia	1 705	4.8	2.0	NA	NA	15.8	3.7	80.5
Nauru	NA	2.3	0.4	NA	NA	86.9	13.1	0.0
Niue	NA	10.8	2.1	NA	NA	24.9	21.9	53.2
Papua New Guinea	3 255	2.4	0.5	NA	NA	34.2	0.6	65.2
Philippines[f]	49 880	6.6	3.0	28	73	21.6	1.4	77.0
Solomon Islands	258	0.9	0.2	NA	NA	26.0	2.6	71.3
Tonga	64	1.0	0.2	NA	NA	28.3	12.6	59.2
Tuvalu	NA	1.5	0.3	NA	NA	54.3	23.4	22.3
Vanuatu	117	1.0	0.2	NA	NA	6.2	26.4	67.4
Vietnam[f]	55 099	2.9	2.1	39	95	94.2	0.0	1.7

NA, not available [a] Calculated by the Working Group from WHO Global Alcohol Database (undated) [b] Numbers in thousands ≥15 years of age [c] Per-capita (age ≥15 years) average consumption per year in litres of absolute alcohol from 2001 to 2003, including unrecorded consumption [d] Unrecorded consumption was mainly derived from surveys by local experts based on fragmented data. [e] Abstainer figures relate to 'last year' and were derived from surveys, which contain measurement errors. Moreover, in some countries, only lifetime abstention rates were available, but no information on abstention during the last year. [f] Estimates of 'last year' abstention based on lifetime abstention

In terms of pricing, locally produced traditional alcoholic beverages tend to be considerably cheaper than their western-style, commercially produced counterparts.

In many regions of the world, illegal alcoholic beverages are approximately 2–6 times cheaper (McKee *et al.*, 2005; Lang *et al.*, 2006) than commercial alcoholic beverages and are thus most likely to be consumed by those who are on the margins of society, are very heavy drinkers or are dependent on alcohol, all of whom are commonly underrepresented in surveys. In spite of the higher price, industrially produced alcoholic beverages are gaining popularity in many of these countries.

1.3.3 *Global consumption in 2002*

Although the global average consumption is 6.2 L of pure alcohol *per capita* per year, there is wide variation around the world (Table 1.8). The countries with the highest overall consumption are those in eastern Europe that surround the Russian Federation; however, other areas of Europe also have high overall consumption. The Americas have the next highest overall consumption. Except for some individual countries, alcoholic beverage consumption is lower in other parts of the world. Globally, 55.2% of adult men and 34.4% of adult women consume alcoholic beverages; in 2002, this constituted more than 1.9 billion adults. The fraction of unrecorded consumption is higher in less developed parts of the world, and is thus highest in the poorest regions of Africa, Asia and South America. In addition, unrecorded consumption is estimated to be proportionally high in the Eastern Mediterranean Region where many of the countries are Islamic, although the level of consumption is very low. Table 1.8 gives further details on consumption.

Table 1.9 shows the rates of drinking more than 40 g pure alcohol per day in different parts of the world. As expected from the per-capita figures, there is huge variation between sexes and by region, with highest prevalence in eastern Europe (Russian Federation and surrounding countries) and lowest prevalence in the WHO Eastern Mediterranean Region where countries are mostly Islamic.

1.3.4 *Trends in recorded per-capita consumption*

Figs. 1.1–1.4 give an overview of trends in alcoholic beverage consumption over the past 40 years. Trends of unrecorded consumption are not available because of the lack of data. However, in regions that have relatively high recorded consumption, these figures also reflect the trend of overall consumption.

Changes in the trend of overall alcoholic beverage consumption have varied between different countries and regions. In Europe, consumption declined in the 1980s and has been stable since 1990. The European trend obscures various developments in different countries, such as an increase in countries with formerly lower consumption such as the Nordic countries, and a decline in consumption in traditional wine-producing countries such as France, Italy, Portugal and Spain. Other regions have remained

Table 1.8 Characteristics of alcoholic beverage consumption throughout the world in 2002[a]

WHO Region[b]	Adult population[c]	Percentage of abstainers[d]		Total alcohol consumption[e]	Unrecorded consumption	Recorded beverage most commonly consumed
		Men	Women			
Africa D	180 316	59.3	69.3	7.2	2.2	Other fermented beverages
Africa E	208 662	55.4	73.3	6.9	2.7	Other fermented beverages and beer
America A	262 651	32.0	52.0	9.4	1.1	Beer
America B	311 514	18.0	39.1	8.4	2.6	Beer
America D	46 049	32.1	51.0	7.4	4.0	Spirits and beer
Eastern Mediterranean B	94 901	86.9	95.0	1.0	0.7	Spirits
Eastern Mediterranean D	219 457	90.8	98.9	0.6	0.4	Beer
Europe A	347 001	11.4	23.0	12.1	1.3	Beer and wine
Europe B	155 544	38.6	62.4	7.5	2.8	Spirits and beer
Europe C	197 891	13.0	26.9	14.9	6.1	Spirits
South East Asia B	215 853	77.6	96.9	2.3	0.9	Spirits

Table 1.8 (continued)

WHO Region[b]	Adult population[c]	Percentage of abstainers[d]		Total alcohol consumption[e]	Unrecorded consumption	Recorded beverage most commonly consumed
		Men	Women			
South East Asia D	854 450	79.0	98.0	1.9	1.6	Spirits
Western Pacific A	131 308	13.0	29.0	9.4	1.7	Spirits
Western Pacific B	1 164 701	26.3	62.5	6.0	1.1	Spirits
World	4 388 297	44.8	65.6	6.2	1.7	Spirits (53%)

[a] Calculated by the Working Group from WHO Global Alcohol Database (undated) [b] Listing of WHO Regions: **Africa D**: Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo; **Africa E**: Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe; **Americas A**: Canada, Cuba, USA; **Americas B**: Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, St Kitts and Nevis, St Lucia, St Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela; **Americas D**: Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru; **Eastern Mediterranean B**: Bahrain, Iran (Islamic Republic of), Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates; **Eastern Mediterranean D**: Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen; **Europe A**: Andorra, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom; **Europe B**: Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Slovakia, The Former Yugoslav Republic of Macedonia, Tajikistan, Turkey, Turkmenistan, Uzbekistan; **Europe C**: Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine; **South East Asia B**: Indonesia, Sri Lanka, Thailand; **South East Asia D**: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal; **Western Pacific A**: Australia, Brunei Darussalam, Japan, New Zealand, Singapore; **Western Pacific B**: Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam [c] Numbers in thousands [d] Abstainer figures relate to 'last year' and were derived from surveys, which contain measurement errors. Moreover, in some countries, only lifetime abstention rates were available, but no information on abstention during the last year. [e] Per-capita (age ≥ 15 years) average consumption in litres of absolute alcohol from 2001 to 2003, including unrecorded consumption [f] Estimates of 'last year' abstention based on lifetime abstention

Table 1.9 Consumption of more than 40 g pure alcohol per day by sex and WHO region, 2002[a]

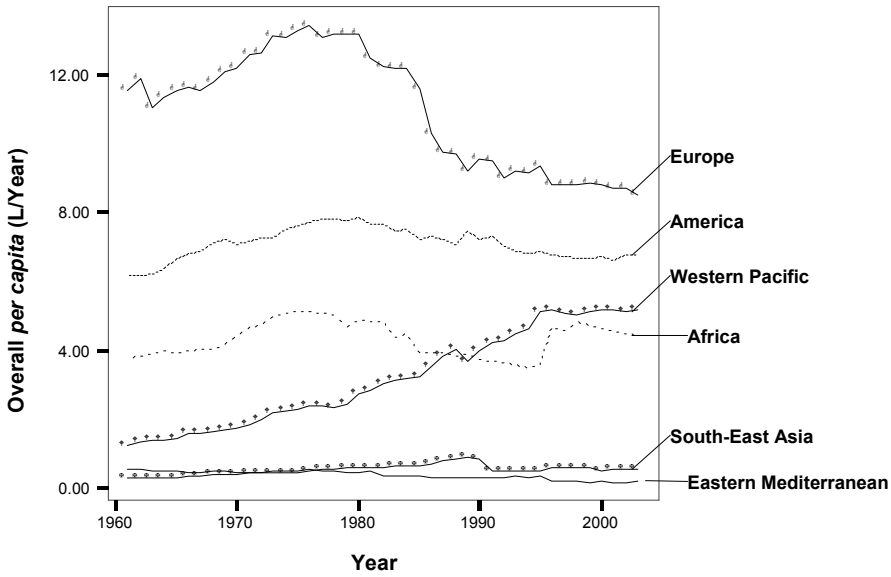
Region[b]	Men	Women
Africa D	27.6%	8.2%
Africa E	30.1%	6.1%
America A	33.9%	5.1%
America B	21.4%	6.5%
America D	20.7%	2.6%
Eastern Mediterranean B	2.1%	0.0%
Eastern Mediterranean D	1.0%	0.0%
Europe A	44.2%	7.6%
Europe B	34.4%	4.7%
Europe C	63.7%	11.1%
South East Asia B	12.0%	0.1%
South East Asia D	8.4%	0.1%

Table 1.9 (continued)

Region[b]	Men	Women
Western Pacific A	29.6%	2.3%
Western Pacific B	20.5%	0.8%
World	22.2%	3.1%

[a] From WHO Global Alcohol Database (undated) [b] Listing of WHO Regions: **Africa D**: Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo; **Africa E**: Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe; **Americas A**: Canada, Cuba, USA; **Americas B**: Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, St Kitts and Nevis, St Lucia, St Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela; **Americas D**: Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru; **Eastern Mediterranean B**: Bahrain, Iran (Islamic Republic of), Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates; **Eastern Mediterranean D**: Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen; **Europe A**: Andorra, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom; **Europe B**: Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Slovakia, The Former Yugoslav Republic of Macedonia, Tajikistan, Turkey, Turkmenistan, Uzbekistan; **Europe C**: Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine; **South East Asia B**: Indonesia, Sri Lanka, Thailand; **South East Asia D**: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal; **Western Pacific A**: Australia, Brunei Darussalam, Japan, New Zealand, Singapore; **Western Pacific B**: Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam

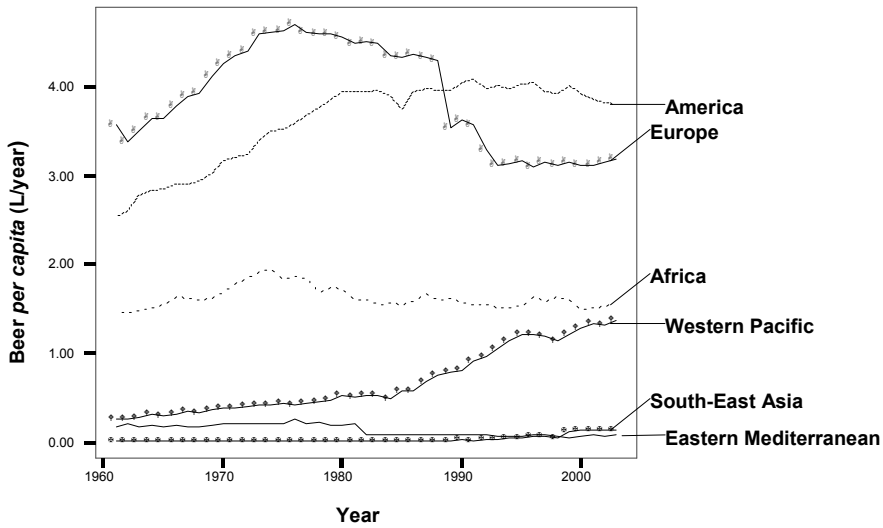
Figure 1.1. Recorded overall adult per-capita consumption of alcoholic beverages in six WHO Regions: Africa, Americas, Eastern Mediterranean, Europe, South-East Asia and Western Pacific, 1961–2003[a]



From FAO Statistical Database [FAOSTAT]

[a] Calculated by the Working Group [population weighted]

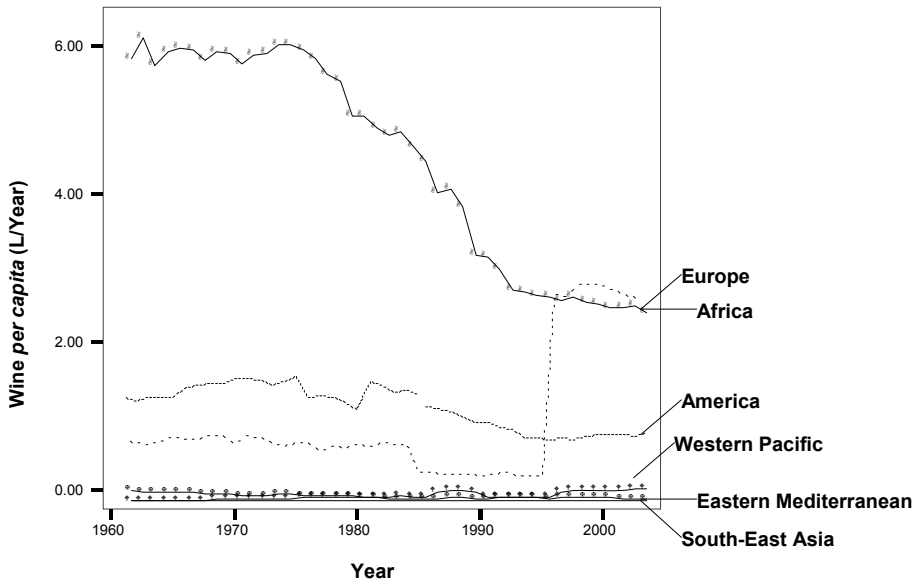
Figure 1.2. Recorded adult per-capita beer consumption in six WHO Regions: Africa, Americas, Eastern Mediterranean, Europe, South-East Asia and Western Pacific, 1961–2003[a]



From FAO Statistical Database [FAOSTAT]
[a] Calculated by the Working Group [population weighted]

Note: In 1989, the Russian Federation, a typically non-beer-drinking nation, was included in calculations of European per-capita consumption. Previously, no estimates were available for the former Soviet Union.
Figures for the Americas were estimated and imputed for the years 1976–80.

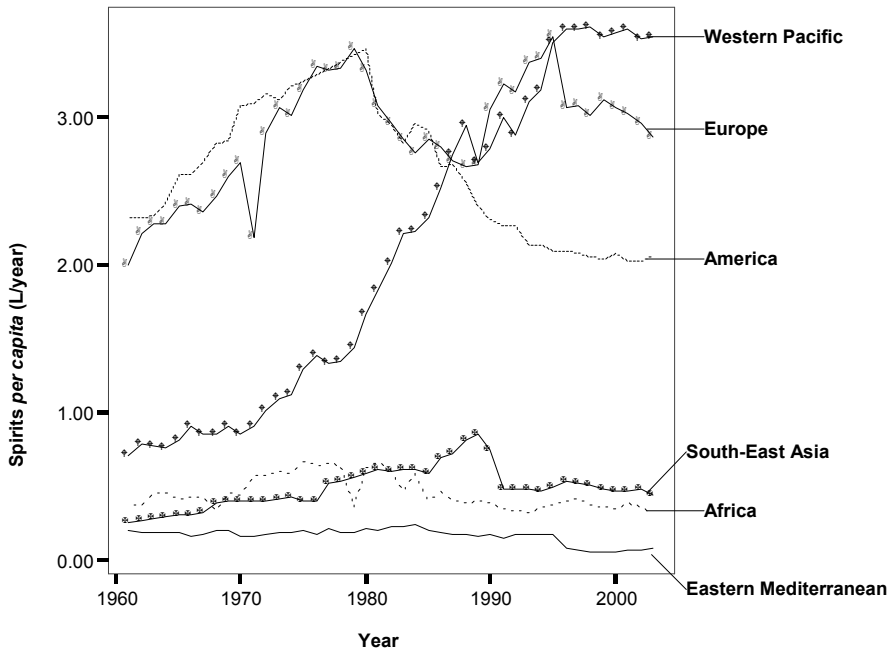
Figure 1.3. Recorded adult per-capita wine consumption in six WHO Regions: Africa, Americas, Eastern Mediterranean, Europe, South-East Asia and Western Pacific, 1961–2003[a]



From FAO Statistical Database [FAOSTAT]
[a] Calculated by the Working Group [population weighted]

Note: The increase in African consumption resulted from the inclusion of fermented beverages into the wine category by FAO.

Figure 1.4. Adult per-capita consumption of spirits in six WHO Regions: Africa, Americas, Eastern Mediterranean, Europe, South-East Asia and Western Pacific, 1961–2003[a]



From FAO Statistical Database [FAOSTAT]

[a] Calculated by the Working Group [population weighted]

Note: Figures for the Americas were estimated and imputed for the years 1976–80.

relatively stable, but consumption in the Western Pacific Region, mostly influenced by China because of the large population there, has almost steadily increased.

The trends in beer consumption follow the same pattern. In addition, beer consumption has been increasing in the Americas; this region now has the biggest beer consumption *per capita* in the world.

Europe and, to a much lesser degree, America are the only regions with notable consumption of wine. The seemingly high consumption in Africa is due to the fact that FAO has been recording fermented beverages under this category since the mid 1990s.

Finally, spirits are the most commonly consumed beverage type around the world. They have also contributed to the large increase in consumption in the Western Pacific Region. In a global perspective, the Western Pacific Region, and especially China, is now the region with the highest consumption of spirits in the world. It should also be noted that the consumption of spirits has decreased in the Americas, where this type of beverage has been replaced by beer.

1.4 Sociodemographic determinants of alcoholic beverage consumption

1.4.1 *Introduction*

As noted in Section 1.3, per-capita consumption figures offer overall a comparable picture of alcoholic beverage consumption across countries and avoid the problems of underestimation as well as other sources of bias present in survey methods (e.g. recall bias). However, per-capita consumption does not provide any information on patterns of consumption within a country; that is, the frequency and quantity of consumption as well as occasions on which a large amount of alcoholic beverages may be consumed at one time. Also, with per-capita consumption, it is not known which subgroups engage in particular patterns of drinking. Survey data, although imperfect in certain respects, still provide the only method to obtain knowledge on the patterns of consumption within a population.

Key measures of patterns of consumption include the assessment, within a given period, of the proportion of the population that drinks at all and, conversely, the proportion that abstains from drinking. Among those who drink, central measures include the frequency of drinking over a pre-defined period and the total amount or volume of ethanol consumed over that period. It is also informative to gather this information for the three major classes of beverage: beer, wine and spirits. In addition, it is helpful to calculate the average amount of alcoholic beverages consumed per day as well as the number of drinking days. The former measure is often used to communicate safe drinking limits to the public (e.g. British Medical Association, 1995). A final important indicator of patterns of consumption is a measure of so-called ‘heavy episodic drinking’. This is defined as an intake of ethanol sufficient to lead to intoxication in a single session of drinking, and is usually 60 g ethanol or more (WHO, 2000).

Knowledge of the patterns and habits of alcoholic beverage consumption in various countries and among cultures has increased markedly over the past decade. This has been due to efforts of various cross-cultural social-epidemiological studies as well as initiatives of various regional and global institutions such as the European Commission and the WHO to conduct general population surveys. Despite these advances, gaps in knowledge still exist; however, it is now possible to obtain a general picture of drinking habits in various regions of the world, which was not the case previously. Such information can help to indicate which geographic and demographic groups may be at greater risk from certain exposures to alcoholic beverage consumption than others.

1.4.2 *Gender*

It has been often observed that men are more frequently drinkers of alcoholic beverages, drink larger amounts and drink more often than women (Wilsnack *et al.*, 2000, 2005). This appears to be a universal gender difference in human social behaviour. However, the magnitude of these gender differences varies by age group, socioeconomic group and by region and/or culture.

With respect to the European Region, gender differences in the rates of current drinkers are small, with gender ratios (i.e. the value of a variable for men divided by that for women) that range between 1.0 and 1.2 (calculated from Mäkelä *et al.*, 2006). In the adult drinking population (20–64 years), gender ratios for overall drinking frequency are between 1.8 and 2.5. Larger variation exists for beverage-specific drinking frequency: men and women are most similar in their wine-drinking habits and the least similar in their beer-drinking habits. This basic pattern holds true for beverage-specific volume. Although in some countries women may drink wine more frequently than men, men almost always consume more of each beverage than women. Gender ratios for mean quantities of specific beverages consumed per drinking day have a narrow range for wine (1.0–1.8) and a wider range for spirits (1.1–2.0) and beer (1.3–2.2). For total mean volume and frequency of heavy episodic drinking, gender ratios are larger than those for drinking status or drinking frequency and most range between 1.8 and 5.8 across the European Region. Gender differences are smaller in the northern European countries for current drinking, frequency of drinking and frequency of heavy episodic drinking, but gender ratios for mean consumption reveal no clear regional pattern (Mäkelä *et al.*, 2006).

In the 14 WHO regions, more women than men are abstainers, yet the rates of current drinking for both men and women are similar across the regions, showing that, where the level of current drinking for men is high, that for women is also high. The gender ratios are extremely variable: western Europe and the Western Pacific (e.g. Australia and Japan) have low ratios of 1.1 while the Eastern Mediterranean (e.g. Afghanistan and Pakistan) has a ratio of 17 and South-East Asia (e.g. Bangladesh and India) has a ratio of 6.5 (Wilsnack *et al.*, 2005). Furthermore, the percentage of alcoholic beverages consumed by women also varies greatly across regions. In Europe, the

share of alcoholic beverages consumed by women generally varies between 20% and 30% (Mäkelä *et al.*, 2006). In developing countries, the percentage share can be much lower: based on recently conducted surveys, it is, for example, 8% in China, 10% in India and 15% in Ecuador (WHO, 2004).

Data – as yet unpublished – obtained from a recent general population survey in many countries (Argentina, Australia, Austria, Brazil, Costa Rica, Czech Republic, Denmark, Finland, France, Germany, Hungary, Iceland, India, Israel, Italy, Japan, Mexico, the Netherlands, Nigeria, Norway, Spain, Sri Lanka, Sweden, Uganda, United Kingdom, USA, Uruguay) in various regions of the world through the GENACIS project (Rahav *et al.*, 2006) confirm the previously mentioned variations in drinking by gender: men are more likely to be drinkers than women, women are more likely to be lifetime abstainers, men are more likely to drink heavily and more frequently and women drinkers are more likely to be light drinkers. These gender differences are more marked for countries outside North America and northern Europe.

1.4.3 *Age*

The relationship of age to drinking habits is very much affected by gender and culture. In general terms, however, among adult populations in the developed world, abstention rates increase with older age and, among those who drink, frequency of drinking increases. Heavy episodic drinking is most frequent among the younger age groups; however, in some countries (e.g. central Europe), such rates do not always decline.

As stated, these general tendencies are very much affected by both age and region. For example, in Europe, a decrease in current drinking rates with age (age categories of 20–34, 35–49, 50–64 years) has been seen for some (e.g. northern and eastern Europe) but not all European countries (Mäkelä *et al.*, 2006). Men and women tend to have similar current drinking rates at a given age. In many European countries, drinking frequency increases with increasing age, which can be attributed mostly to an increase in the frequency of drinking wine. This holds for both sexes. Typical amounts of alcoholic beverage consumed also generally decrease with age across many European countries and across the genders, although a slight increase in wine consumption with increasing age can be observed in France (Mäkelä *et al.*, 2006). In most northern European countries, heavy episodic drinking clearly declines with increasing age, but such reductions are not as observed in more central European countries.

Age also interacts variously with gender across the GENACIS study countries. For example, drinking status and frequency of drinking do not decline with age everywhere. For most European countries, the gender ratio for current drinking status remains rather stable across age groups and, in low- and middle-income countries, there is no clear pattern of the gender gap being larger at younger or older ages. The proportion of heavy drinkers (e.g. 23.2 g ethanol per day or more) tends to decline with increasing age (age categories of 18–34, 35–49, 50–65 years) among the North

American and European countries (central and southern European countries tend to be exceptions). The non-European, non-North American countries have varying patterns: in several low- and middle-income countries (e.g. Brazil, India, Nigeria) as well as Japan, heavy drinking is positively correlated with increasing age, especially among men. Heavy episodic drinking has much clearer patterns. In almost all of the GENACIS study countries, the prevalence of heavy episodic drinking decreases with increasing age. However, this reduction is not always proportional across the sexes, leading to higher gender ratios in the older age categories (Rahav *et al.*, 2006).

1.4.4 *Socioeconomic status*

In developed economies, people with higher socioeconomic status are more likely to be current drinkers than those with lower socioeconomic status. Among those who drink, drinking frequency is higher among those with higher status. Heavy drinking and heavy episodic drinking are, in general, found to be more common among women of higher socioeconomic status; for men, the trend for both indicators is converse (e.g. Bloomfield *et al.*, 2006). Further, in the USA, it is known that household income, education and employment status are positively associated with current drinking status and more frequent drinking, but are negatively correlated with measures of heavier drinking such as weekly heavy drinking (Midanik & Clark, 1994; Greenfield *et al.*, 2000).

In the Netherlands, van Oers *et al.* (1999) found that lower educational status was positively related to abstinence from alcohol for both men and women; however, among men, very excessive drinking was more prevalent in the lowest educational group. Among women, higher educational level was associated with fewer reports of psychological dependence and symptomatic drinking, while among men higher educational level was associated with fewer reports of social problems.

Bloomfield *et al.* (2000) investigated socioeconomic status and drinking behaviour in a sample of the German general population and found, in comparison with men of high socioeconomic status, that men of middle status had increased odds for heavy episodic drinking, while men of lower status had higher odds for symptoms of alcohol dependence. Women of middle socioeconomic status had significantly lower odds for reporting alcohol-related problems and symptoms of alcohol abuse in comparison with women of higher status.

Marmot (1997) examined data from the Whitehall II Study in the United Kingdom and found variations in prevalence of alcoholic beverage consumption by grade of employment. Higher rates of abstention were evident for both sexes among those in the lower employment grades. More moderate drinking was found among men in the higher employment grades, but the proportion of heavier drinkers was rather constant from the highest to lowest grades. However, among women, there was not only a higher proportion of women in the higher grades who drank moderately, but also a much higher rate of heavier drinking.

In a comparative study of socioeconomic position and health, Kunst *et al.* (1996) found differing associations between heavy drinking and level of education among men and women in eight European countries. Excessive (four glasses or more per day) alcoholic beverage consumption was more common among men with a lower level of education. Among women, no substantial differences were found.

A less consistent pattern has emerged in some low- and middle-income countries such as Brazil, where the higher classes tend to have higher rates of heavier drinking among both genders (Almeida-Filho *et al.*, 2005; Bloomfield *et al.*, 2006). Similarly, among Argentinean men, more of those with a low level of education (less than 8 years of schooling) are abstainers, while more of those who drink weekly or engage in heavy episodic drinking are more highly educated; for Argentinean women, however, more of those who usually drink three or more drinks or engage in heavy episodic drinking are less educated (Munné, 2005). In a regional sample of China, Wei *et al.* (2001) reported that men and women with a lower level of education (0–6 years of schooling) were more frequently abstainers, but also more men with a lower level of education drank daily or more frequently than those with a higher level.

1.4.5 *Socioeconomic status and beverage preferences*

Those who prefer wine compared with beer, spirits or a more mixed consumption come from higher sociodemographic backgrounds (higher socioeconomic status, higher education) and are more frequently light or moderate drinkers. Men and younger individuals more frequently tend to be beer drinkers and women and older people are more frequently wine drinkers (see e.g. the literature reviews in Wannamethee & Shaper, 1999; Graves & Kaskutas, 2002; Klatsky *et al.*, 2003; Nielsen *et al.*, 2004). With regard to age, Gmel *et al.* (1999) have shown, in a longitudinal study in Switzerland with clearly different drinking cultures between the German- and Latin-speaking regions, that young people across all regions more often preferred beer, but were more likely when growing older to change to the typical regional pattern. The preference for beer at younger ages was probably related to the fact that beer is the cheapest alcoholic beverage.

Most of the studies on background characteristics of individuals who have different beverage preferences were conducted in only very few countries such as the North American countries, the United Kingdom or Denmark, which are commonly 'beer countries', and thus wine consumption might be more closely associated with the habits of the more prosperous sectors of the population. Some similarities have also been found for southern European 'wine' countries, such as a higher proportion of heavy drinkers among those who do not drink exclusively wine in Greece (San José *et al.*, 2001), consumption of more beer and spirits compared with wine among younger individuals in Spain (Del Rio *et al.*, 1995) and the proportion of beer in total alcoholic beverage consumption increasing with total ethanol intake in France (Ruidavets *et al.*, 2002). There is nevertheless sufficient evidence that harm from chronic heavy drinking

of wine is found in southern European countries where wine is the culturally preferred and therefore often also the cheapest alcoholic beverage.

The price of alcoholic beverages seems to be a main determinant of which type of beverage is usually preferred, and thus wine as the 'drink of moderation' in many established market economies may reflect the better economical status of wine drinkers, which in turn is related to better education and other healthier lifestyles. Decades ago, excessive drinkers or even alcoholics in the USA were called 'winos' because they drank the cheapest wines from which they could obtain the most alcohol for their money (Klatsky, 2002). It has been argued that there has been a worldwide shift away from cheap wines to quality wines marketed to middle-class consumers, which may have helped to make table wine the more frequent choice of alcoholic beverage among the better-educated segments of society in Denmark, the USA and some other countries.

Outside the established market economies, the gender and sociocultural backgrounds of beverage preferences are much less consistent. It appears that beverage preference is mostly determined by economic conditions, and the poorest people drink the cheapest and most readily available beverages, which can be wine, beer or locally produced beverages. In contrast, people who have a higher standard of living drink the more expensive beverages, which can be industrial, lager type beers or foreign spirits such as whiskies (WHO, 2005).

According to Benegal (2005), 95% of the total alcoholic beverages consumed in India by both male and female drinkers is in the form of licit and illicitly distilled spirits; the remainder is mainly beer. The market for wine is small and wine is mainly drunk by people in high socioeconomic classes and predominantly by women. In contrast, consumption of illicit 'moonshine' by women was more frequently found among rural and working classes. Men who drink beer consume less alcohol than those who drink spirits in India. On the basis of equal quantities of alcohol, beer is more expensive than spirits, and thus beer is drunk by the middle and upper socioeconomic classes (Saxena, 1999). Beer is also more expensive in Brazil than locally produced spirits such as cachaça and thus the latter is more often consumed by heavy drinkers and is preferred by the poorest and least educated (Carlini-Cotrim, 1999). In Mexico (Romero-Mendoza *et al.*, 2005), most women drink beer and spirits, but not table wine. Table wine is consumed by the highest socioeconomic classes, whereas the poorest people drink pulque and aquardiente which are often produced illicitly (Medina-Mora, 1999). Among men, more than half of the pulque drinkers were heavy drinkers. In Nigeria (Ibanga *et al.*, 2005), although wine is the only alcoholic beverage consumed by more women than men, a higher percentage of women (but fewer men) drink beer and local beverages such as burukutu, palmwine and ogogoro (distilled from palmwine) compared with wine. Among men, lower socioeconomic classes prefer traditional African beers and other local beverages whereas commercial western-style beers are preferred by higher socioeconomic classes (Gureje, 1999). In Zimbabwe, the traditional opaque beer is most frequently consumed. Among people with higher incomes, this is

replaced by clear (lager-style) beer, fortified wines and imported spirits that are more expensive than the cheapest opaque beer (Jernigan, 1999). Beer and cheap local brews are also more popular than wine among women who drink in Sri Lanka (Hettige & Paranagama, 2005) where women in higher socioeconomic classes also drink wine and whisky, and those in the lower classes also drink hard liquor such as arrak and illicit liquor. In Papua New Guinea (Marshall, 1999), beer is again by far the most popular beverage, followed by rum and Scotch whiskies. White wines are consumed regularly by only a small number of modern, well educated urban women.

The poorest populations and those on the fringe of society, very heavy drinkers and those who are dependent on alcohol are also the people who show the highest prevalence of consumption of surrogate and illegally produced alcoholic beverages (see Sections 1.3 and 1.5). The reasons for using illicit and surrogate alcoholic beverages are mainly twofold. Illegal alcoholic beverages are much cheaper, e.g. around 2–6 times less expensive in Estonia and the Russian Federation (McKee *et al.*, 2005; Lang *et al.*, 2006) than commercial alcoholic beverages. Another reason can be the restricted availability of alcoholic beverages during particular periods (e.g. war or economic crises), or in particular regions such as the native American reservations in the USA (see Section 1.4). Particularly in developing countries, illegally produced alcoholic beverages are often the main source of alcohol intake in the lower socioeconomic groups (Marshall, 1999; WHO, 2001).

Few representative population surveys on the use of illicit and surrogate alcoholic beverages have been carried out to date. Nevertheless, there is evidence from small-scale studies that their use can be substantial. Lang *et al.* (2006) reported that 8% of alcoholic beverage consumers in Estonia drink illegal and surrogate alcohols. Mc Kee *et al.* (2005) estimated that among 25–54-year-olds in Izhevsk, the Russian Federation, 7.3% have drunk surrogate alcoholic beverages in the past year and 4.7% drink them weekly. Consumption of illegally produced alcoholic beverages is very high and can represent up to more than 50% of total alcoholic beverage consumption (see Section 1.5) in developing countries (WHO, 2001).

1.5 Non-beverage alcohol consumption

Particularly in central and eastern Europe, but also in developing countries, large discrepancies between recorded alcoholic beverage consumption and potentially alcohol-related mortality can be found. One example is Hungary where mortality from liver disease is approximately fourfold higher than that in countries with similar per-capita consumption of alcohol (e.g. Szücs *et al.*, 2005; Rehm *et al.*, 2007). One reason might be the particularly high unrecorded consumption in parts of eastern and central Europe (see Section 1.4), which may account for even more alcoholic beverage consumption from unrecorded sources in some countries than from recorded sources (Szücs *et al.*, 2005). In addition to smuggled commercial and illegally produced, home-made alcoholic beverages, the latter of which are commonly called ‘samogon’ in the

Russian Federation or 'moonshine' in the USA, a proportion of unrecorded consumption is so-called 'surrogate alcohol'.

Surrogate alcohol is not defined consistently in the literature. Some authors also include under 'surrogate alcohol' illegally produced alcoholic beverages that are intended for consumption as well as alcohols that are not initially intended for consumption (McKee *et al.*, 2005). Others define surrogate alcohol more strictly as substances that contain ethanol but are 'not intended' for consumption such as medicinal alcohol, aftershaves, technical spirits or fire-lighting liquids. Even more strictly, Nordlund and Osterberg (2000) divided the 'not intended for consumption alcohols' into alcohol produced for industrial, technical and medical purposes and what they call 'surrogate alcohol', namely denatured spirits, medicines and car chemicals that contain alcohol, but which are meant, for example, for car washing. In this section, only surrogate alcohol that is apparently not intended for consumption is discussed. In fact, as argued by McKee *et al.* (2005), in some countries, mainly in eastern Europe, it is questionable that part of the production of surrogate alcohols is truly not intended for consumption, e.g. medicinal alcohols sold in bottles with colourful labels that are much larger than those in western Europe or aftershaves that have no discernible warning labels such as 'for external use only'.

A few studies have used gas chromatography/mass spectrometry to analyse the compounds in such products, mainly in eastern Europe. In these, surrogate alcohol commonly consisted of relatively pure ethanol but at a very high concentration: medicinal spirits contained 60–70% vol ethanol, aftershaves slightly less and other non-medicinal (fire-lighting liquids) contained very high concentrations of > 90% (McKee *et al.*, 2005; Lang *et al.*, 2006). Methanol was undetected in theses studies. This, however, might be related to the kind of surrogate alcohol that was analysed, namely medicines, aftershaves and fire-lighting liquids and not industrial alcohol, and to the way in which the alcohol was denatured (e.g. by bitter constituents or methanol) to make it undrinkable. [The Working Group noted that the usual denaturing agents were not analysed in these studies, but the undetected methanol points to the fact that only bitterants were used.] Alcohol is denatured for the purposes of exemption from excise duty. Different substances may be used, e.g. 5 L methylene per 100 L ethanol. Methylene is raw methanol and is produced from the dry distillation of wood that contains at least 10% by weight acetone or a mixture of methylene and methanol. Other denaturing substances include methylethylketone (approx. 1 L per 100 L alcohol) or bitterants such as denatonium benzoate (Lachenmeier *et al.*, 2007).

Industrial alcohol is often denatured by addition of up to 5% methanol (methylated). So-called 'meths' drinking is known all over the world and often has fatal consequences. One of the problems is unintentional 'meths' drinking. Alcohol that is offered for consumption on the illegal market is often adulterated by non-drinkable alcohol (e.g. sold as aquardiente in Mexico) (Medina-Mora, 1999), and thus consumers are not aware of the potential risks. However, there is also evidence that some heavy drinkers, commonly the most economically disadvantaged, mix beverage alcohol with industrial

methylated alcohol. Although there is no comprehensive review of 'meths' drinking worldwide, it probably occurs in numerous countries. Examples are mainly found in developing countries such as Papua New Guinea (Marshall, 1999), Mexico (Medina-Mora, 1999) and India (Saxena, 1999). However, 'meths' drinking was also reported not to be uncommon in New Zealand (Meyer *et al.*, 2000), and the use of denatured alcohol, particularly in form of hairspray and spray disinfectants ('Montana Gin'), was reported to be widespread among native Americans, at least in the 1980s (Burd *et al.*, 1987). Ingestion of hairspray still seems to exist in the USA (Carnahan *et al.*, 2005). The use of industrial alcohol denatured by bitterants (bitrex) was also reported in the late 1980s in Sweden among heavily intoxicated drivers. According to Nordlund and Osterberg (2000), the phenomenon of drinking surrogate alcohol (mainly medicinal alcohol) still exists in Nordic countries but only on a very small scale.

1.6 Chemical composition of alcoholic beverages, additives and contaminants

1.6.1 *General aspects*

Ethanol and water are the main components of most alcoholic beverages, although, in some very sweet liqueurs, the sugar content can be higher than that of ethanol. Ethanol for human consumption is exclusively obtained by the alcoholic fermentation of agricultural products. The use of synthetic ethanol manufactured from the hydration of ethylene for food purposes is not permitted in most parts of the world. However, surrogate alcohol, denatured alcohol or illegally produced alcohol may be used for consumption in certain parts of the world because they may be less expensive than food-grade alcohol.

Some physical and chemical characteristics of anhydrous ethanol are as follows (O'Neil, 2001):

Chem. Abstr. Services Reg. No.: 64–17.5
Formula: C_2H_5OH
Relative molecular mass: 46.07
Synonyms: Absolute alcohol, anhydrous alcohol, dehydrated alcohol, ethanol, ethyl alcohol, ethyl hydrate, ethyl hydroxide
Description: Clear, colourless, very mobile, flammable liquid; pleasant odour; burning taste
Melting-point: –114.1 °C
Boiling-point: 78.5 °C
Density: d_4^{20} 0.789
Refractive index: n_D^{20} 1.361

Ethanol is widely used in laboratories and in industry as a solvent for resins, fats and oils. It is also used in the manufacture of denatured alcohol, in pharmaceuticals and cosmetics (lotions, perfumes), as a chemical intermediate and as a fuel, either alone or in mixtures with gasoline.

In addition to ethanol and water, wine, beer and spirits may contain volatile and non-volatile compounds. Although the term 'volatile compound' is rather diffuse, most of the compounds that occur in alcoholic beverages can be grouped according to whether they are distilled with alcohol and steam or not. Volatile compounds include aliphatic carbonyl compounds, alcohols, monocarboxylic acids and their esters, nitrogen- and sulfur-containing compounds, hydrocarbons, terpenic compounds, and heterocyclic and aromatic compounds. Non-volatile extracts of alcoholic beverages comprise unfermented sugars, di- and tribasic carboxylic acids, colouring substances, tannic and polyphenolic substances and inorganic salts. The flavour composition of alcoholic beverages has been described in detail in several reviews (Rapp, 1988, 1992; Jackson, 2000; Ribéreau-Gayon *et al*., 2000; Briggs *et al*., 2004). During maturation, unpleasant flavours disappear. Extensive investigations on the maturation of wine and distillates in oak casks have shown that many compounds are liberated by alcohol from the walls of the casks (Mosedale & Puech, 1998).

The distillation procedure influences the occurrence and concentration of volatile flavour compounds in the distillate. Particularly in the manufacture of strong spirits, it is customary to improve the flavour of the distillate by the removal of low-boiling and high-boiling compounds to a greater or lesser degree.

Extensive literature is available on aroma components that are usually present at low levels. A list of more than 1100 aroma compounds in wine has been provided (Rapp, 1988). Approximately 1300 substances were listed in Appendix 1 of the previous IARC monograph on alcohol drinking (IARC, 1988). Due to advances in analytical chemistry with improved detection limits down to the picograms per litre range, the compilation of such a list would now go beyond the scope of this monograph.

The following text gives only a summarized overview of the main components of individual alcoholic beverages. For further information, the publications of Jackson (2000) and Ribéreau-Gayon *et al.* (2000) on wine, those of Briggs *et al.* (2004) and Bamforth (2004) on beer and those of Kolb (2002) and Bryce and Stewart (2004) on spirits are recommended.

The main focus of this section is on additives and contaminants of alcoholic beverages and especially potentially carcinogenic substances.

1.6.2 *Compounds in grape wine*

Other than alcohol, wines generally contain about 0.8–1.2 g/L aromatic compounds, which constitute about 1% of their ethanol content. The most common aromatic compounds are fusel alcohols, volatile acids and fatty acid esters. Of these, fusel alcohols often constitute 50% of all volatile substances in wine. Although present in

much smaller concentrations, carbonyls, phenols, lactones, terpenes, acetals, hydrocarbons and sulfur and nitrogen compounds are more important to the varietal and unique sensory features of wine fragrance (Jackson, 2000).

The taste and oral/lingual sensations of a wine are primarily due to the few compounds that occur individually at concentrations above 0.1 g/L. These include water, alcohol (ethanol), fixed acids (primarily tartaric and malic or lactic acids), sugars (glucose and fructose) and glycerol. Tannins are important sapid substances in red wines, but they rarely occur in significant amounts in white wines without maturation in oak casks (Jackson, 2000).

(a) Alcohols

Ethanol is indisputably the most important alcohol in wine. Under standard conditions of fermentation, ethanol can reach up to about 14–15% vol. The prime factors that control ethanol production are sugar content, temperature and strain of yeast (Jackson, 2000). The alcoholic strength of wine is generally about 100 g/L (12.6% vol) (Ribéreau-Gayon *et al*., 2000).

Methanol is not a major constituent in wines, nor is it considered important in the development of flavour. Within the usual range (0.1–0.2 g/L), methanol has no direct sensory effect. The limited amount of methanol that is found in wine is primarily generated from the enzymatic breakdown of pectins. After degradation, methyl groups associated with pectin are released as methanol. Thus, the methanol content of fermented beverages is primarily a function of the pectin content of the fermentable substrate. Unlike most fruit, grapes have a low pectin content. As a result, wine generally has the lowest methanol content of any fermented beverage (Jackson, 2000). Red wines have a higher methanol concentration than rosé wines, while white wines contain even less (Ribéreau-Gayon *et al*., 2000).

Alcohols that have more than two carbon atoms are commonly called higher or fusel alcohols. Most of the higher alcohols that are found in wine occur as by-products of yeast fermentation. They commonly account for about 50% of the aromatic constituents of wine, excluding ethanol. Quantitatively, the most important higher alcohols are the straight-chain alcohols, 1-propanol, 2-methyl-1-propanol (isobutyl alcohol), 2-methyl-1-butanol and 3-methyl-1-butanol (isoamyl alcohol). 2-Phenylethanol is the most important phenol-derived higher alcohol (Jackson, 2000).

(b) Sugars

Unfermented sugars are collectively termed residual sugars. In dry wines, the residual sugar content consists primarily of pentose sugars, such as arabinose, rhamnose and xylose, and small amounts of unfermented glucose and fructose (approximately 1–2 g/L). These levels may increase slightly during maturation in oak casks through the breakdown of glycosides in the wood. The residual sugar content in dry wine is generally less than 1.5 g/L (Jackson, 2000).

(c) Polyols and sugar alcohols

The diol 2,3-butanediol can be found in wine. By far the most prominent polyol in wine is glycerol. In dry wine, it is commonly the most abundant compound, after water and ethanol. Glycerol has a slightly sweet taste but this is probably not noticeable in a sweet wine. It may be slightly noticeable in dry wines, in which the concentration of glycerol often surpasses the sensory threshold for sweetness (> 5 g/L).

Sugar alcohols, such as alditol, arabitol, erythritol, mannitol, myo-inositol and sorbitol, are commonly found in small amounts in wine (Jackson, 2000).

(d) Acids

For the majority of table wines, a range of 5.5–8.5 g/L total acidity is desired. It is typically preferred that white wines be at the higher end of the scale and that red wines be at the lower end. Thus, a pH range of 3.1–3.4 is the goal for white wines and that of 3.3–3.6 for most red wines.

Acidity in wine is customarily divided into two categories—volatile and fixed. Volatile acidity refers to acids that can readily be removed by steam distillation, whereas fixed acidity describes those acids that are only slightly volatile. Total acidity is the combination of both categories. As a group, acids are almost as important to wines as alcohols. They not only produce a refreshing taste (or sourness, if in excess), but they also modify the perception of other tastes and oral/lingual sensations.

Acetic acid is the main volatile acid but other carboxylic acids, such as formic, butyric and propionic acids, may also be involved. Small amounts of acetic acid are produced by yeasts during fermentation. At normal levels in wine (< 300 mg/L), acetic acid is a desirable flavourant and adds to the complexity of taste and odour. It is equally important for the production of several acetate esters that give wine a fruity character.

Fixed acidity is dominated by tartaric and malic acid. However, lactic acid may also occur if so-called malolactic fermentation by lactic acid bacteria is encouraged. The major benefit of malolactic fermentation is conversion of the harsher-tasting malic acid to the smoother-tasting lactic acid (Jackson, 2000).

(e) Aldehydes and ketones

Acetaldehyde (ethanal) is the major aldehyde found in wine, and often constitutes more than 90% of the aldehyde content. It is one of the early metabolic by-products of fermentation. As fermentation approaches completion, acetaldehyde is transported back into yeast cells and is reduced to ethanol. Thus, the acetaldehyde content usually falls to a low level by the end of fermentation. [The Working Group noted that it is therefore not possible to specify an average acetaldehyde content in wine.] For information on acetaldehyde as a direct metabolite of ethanol in the human body, see Section 4 of this monograph. Other aldehydes that occur in wine are hexanal, hexenal, furfural and 5-(hydroxymethyl)-2-furaldehyde. Phenolic aldehydes such as cinnamaldehyde and vanillin may accumulate in wines that have matured in oak casks.

Only few ketones are found in grapes, but those that are present usually survive fermentation. Examples are the norisoprenoid ketones, β-damascenone, α-ionone and β-ionone. Diacetyl (2,3-butanedione) and 2,3-pentanedione may be produced during fermentation (Jackson, 2000).

(f) Esters

Of all the functional groups in wine, esters are the most frequently encountered. Over 160 specific esters have been identified (Jackson, 2000).

The most prevalent ester in wine is ethyl acetate. A small quantity is formed by yeast during fermentation, but larger amounts result from the activity of aerobic bacteria, especially during maturation in oak barrels. Ethyl acetates of fatty acids, mainly ethyl caproate and ethyl caprylate, are also produced by yeast during fermentation. Ethyl acetates of fatty acids have very pleasant odours of wax and honey, which contribute to the aromatic finesse of white wines. They are present at total concentrations of a few milligrams per litre. The formation of esters continues throughout the ageing process due to the presence of many different acids and large quantities of ethanol. In vintage wines, approximately 10% of the acids are esterified (Ribéreau-Gayon *et al.*, 2000).

(g) Lactones

Volatile lactones are produced during fermentation and probably contribute to the aroma of wine. The best known is γ-butyrolactone, which is present in wine at milligram-per-litre concentrations. Lactones may also derive from the grapes, as is the case in Riesling wines in which they contribute to the varietal aroma. Lactones are released into wine during ageing in oak barrels. The *cis* and *trans* isomers of 3-methyl-γ-octalactone are known as 'oak lactones' or 'whisky lactones'. Concentrations in wine are of the order of a few tens of milligrams per litre (Ribéreau-Gayon *et al.*, 2000).

(h) Terpenes

Approximately 40 terpene compounds have been identified in grapes. Some of the monoterpene alcohols are among the most odiferous, especially linalool, α-terpineol, nerol, geraniol, citronellol and ho-trienol. Furthermore, the olfactory impact of terpene compounds is synergistic. They play a major role in the aromas of grapes and wines from the Muscat family (Ribéreau-Gayon *et al.*, 2000). The monoterpenes found in wine have been reviewed (Mateo & Jiménez, 2000).

(i) Nitrogen-containing compounds

Many nitrogen-containing compounds are found in wine. These include inorganic forms, such as ammonia and nitrates, and diverse organic forms, including amines, amides, amino acids, pyrazines, nitrogen bases, pyrimidines, proteins and nucleic acids (Jackson, 2000). Red wines have average nitrogen concentrations that are almost

twice those of white wines. The total nitrogen concentration in red wines varies from 143 to 666 mg/L, while values in white wines range from 77 to 377 mg/L (Ribéreau-Gayon *et al.*, 2000).

Several simple volatile amines have been found in wine, including ethylamine, phenethylamine, methylamine and isopentylamine. Wine also contains small amounts of non-volatile amines, the most well studied of which is histamine. Other physiologically active amines include tyramine and phenethylamine. Polyamines such as putrescine and cadaverine may be present as a result of bacterial contamination (Jackson, 2000).

Urea is found at concentrations of less than 1 mg/L in wine, and is significant in winemaking as it may be a precursor of ethyl carbamate (Ribéreau-Gayon *et al.*, 2000). For a detailed discussion of the occurrence of ethyl carbamate in wine, see Section 1 in the monograph on ethyl carbamate in this Volume.

(j) Sulfur-containing compounds

Hydrogen sulfide and sulfur-containing organic compounds generally occur in trace amounts in finished wines, except for non-volatile proteins and sulfur-containing amino acids (Jackson, 2000). Sulfur-containing compounds in wine have been studied extensively because of their effect on wine aroma. The significance of organic sulfur compounds in wine aroma has been reviewed (Mestres *et al.*, 2000).

(k) Phenols and phenyl derivatives

Phenols are a large and complex group of compounds that are of particular importance to the characteristics and quality of red wine. They are also significant in white wines, but occur at much lower concentrations (Jackson, 2000).

Phenolic compounds are partly responsible for the colour, astringency and bitterness of wine. The term ‘phenolic’ or ‘polyphenolic’ describes the compounds that possess a benzenic ring substituted by one or several hydroxyl groups (-OH). Their reactivity is due to the acidic character of the phenolic function and to the nucleophilic character of the benzene ring. Based on their carbon skeleton, polyphenols are classified in non-flavonoid and flavonoid compounds. Grapes contain non-flavonoid compounds mainly in the pulp, while flavonoid compounds are located in the skin, seeds and stems. The phenolic composition of wines is conditioned by the variety of grape and other factors that affect the development of the berry, such as soil, geographical location and weather conditions. In contrast, winemaking techniques play an important role in the extraction of polyphenols from the grape and in their further stability in wine; the duration of maceration and fermentation in contact with grape skins and seeds, pressing, maturation, fining and bottle ageing are all factors that affect the phenolic composition of wines (Monagas *et al.*, 2005).

In recent years, much effort has been devoted to the study of grape and wine polyphenols, an area that is essential to evaluate the potential of different varieties of

grape, to optimize enological processes, to obtain products with peculiar and improved characteristics and to achieve a better understanding of the polyphenolic properties of wine. The main types of phenolic compound found in wine include hydroxybenzoic and hydroxycinnamic acids, stilbenes, flavones, flavonols, flavanonols, flavanols and anthocyanins (Monagas *et al.*, 2005).

Phenolic compounds in wine have been reviewed (Ribéreau-Gayon *et al.*, 2000; Monagas *et al.*, 2005; Makris *et al.*, 2006).

(l) Inorganic anions and cations

The chloride concentration in most wines is below 50 mg/L, but may exceed 1 g/L in wine made from grapes that are grown near the sea. Natural wine contains only low concentrations of sulfates (between 100 and 400 mg/L), but these may gradually increase during ageing due to repeated sulfuring and oxidation to sulfur dioxide. In heavily sulfured sweet wines, sulfate concentrations may exceed 2 g/L after a few years of barrel ageing. White wine contains 70–500 mg/L phosphate, whereas concentrations in red wines range from 150 mg/L to 1 g/L. These wide variations are related to the addition of diammonium phosphate to must to facilitate alcoholic fermentation.

Potassium is the dominant cation in wine, and concentrations range between 0.5 and 2 g/L, with an average of 1 g/L. Sodium concentrations range from 10 to 40 mg/L, and calcium concentrations range between 80 and 140 mg/L in white wines, but are slightly lower in red wines. Wine contains more magnesium (60–150 mg/L) than calcium and concentrations do not decrease during fermentation or ageing (Ribéreau-Gayon *et al.*, 2000).

Further inorganic constituents and contaminants are discussed in detail in Section 1.6.7 of this monograph.

1.6.3 *Compounds in beer*

Beer is currently a highly consistent commodity. Despite its reliance on agricultural products, the control and predictability of the processes by which beer is made provide that seasonal and regional variations can be overcome such that the taste, appearance and composition of a beer are generally consistent from batch to batch. Vintage in brewing does not exist (Bamforth, 2004).

Most beers comprise at least 90% water, with ethanol and carbon dioxide being quantitatively the next major individual components. Beer also contains a wide range of chemical species in relatively small quantities that determine its properties in respect to appearance and flavour (Bamforth, 2004). More than 450 constituents of beer have been characterized; in addition, it contains macromolecules such as proteins, nucleic acids, polysaccharides and lipids (Briggs *et al.*, 2004).

(a) Alcohols

Beers vary substantially in their alcoholic strength from brand to brand; however, most are in the range of 3–6% vol. In the United Kingdom, the mean alcohol content of all beers is 4.1% vol whereas, in the USA, the average alcoholic strength is 4.6% vol (Bamforth, 2004). Other authors reported a mean alcoholic strength of 5.5% vol for ales and 5.3% vol for lagers on the US market (Logan *et al.*, 1999; Case *et al.*, 2000). In the United Kingdom, the average alcoholic strength of the top five best-selling brands was 3.7% vol for ales and 4.5% vol for lagers (Thomas, 2006).

(b) Carbon dioxide

Carbon dioxide is produced together with ethanol during fermentation, and plays a substantial role in establishing the quality of beer. Apart from its influence in oral/lingual sensation, carbon dioxide determines the extent of foam formation and naturally influences the delivery of volatiles into the headspace of beers. Most cans or bottles of beer contain between 2.2 and 2.8 volumes of carbon dioxide (that is, between 2.2 and 2.8 cm^3 carbon dioxide is dissolved in every cubic centimetre of beer) (Bamforth, 2004).

(c) Non-volatile constituents

While most of the sugar found in wort is fermented to ethanol by yeast, some carbohydrates remain in the beer. The carbohydrates that survive in beer from the wort are non-fermentable dextrins and some polysaccharide material (Bamforth, 2004).

Quantitatively, glycerol is an important constituent of beers, in which a range of 436–3971 mg/L has been found. Significant amounts of higher polyols have not been found, but beer contains butane-2,3-diol (up to 280 mg/L) and smaller amounts of pentane-2,3-diol together with 3-hydroxybutan-2-one (acetoin; 3–26 mg/L) and 3-hydroxypentan-2-one. These are reduction products of volatile vicinal diketones. Cyclic acetals (1,3-dioxolanes) may be formed between butan-2,3-diol and acetaldehyde, isobutanal or isopentanal. Another non-volatile alcohol found in beer is tyrosol (Briggs *et al.*, 2004).

A range of non-volatile acids (C_4–C_{18}) was found in beer. The highest levels of lactic acid were found in Belgian 'acid' beers (Briggs *et al.*, 2004). The normal levels of lactic acid in uninfected bottom-fermented beers are up to 200–300 mg/L, whereas top-fermented beer may contain up to 400–500 mg/L (Uhlig & Gerstenberg, 1993). The native content of citric acid in beer is in the range of 140–232 mg/L (average, 187 mg/L). Lower contents may be found due to decomposition of citrate by lactic acid bacteria or by the use of adjuncts (e.g. rice, maize or sugars) (Gerstenberg, 2000).

Autoxidation of linoleic acid gives rise to isomers of dihydroxy- and trihydroxyoctadecenoic acids. These hydroxyl acids are potential precursors of 2-*trans*-nonenal, which contributes a cardboard flavour to stale beer (Briggs *et al.*, 2004). The formation of 2-*trans*-nonenal and other stale flavours has been reviewed (Vanderhaegen *et al.*,

2006). During storage, the chemical composition may change, which alters the sensory properties. In contrast to some wines, the ageing of beer is usually considered to be negative for flavour quality.

(d) Volatile constituents

One hundred and eighty-two volatile compounds were recently detected in beer samples (Pinho *et al.*, 2006). The majority of the volatile constituents of beer are fermentation products. As in wine, the largest group of volatile constituents in beer are higher alcohols, principally 3-methylbutanol (isoamyl alcohol), 2-methylbutanol, isobutyl alcohol, propanol and phenylethanol. Other volatile constituents are 4-vinylphenol and 4-vinylguaiacol, which are regarded as off-flavours in most beers. However, 4-vinylguaiacol, which has a clove-like flavour, provides part of the essential character of wheat beer (Briggs *et al.*, 2004).

Only low levels of aldehydes are found in beer, the principal of which is acetaldehyde. During the storage of bottled beer, higher alcohols are oxidized to aldehydes by melanoidins. During fermentation, acetaldehyde is normally reduced to ethanol but it can be oxidized to acetic acid, which is the major volatile acid in beer (Briggs *et al.*, 2004). Minor aldehydes identified in beer include the so-called Strecker aldehydes—2-methylpropanal, 2-methylbutanal, 3-methylbutanal, methional and phenylacetaldehyde. The increase in these aldehydes may play a central role in flavour changes during the ageing of beer. Aldehydes related to the autoxidation of linoleic acid are pentanal and hexanal (Vesely *et al.*, 2003).

Flavour-active esters have been reviewed (Verstrepen *et al.*, 2003). Ethyl acetate is the major ester found in beer (8–32 mg/L); further aroma-active esters in lager beer include isoamyl acetate (0.3–3.8 mg/L), ethyl caproate (0.05–0.3 mg/L), ethyl caprylate (0.04–0.53 mg/L) and phenyl ethyl acetate (0.10–0.73 mg/L).

Odour-active compounds derived from hops include linalool, geraniol, ethyl 2-methylbutanoate, ethyl 3-methylbutanoate and ethyl 2-methylpropanoate (Kishimoto *et al.*, 2006); 40 odour-active constituents were identified in Pilsner beer, among which ethanol, β-damascenone, linalool, acetaldehyde and ethyl butanoate had the highest values for odour activity, followed by ethyl 2-methylpropanoate and ethyl 4-methylpentanoate (Fritsch & Schieberle, 2005). The concentration of linalool was found to be correlated with the intensity of the aroma of hops (Steinhaus *et al.*, 2003).

(e) Nitrogen-containing compounds

Most beers contain 300–1000 mg/L total nitrogen (Briggs *et al.*, 2004). The breakdown of a wide range of amino acids was determined during the ageing in beer. The content of phenylalanine, histidine and tyrosine decreased most rapidly followed by that of isoleucine, leucine and lysine. The decrease in amino acids was greater in beers that had a higher content of dissolved oxygen (Basarová *et al.*, 1999).

The presence of biogenic amines in beer is important toxicologically. During brewing, the types of amine are dependent on the raw materials used in the beverage as well as the method of brewing and any microbiological contamination that may have occurred during the brewing process or during storage. The amines in beer can be divided into two groups. One includes putrescine, spermidine, spermine and agmatine and can be considered as natural beer constituents that primarily originate from the malt, while the other, which includes mainly histamine, tyramine and cadaverine, usually indicates the activity of contaminating lactic acid bacteria during brewing (Kalac & Križek, 2003). The level of biogenic amines in beer was found to reflect the microbiological quality of the fermentation process (Loret *et al.*, 2005).

(f) Sulfur-containing compounds

Beer contains 100–400 mg/L sulfate. The major non-volatile organic sulfur compounds in beer are the amino acids, cysteine and methionine, and the peptides and proteins that contain them. Dimethyl sulfide is an important flavour component of lager beers. It is mainly formed by the breakdown of *S*-methylmethionine which is present in malt (Briggs *et al.*, 2004). Sulfur compounds, including thioesters, thiophenes, polysulfides, terpens and thiols, may also derive from hops (Lermusieau & Collin, 2003). Polyfunctional thiols were recently detected in lager beers (Vermeulen *et al.*, 2006).

(g) Flavours and constituents from hops

Of all the herbs that have been used to flavour and preserve beer over the ages, only the hop (*Humulus lupulus* L.) is now regarded as a raw material that is essential to brewing throughout the world (Moir, 2000).

α-Acids can account for between 2% and 15% of dry weight of hops, depending on the variety and the environment. When wort is boiled, α-acids are isomerized to form *iso*-α-acids, which are much more soluble and stable than α-acids. In addition to imparting bitterness to beer, *iso*-α-acids also promote foaming by cross-linking the hydrophobic residues on polypeptides with their own hydrophobic side-chains. Furthermore, they have strong antimicrobial properties (Bamforth, 2004). Bitter acids in beer have been reviewed (de Keukeleire *et al.*, 1992; Schönberger, 2006). The amount of *iso*-α-acids varies significantly between different types of beer; Pilsner-type beers usually contain the largest amount of bitter hop substances (Lachenmeier *et al.*, 2006a).

Hop is the raw material in beer that serves as an important source of phenolic compounds (see below). A recent review summarized 78 known phenolic constituents of beer (Gerhäuser, 2005). Xanthohumol and related prenylflavonoids have also been reviewed (Stevens & Page, 2004).

(h) Phenolic compounds and antioxidants

Phenolic constituents of beer are derived from malt (70–80%) and hops (20–30%). Structural classes include simple phenols, benzoic and cinnamic acid derivatives, coumarins, catechins, di-, tri- and oligomeric proanthocyanidins, (prenylated) chalcones and flavonoids as well as the previously mentioned α- and *iso*-α-acids derived from hops (Gerhäuser, 2005).

According to some studies, levels of antioxidants in beer are of the same order of magnitude as those found in fruit juices, teas and wines (Vinson *et al.*, 1999; Gorinstein *et al.*, 2000). Beer may provide more antioxidants per day than wine in the US diet (Vinson *et al.*, 2003). More than 80% of the antioxidant activity of beer *in vitro* derives from non-tannin non-flavonoid compounds (mainly phenolic acids). However, there is some concern about the activity of different classes of phenols *in vivo* due to low bioavailability and breakdown into inactive fragmentation products (Fantozzi *et al.*, 1998).

(i) Vitamins

Beer contains many water-soluble vitamins, notably folate, riboflavin, pantothenic acid, pyridoxine and niacin. As much as 10% of the daily intake of folate may derive from beer in some countries. Fat-soluble vitamins do not survive in beer and are lost with insoluble components during processing. Some beers contain vitamin C, because this material may be added to protect the beer from oxidation (Bamforth, 2004). Half a litre of beer could cover 20–25% of the daily requirements of riboflavin, niacin and pyridoxine (Billaud & Delestre, 2000).

(j) Minerals

Beer is rich in magnesium and potassium but relatively deficient in iron, zinc and calcium. The presence of iron in beer is avoided deliberately by brewers because it acts as a pro-oxidant (Bamforth, 2004). Beer may also be a main nutritional source of selenium (Darret *et al.*, 1986). The inorganic composition of beer has been reviewed (Briggs *et al.*, 2004). Further inorganic constituents and contaminants in beer are discussed in detail in Section 1.6.7 of this monograph.

1.6.4 *Compounds in spirits*

A large range of very diverse products constitute the category ‘spirits’. The alcoholic strength of spirits is usually higher than 15% vol and may be up to 80% vol in some kinds of absinthe. The typical alcoholic strength of the most common spirits (e.g. brandy, whisky and tequila) is ~40% vol.

A classification of spirits can be made according to their sugar content. Several spirits contains no sugar, or sugar is used only to soften the final taste of the product (up to 10 g/L of sugar). Spirits with high sugar contents (> 100 g/L) are commonly designated as ‘liqueurs’.

Another differentiation can be made between spirits produced exclusively by alcoholic fermentation and distillation of natural products (e.g. sugar cane, fruit and cereals) and products that are made from highly rectified ethanol of agricultural origin (so-called neutral alcohol; e.g. gin, aniseed-flavoured spirit drinks and most liqueurs).

The volatile compounds in alcoholic beverages are usually expressed in units of 'g/hL pure alcohol' or 'g/hL of 100% vol alcohol' (i.e. the concentrations are standardized with regard to alcoholic strength). This enables high-proof distillates and distillates diluted to drinking strength to be compared directly.

Because the chemical compositions of the various types of spirits differ significantly (e.g. the methanol content may vary from not detectable concentrations in vodka up to about 1000 g/hL pure alcohol in certain fruit spirits), some types of spirits are discussed separately in the following sections. The groups of spirits were selected on the basis of knowledge of their production methods and constituents and not necessarily because of their prevalence in the world market. [The Working Group noted that the major focus of research in the past has been on European-style spirits, and found a lack of information on Asian-type products.]

(a) Sugar-cane spirits (rum, cachaça)

The two most important types of sugar-cane spirits are rum (usually produced in the Carribean) and cachaça from Brazil.

The production of rum has been reviewed (Delavante, 2004). The sugar in cane molasses is used as the fermentation substrate in the production of rum. The chemical constituents of rum were found to be so heterogeneous that it was not possible to determine an average composition. The contents of 1-propanol, isobutanol and amyl alcohols were < 10–400, 70 and 100 g/hL pure alcohol, respectively. Some samples also showed high levels of acetaldehyde and 1,1-diethoxyethan, whereas these constituents were not detected in other samples. The number of detectable esters in rum was smaller than that in brandies, whiskies or fruit spirits (Postel & Adam, 1982a). The concentrations of volatile fatty acids, acetic acid and formic acid varied greatly between different samples of rum. The maxima were 12 mg/L propionic acid, 5.1 mg/L butyric acid and 24 mg/L decanoic acid (Sponholz *et al.*, 1990). Low concentrations of ethyl hexanoate, ethyl octanoate, ethyl decanoate and ethyl dodecanoate were found in white rums (Pino *et al.*, 2002). The average level of ketones in rum was 2.15 mg/L acetone, 0.35 mg/L cyclopentanone and 1.75 mg/L 2,3-butanedione (Cardoso *et al.*, 2003).

The production of cachaça has been reviewed (Faria *et al.*, 2004). The Brazilian spirits, cachaça, caninha and aguardente de cana, are made from fermented sugar-cane juice. The term caipirinha refers to the lemon drink made from cachaça. The major volatile compounds in cachaça are the higher alcohols, isoamyl alcohol, isobutyl alcohol and propanol; however, significant variations were detected depending on the strain of yeast used for fermentation (Souza Oliveira *et al.*, 2005). During ageing in wood casks, the levels of higher alcohols decrease, whereas the concentrations of aldehydes, ethyl

acetate and acetic acid increase (Bolini *et al.*, 2006). The most abundant acid in cachaça is acetic acid, which represents up to 90–95% of the total content of acids found. The concentration of acids (C_2–C_{18}) in cachaça is in the same order of magnitude as that in whiskies, rums and cognacs (Ferreira Do Nascimento *et al.*, 2000). The major aldehyde in cachaça is acetaldehyde (average, 11 g/hL pure alcohol). Minor aldehydes include formaldehyde, 5-hydroxymethylfurfural, acrolein, furfural, propionaldehyde, butyraldehyde, benzaldehyde, isovaleraldehyde and *n*-valeraldehyde (all below 5 g/hL pure alcohol) (Nascimento *et al.*, 1997). The levels of 5-hydroxymethylfurfural can be attributed to the use of very old barrels or barrels that undergo no treatment before re-utilization. Other markers of ageing detected in cachaça include gallic acid, vanillic acid, syringic acid, vanillin, syringaldehyde, coniferaldehyde, sinapaldehyde and coumarin (de Aquino *et al.*, 2006). Quantification of ketones in cachaças yielded the following average levels: 3.31 mg/L acetone, 1.24 mg/L acetophenone, 1.15 mg/L cyclopentanone and 4.34 mg/L 2,3-butanedione. Except for acetophenone, cachaça and rum exhibited the same qualitative profile of ketones (Cardoso *et al.*, 2003). Large variations in the phenol content of cachaça were noted. Concentrations of total phenols were between 1.5 and 70 mg/L, and those of flavonoids were from below detection to 3.5 mg/L (Bettin *et al.*, 2002).

Differences in the composition of cachaça and rum were found using multivariate data analysis. Protocatechuic acid, propanol, isobutanol, isopentanol, copper, manganese and magnesium were selected as chemical discriminators from a range of volatile components, acids, polyphenols and metals (Cardoso *et al.*, 2004). Flavour differences between cachaça and rum were easily recognizable; the flavour compounds β-damascenone, ethyl butyrate, isobutyrate and 2-methylbutyrate were found at the same levels in both cachaça and rum, whereas levels of spicy-smelling eugenol, 4-ethylguaiacol and 2,4-nonadienal were much higher in cachaça (de Souza *et al.*, 2006).

(b) Whisky or whiskey

Scotch whisky has been reviewed (Halliday, 2004). Further important international types of whisky include American whiskey (e.g. bourbon) and Canadian whiskey, and the production of whiskey has also been reviewed (Ströhmer, 2002).

Scotch whisky and Irish whiskey are produced exclusively from the distillation of a mash made from malted cereals that has been saccharified, fermented by the action of yeast and distilled by one or more distillations at less than 94.8% vol, so that the distillate has an aroma and taste derived from the raw materials. The final distillate must mature for at least 3 years in wooden casks that do not exceed 700 L in capacity. The minimum alcoholic strength of such beverages is 40% vol (European Council, 1989).

The composition of the different whiskies was compared and significant differences in their volatile composition were detected (Postel & Adam, 1977, 1978, 1979). The American bourbons contained the largest amount of volatile compounds (> 500 g/hL pure alcohol), followed by Scotch (~250 g/hL pure alcohol) and Canadian blends (~100

g/hL pure alcohol) (Postel & Adam, 1982b). In a more recent study, 40 blended Scotch whiskies were characterized, and four categories could be distinguished. Deluxe blends contained higher concentrations of ethyl (C_6–C_{10}) esters, isoamyl hexanoate and alcohol. Standard blends were differentiated by their contents of acetate esters (dodecyl, phenyl ethyl and 3-methylbutyl acetates). In contrast, retailer blends were dominated by high contents of longer (> C_{10}) aliphatic esters, alcohols and unsaturated fatty acid ethyl esters. Furfural, ethyl benzoate, isobutyl octanoate and medium-chain esters, notably ethyl nonanoate, were characteristic of West Highland blends (Lee *et al.*, 2001). Seventy volatile compounds were identified in Scotch whisky—mainly fatty acid ethyl esters, higher alcohols, fatty acids, carbonyl compounds, monoterpenols, C_{13} norisoprenoids and some volatile phenols. The ethyl esters form an essential group of aromatic compounds in whisky, to which they confer a pleasant aroma with fruity odours. Qualitatively, isoamyl acetate, which has a 'banana' aroma, was the most interesting. Quantitatively, significant components were ethyl esters of caprilic, capric and lauric acids. The highest concentrations of fatty acids were observed for caprilic and capric acids. Of the higher alcohols, fusel oils (3-methylbutan-1-ol and 2-phenylethanol) were the most abundant (Câmara *et al.*, 2007). The nature and origin of flavours in whiskies have been reviewed (Lee *et al.*, 2001). Furfural and 5-hydroxymethyl-2-furaldehyde were proposed as a standard to identify authentic straight American whiskeys as opposed to those blended with neutral spirit (Jaganathan & Dugar, 1999).

(c) Brandy

The production of brandy has been reviewed (Ströhmer, 2002). Brandies are typically derived from distilled wine. Traditional products include the French 'cognac' and 'armagnac', the Spanish 'brandy de Jerez' and the German 'Weinbrand'. European legislation prescribes that brandy must be produced from wine spirit (the term 'brandy' may not be used for other products such as fruit spirits). Brandies must be matured for at least 1 year in oak receptacles or for at least 6 months in oak casks with a capacity of less than 1000 L. They must contain a quantity of volatile substances (other than ethanol and methanol) that is equal to or exceeds 125 g/hL pure alcohol and derived exclusively from the distillation or redistillation of the raw materials used. The maximum methanol content is 200 g/hL pure alcohol. The minimum alcoholic strength of brandy is 36% vol (European Council, 1989).

The volatile composition of brandy differs according to the region of origin. In all brandies, acetaldehyde, 1,1-diethoxyethan and furfural are the main carbonyl compounds, amyl alcohols, isobutanol, propanol-1 and methanol are the major alcohols and ethyl acetate and ethyl lactate are the major esters. German brandies showed a larger variation in their volatile composition than cognac and armagnac. Brandies usually contain a larger amount of volatile substances than that legally required of about 500 g/hL pure alcohol (Postel & Adam, 1982c). The amounts of ethyl ester vary widely, depending on the different raw materials used and the technology applied.

Methyl esters are present in very small amounts only, generally less than 0.05 g/hL pure alcohol. Ethyl heptoate and ethyl nonanoate contents are generally less than 0.1 g/hL pure alcohol (Postel & Adam, 1984). In comparison with German and French brandies, Spanish brandies contain on average larger amounts of methanol, acetaldehyde and 1,1-diethoxyethane and smaller amounts of higher alcohols and higher esters (Postel & Adam, 1986a,b). Later investigations showed that the average composition of German or French brandy had not changed considerably; however, considerable differences exist between the various brands (Postel & Adam, 1987, 1990a,b,c). In German brandy, the methanol content was in the range of 46–110 g/hL pure alcohol, the content of higher alcohols varied between 235 and 382 g/hL pure alcohol (Postel & Adam, 1987), acetaldehyde content was in the range of 18–45 g/hL pure alcohol, the sum of carbonyls and acetals was in the range of 30–77 g/hL pure alcohol, the concentrations of terpenes were in the range of 0.06–0.38 g/hL pure alcohol (Postel & Adam, 1988a) and the amount of esters was between 27 and 101 g/hL pure alcohol (Postel & Adam, 1988b). Trace volatile compounds in cognac were studied by Ledauphin *et al.* (2004, 2006a). Compounds specific to cognac include numerous hexenyl esters and norisoprenoidic derivatives.

Esterification and formation of methyl ketone may be two of the most important processes in the ageing of cognac over a long time period. Using multivariate regression of 17 volatile compounds (13 ethyl esters and four methyl ketones), it was possible to predict the age of a cognac with a high degree of accuracy (Watts *et al*., 2003). In brandy de Jerez, an increase in sugar concentration during ageing was detected, and arabinose was especially strongly correlated with ageing (Martínez Montero *et al*., 2005). Caramel, which is used as a colouring agent, may be detected by the ratio between furfural and 5-hydroxymethylfurfural which is greater than 1 in brandies that do not contain caramel and lower than 1 in those that do contain caramel (Quesada Granados *et al*., 1996). Genuine ageing in oak is also indicated by a total syringyl compound content that is higher than the total vanillyl compound content. An increase in vanillin concentration indicates added substances, possibly almond shells (Delgado *et al*., 1990). The quality control of cognacs and cognac spirits was recently reviewed and methods to detect adulterated samples were given (Savchuk & Kolesov, 2005).

(d) Grape marc spirit

Grappa is the most prominent example of grape marc spirit, and may be produced solely in Italy (European Council, 1989). Marc spirit contains a significantly higher content of volatile compounds than brandy (about 2000 g/hL pure alcohol) (Postel & Adam, 1982c). The maximum methanol content is 1000 g/hL pure alcohol and the minimum alcoholic strength of marc is 37.5% vol.

Fusel alcohols were quantitatively the largest group of flavour compounds in Portuguese marcs of the Alvarinho and Loureiro varieties, and their concentrations ranged from 395 to 2029 mg/L. Ethyl acetate and ethyl lactate were the most abundant

esters, with concentrations ranging from 176 to 9614 and from 0 to 310 mg/L, respectively. The duration of fermentation most strongly affected the composition of marcs in terms of higher alcohols, while the addition of pectinases and the material of the containers most strongly affected composition in terms of methanol (concentration range, 2694–6960 mg/L) and 2-butanol (concentration range, 0–279 mg/L). The addition of pectinase had the most statistically significant effect on methanol content, whereas duration of fermentation time had the most significant effect on the 2-butanol content (Luz Silva & Xavier Malcata, 1998).

(e) Fruit spirits

Fruit spirits (formerly sometimes called 'fruit brandies') are relatively inhomogeneous chemically, because their composition varies greatly between the different types of fruit. In Europe, fruit spirits must be produced exclusively by the alcoholic fermentation and distillation of fleshy fruit or must of such fruit, with or without stones. In general, the quantity of volatile substances (other than ethanol and methanol) should exceed 200 g/hL pure alcohol and the maximum methanol content is 1000 g/hL pure alcohol (European Council, 1989).

Methanol is quantitatively the main component of stone and pome fruit spirits in addition to water and ethanol. Plum, mirabelle and Williams distillates generally contain more than 1000 g/hL pure alcohol (an exception to the maximum methanol content was made for these fruits), whereas cherry distillates contain less. Since a certain minimum amount of methanol is formed by enzymatic cleavage of pectin during fermentation of the fruit mash, the methanol content of fruit spirits may be used to evaluate their authenticity and possible adulteration such as by the addition of neutral alcohol (Postel & Adam, 1989). These high methanol concentrations in fruit spirits are nevertheless below the concentration of 2% vol that was proposed as a tolerable concentration in alcoholic beverages (Paine & Davan, 2001). However, with regard to the toxicological effects of methanol, a reduction is desirable to ensure a greater margin of safety. Several ways to decrease the methanol content have been discussed, such as heat treatment of the mash to inactivate proteolytic enzymes (Postel & Adam, 1989). Other authors demonstrated that acid treatment of the mash might delay methanol de-esterification and reduce methanol content by up to 50% (Glatthar *et al.*, 2001). A significant linear decrease in methanol in cherry spirits was noted between 1980 and 2003 (Lachenmeier & Musshoff, 2004).

In comparison with other groups of spirits, fruit spirits contain large amounts of 1-propanol, 1-butanol, 2-butanol and 1-hexanol. Concentrations of isobutanol and amyl alcohols are approximately in the same range as those in other groups of spirits such as whiskies and brandies. Some terpene compounds, such as α-terpineol, geraniol, linalool, *cis*- and *trans*-linalooloxide, were found in fruit spirits (< 1 g/hL pure alcohol). Among the carbonyl compounds, acetaldehyde and 1,1-diethoxyethane dominate; the mean values of their concentrations range from 9 to 17 and 4.5 to 9.5 g/hL pure alcohol,

respectively. Other carbonyl compounds present in fruit spirits are propionaldehyde, isobutyraldehyde, acrolein, benzaldehyde, furfural, acetone, methylethylketone, acetoin and 1,1,3-triethoxypropane and some others in minor amounts. There are marked differences between stone-and pome-fruit distillates. Stone-fruit distillates are characterized by relatively large amounts of benzyl alcohol and benzaldehyde and pome-fruit distillates by large amounts of 1-hexanol. In general, terpenes were found at higher concentrations in stone-fruit spirits than in pome-fruit spirits (Postel & Adam, 1989).

The main ester component of fruit spirits is ethyl acetate followed by ethyl lactate; together, these two compounds amount to ~80% or more of the total ester content. The number of other esters is large, but their concentrations are relatively small. Most of the esters are ethyl esters beginning with formate up to palmitate, phenylacetate, benzoate and cinnamate, including some hydroxyl esters. The number of isoamyl and methyl esters is smaller; in addition, propyl, butyl, hexyl, 2-phenethyl and benzyl esters (mainly acetates) are also present. Moreover, fruit spirits (as well as pomace distillates) are the only groups of spirits that have higher levels of methyl acetate, which occurs only in traces in grape wine brandies and whiskies (Postel & Adam, 1989).

The ethyl carbamate content of stone-fruit spirits is reviewed in Section 1 of the monograph on ethyl carbamate in this Volume.

(f) Mexican spirits (mezcal, tequila)

The *Agave* genus comprises more than 200 species that are native to arid and tropical regions from southern USA to northern South America and throughout the Carribean. The most important economic use of *Agave* is the production of alcoholic beverages such as mezcal (*Agave angustifolia* Haw., *A. potatorum* Zucc., *A. salmiana* Otto, and other species), sotol (*Dasylirion ssp.*,) and bacanora (*A. angustifolia* Haw.). All of these spirits are obtained from the fermentation of agavins (fructooligosaccharides) from the different *Agave* species (Lachenmeier *et al.*, 2006b). However, the most popular contemporary alcoholic beverage made from *Agave* is tequila, which is recognized worldwide. The production of tequila is restricted to the blue *Agave* (*A. tequilana* Weber var. *azul*, Agavaceae) and to defined geographical areas, primarily to the State of Jalisco in West Central Mexico (Lachenmeier *et al.*, 2006b). Two basic categories of tequila can be distinguished: '100% agave' and 'mixed' tequila. For the high-quality category, '100% agave', only pure agave juice is permitted to be fermented and distilled (Cedeño, 1995).

Following the bestowal of the appellation of origin of tequila, other distilled *Agave* beverages from the States of Oaxaca, Guerrero, San Luis Potosi, Chiapas, Guajanuato and Zacatecas (mezcal), Chihuahua, Coahuila and Durango (sotol) and Sonora (bacanora) were granted equal recognition. All of these regional drinks are subject to official standards, and their production is supervised by the Mexican Government. Until now, only tequila, and more recently, mezcal have reached international recognition. Especially in the last decade, the consumption of tequila has increased

tremendously worldwide. Tequila and mezcal are protected under the North American Free Trade Agreement and an agreement between the European Union and the United Mexican States on the mutual recognition and protection of designations for spirit drinks (Lachenmeier *et al.*, 2006b).

Due to their production from plant material that contains oxalate, all *Agave* spirits contain significant concentrations of this compound (0.1–9.7 mg/L). The composition of Mexican *Agave* spirits was found to vary over a relatively large range. The two tequila categories ('100% agave' and 'mixed') showed differences in concentrations of methanol, 2-/3-methyl-1-butanol and 2-phenylethanol, with lower concentrations in the 'mixed' category (Lachenmeier *et al.*, 2006b).

Quantitative differences in ethyl esters were found in tequila depending on the duration of ageing. Ethyl hexadecanoate and octadecanoate were the most abundant ethyl esters in all tequila types; Añejo (extra aged) tequila presented the highest concentration of ethyl esters (Vallejo-Cordoba *et al.*, 2004). Isovaleraldehyde, isoamyl alcohol, β-damascenone, 2-phenylethanol and vanillin were the most powerful odourants of tequila from a range of 175 components identified (Benn & Peppard, 1996). The most potent odourants were: phenylethanol and phenylethyl acetate in Blanco tequila; phenylethanol, phenylethyl acetate and vanillin in Reposado (aged) tequila; and phenylethanol, vanillin and an unknown substance in Añejo tequila (López & Dufour, 2001).

Considerably higher concentrations of 2-furaldehyde and 5-methylfuraldehyde were found in tequilas than in brandies. Furthermore, 100% agave tequilas contained higher levels of these two compounds (mean values, 18.6 and 5.97 mg/L, respectively) than the mixed brands (mean values, 6.46 and 3.30 mg/L). The profile of furanic aldehydes depends on the type of fructans contained in the raw material and also on heat treatment before fermentation. In contrast to other polysaccharides, inulin hydrolyses at elevated temperature and the contribution of Maillard browning reactions increases the production of furanic compounds (Munoz-Rodriguez *et al.*, 2005).

Saturated alcohols, ethyl acetate, ethyl 2-hydroxypropanoate and acetic acid are the major compounds in mezcal produced from *A. salmiana*. Minor compounds in mezcal include other alcohols, aldehydes, ketones, large-chain ethyl esters, organic acids, furans, terpenes, alkenes and alkynes. Most of the compounds found in mezcals are similar to those present in tequilas and other alcoholic beverages. However, mezcals contain unique compounds such as limonene and pentyl butanoate, which can be used as markers for the authenticity of mezcal produced from *A. salmiana*. Mezcals (but not tequilas) are sometimes conditioned with one to four larvae of Agave worms. Only mezcals with worms contained the compounds 6,9-pentadecadien-1-ol, 3-hexen-1-ol, 1,8-nonadiene and 1-dodecine. Thus, it may be possible that these unsaturated compounds come from the larvae (De León-Rodríguez *et al.*, 2006).

(g) Wood maturation of distilled beverages

A wide range of distilled beverages, including whisky and cognac, are matured for many years in oak barrels. Other spirits, such as rum, cachaça, tequila and fruit spirits, are also often matured in oak. During maturation, a range of physical and chemical interactions take place between the barrel, the surrounding atmosphere and the maturing spirit which transform both the flavour and composition of the drink. The effects and time required for maturation are highly variable and are influenced by a wide range of factors, particularly the type of barrel used (Mosedale & Puech, 1998). Wood ageing is the most probable source of phenols and furans in distilled spirits. Ellagic acid was the phenol present at the highest concentration in 12 categories of spirit. Moderate amounts of syringaldehyde, syringic acid and gallic acid, as well as lesser amounts of vanillin and vanillic acid, were measurable in most samples of whisky, brandy and rum. 5-Hydroxymethylfurfural was the predominant furan, notably in cognac, followed by 2-furaldehyde. Beverages that are subjected to wood ageing also contain significant antioxidant activity, the level of which is between the ranges observed in white and red wines. Highest total antioxidant values were exhibited in armagnac, cognac and bourbon whiskey, and no antioxidants were found in rum, vodka, gin and miscellaneous spirits, correlating with low or undetectable phenol concentrations in these spirits (Goldberg *et al.*, 1999).

(h) Vodka

Vodka is a spirit beverage produced by rectifying ethanol of agricultural origin or filtering it through activated charcoal, possibly followed by straightforward distillation or an equivalent treatment. This selectively reduces the organoleptic characteristics of the raw materials. Flavouring may be added to give the product special organoleptic characteristics, such as a mellow taste (European Council, 1989). The raw spirit put through rectification is usually produced from grain (rye and wheat) and potatoes. In the production of vodka, the quality of the water used is of the utmost importance. For premium vodka brands, demineralized water is filtered through activated carbon to absorb unwanted organic and inorganic materials.

The contents of anions in Russian vodkas usually lie in the ranges of 0.5–10 mg/L chloride, 0.5–3.5 mg/L nitrate, 3.5–30 mg/L sulfate and < 0.1 mg/L phosphate (Obrezkov *et al.*, 1997). Vodkas bottled in Germany were found to contain significantly higher amounts of anions (up to 147.6 mg/L) (Lachenmeier *et al.*, 2003).

Since vodkas are manufactured in such a way that they have no distinctive aroma or taste, residual congeners are present at levels much lower than those found in other spirits that have various flavour characteristics. The congeners present at microgram per litre levels were isolated using solid-phase microextraction. Ethyl esters of C_8–C_{18} fatty acids were detected and differentiation between Canadian and American vodkas was possible (Ng *et al.*, 1996).

Table 1.10 Properties of neutral alcohol in Europe

Alcoholic strength	>96.0% vol
Total acidity (expressed as acetic acid)	<1.5 g/hL pure alcohol
Esters (expressed as ethyl acetate)	<1.3 g/hL pure alcohol
Aldehydes (expressed as acetaldehyde)	<0.5 g/hL pure alcohol
Higher alcohols (expressed as 2-methyl-1-propanol)	<0.5 g/hL pure alcohol
Methanol	<50 g/hL pure alcohol[a]
Dry extract	<1.5 g/hL pure alcohol
Volatile bases that contain nitrogen (expressed as nitrogen)	<0.1 g/hL pure alcohol
Furfural	Not detectable

From European Council (1989) [a] The methanol content of commercial neutral alcohol is usually significantly below the limit of 50 g/hL pure alcohol.

(i) Spirits produced from neutral alcohol

In contrast to spirits such as whisky or brandy, which are manufactured by fermentation and retain the organoleptic properties of the raw materials, a range of spirits is manufactured using highly rectified alcohol (so-called 'neutral alcohol' or 'ethanol of agricultural origin'). The European requirements for neutral alcohol are shown in Table 1.10. Neutral alcohol contains significantly lower concentrations of volatile constituents than the spirits discussed previously (e.g. whisky, rum, brandy). However, the composition of vodka is relatively similar to that of neutral alcohol. The typical components and flavour characteristics of spirits manufactured from neutral alcohol derive from other materials and not from the alcohol or fermentation products.

A prominent type of a spirit manufactured from neutral alcohol is gin. The most popular is London Dry Gin. It belongs to the 'distilled gin' class in European legislation and is produced by redistillation of neutral alcohol in the presence of juniper berries (*Juniperus communis*) and other natural ingredients (European Council, 1989). Gin was found to contain over 70 components (mainly mono- and sesquiterpenic compounds) (Vichi *et al.*, 2005).

Most liqueurs are also produced by mixing neutral alcohol with sugars and a wide range of plant extracts or fruit juices. For example, Italian lemon liqueurs (Limoncello) are obtained by alcoholic extraction of essential oils from lemon peel and dilution with sugar syrup. The liqueur, therefore, shows a composition similar to lemon essential oil with a high content of β-pinene, myrcene, trans-α-bergamottene and β-bisabolene (Versari et al., 2003). Another example is traditional walnut liqueur that contains phenolic compounds extracted from walnut husks (Stampar *et al.*, 2006).

Table 1.11 Differences in the composition of ciders from England, France and Germany

	English cider	French cidre	German Apfelwein
Alcoholic strength	1.2–8.5% vol	>1.5% vol	>5% vol
Sugar-free extract	>13 g/L	>16 g/L	>18 g/L
Volatile acidity	<1.4 g/L	<1 g/L	<1 g/L
Sulfur dioxide	<200 mg/L	<175 mg/L	<300 mg/L
Raw materials	Apple juice, concentrate, glucose syrup, water	Apple juice, concentrate (up to 50%)	Apple juice, concentrate, certain amounts of sugar
Additives	Organic acids, sugars, sweeteners, colours, sorbic acid	Organic acids, sugars, colours	Lactic acid (<3 g/L), sugar (<10 g/L), caramel sugar, sorbic acid

From Anon. (1992)

1.6.5 *Compounds in other alcoholic beverages*

(a) Cider (apple wine)

Cider is an alcoholic beverage made from apples and has very different characteristics according to the origin of the fruit and methods of production. French cider (Breton and Norman) has a low alcohol content and contains significant residual unfermented sugar. German cider, mostly from the state of Hessen, is fully fermented and very dry. Spanish (mostly Asturian) cider is characterized by a high volatile acidity and by its foaming characteristics when served. Modern English ciders are for the most part characterized by light flavours, which arise from chaptalization with glucose syrup before fermentation to give high-alcohol apple wines, which are then diluted with water and sweetener before retailing (Lea, 2004).

The differences between English, French and German ciders are compared in Table 1.11.

The standard German 'apple wine' should have an alcoholic strength of 7.0% vol, a total dry extract of 25 g/L, a sugar content of 2 g/L, a pH of 3.1, a volatile acidity of 0.5 g/L, a glycerine content of 4.7 g/L, a potassium content of 1100 mg/L, a magnesium content of 60 mg/L, a calcium content of 60 mg/L and a copper content of 0.3 mg/L (Scholten, 1992).

French ciders can be classified according to their residual sugar content into 'brut' (< 28 g/L of residual sugar), 'demi-sec' (28–42 g/L of residual sugar) and 'doux' (< 3% vol alcohol and > 35 g/L of residual sugar) (Anon., 1992).

During the fermentation of apple juice, organic acids undergo several changes. It was shown that concentrations of malic and citric acid decrease, while those of lactic and succinic acid increase (Blanco Gomis *et al.*, 1988).

More than 200 volatile flavour components, 100 of which could be identified, were found in apple wines manufactured from Turkish apples (Yavas & Rapp, 1992). The flavour composition of two Spanish ciders was studied by Mangas *et al.* (1996a). The major aromatic components were amyl alcohols (134–171 mg/L) and 2-phenylethanol (57–185 mg/L); minor compounds were alcohols, esters and fatty acids.

Forty-three compounds identified in Chinese Fuji apple wine were mainly esters, alcohols and lower fatty acids, as well as lesser amounts of carbonyls, alkenes, terpenes and phenols. Total concentrations of esters, alcohols and lower fatty acids were 242 mg/L, 479 mg/L and 297 mg/L, respectively. The highest concentration of aromatic components in apple wine was for isoamyl alcohol (232 mg/L) which constituted 32% of the total esters and alcohols (Wang *et al.*, 2004).

A total of 16 phenolic compounds (catechol, tyrosol, protocatechuic acid, hydrocaffeic acid, chlorogenic acid, hydrocoumaric acid, ferulic acid, (–)-epicatechin, (+)-catechin, procyanidins B2 and B5, phloretin-2'-xyloglucoside, phloridzin, hyperin, avicularin and quercitrin) were identified in natural ciders from the Asturian community (Spain). A fourth quercetin derivative, one dihydrochalcone-related compound, two unknown procyanidins, three hydroxycinnamic derivatives and two unknown compounds were also found. Among the low-molecular-mass polyphenols, hydrocaffeic acid was the most abundant compound, and represented more than 80% of total polyphenolic acids. Procyanidins were the most important family among the flavonoid compounds. Discriminant analysis allowed correct classification of more than 93% of the ciders according to the year of harvest; the most discriminant variables were an unknown procyanidin and quercitrin (Rodríguez Madrera *et al.*, 2006).

The polyphenolic profile was used to identify ciders according to their geographical origin (Basque or French regions). Polyphenolic contents of Basque ciders are lower than those of French ciders, which indicates that Basque cider-making technology involves a higher loss of native apple polyphenols, probably due to oxidation processes and microflora metabolism (Alonso-Salces *et al.*, 2004). The polyphenolic composition may also be used to distinguish ciders made with Basque apples from those made with apples imported from other parts of Europe to Spain (Alonso-Salces *et al.*, 2006).

Free amino acids were studied in Spanish sparkling ciders. The amount of amino acids significantly decreased during second fermentation in the bottle, and their composition was dependent on the yeast strain and the duration of ageing (Suárez Valles *et al.*, 2005). The average level of total biogenic amines in Spanish ciders was 5.9±8.4 mg/L. Putrescine, histamine and tyramine were the prevailing amines and were present in 50, 38 and 33% of the ciders studied, respectively; very small amounts of ethylamine and phenylethylamine were observed in only one sample. Ciders that had lower glycerol contents and larger amounts of 1,3-propanediol had much higher levels of histamine, tyramine and putrescine, which suggests a high activity of lactic acid bacteria during cider making and thus the need for their effective control (Garai *et al.*, 2006).

Acrolein may be formed in apple-derived products through the degradation of glycerol. Due to its high volatility and high reactivity, acrolein disappears rapidly

from ciders. The concentration of acrolein in two French ciders was 7 and 15 μg/L. Acrolein was also detected in freshly distilled calvados (a distillate of cider) at concentrations of between 0.7 and 5.2 mg/L; however, the concentrations decreased during ageing (Ledauphin *et al.*, 2006b). Ledauphin *et al.* (2004, 2006a) provided information on a range of volatile compounds in distilled calvados. The method of production of cider (by traditional methods or from concentrates) influences the composition of the resulting calvados. The spirits manufactured from traditional ciders had higher concentrations of decanoic and dodecanoic esters and long-chain fatty acids (Mangas *et al.*, 1996b).

(b) Other fruit wines

Berry fruit or stone fruit are predominantly used to manufacture wine. The manufacture of fruit wine has been reviewed (Röhrig, 1993).

Fruit wines produced from different varieties of sour cherry contained 7.7–9.6% vol alcohol, 8.4–9.9 g/L total acid and 35–60 g/L residual sugar. The concentrations of colourless polyphenols varied considerably. Neochlorogenic acid (48–537 mg/L), chlorogenic acid (31–99 mg/L) and 3-cumaroylquinic acid (43–196 mg/L) were the predominant phenolcarbonic acids followed by the flavonoids, procyanidin B1 (6–32 mg/L), catechin (2–27 mg/L) and epicatechin (8–130 mg/L). Quercetin glycosides were present at concentrations of 12–46 mg/L. The four major anthocyanins were identified as cyanidin-3-(2^G-glucosylrutinoside), cyanidin-3-(2^G-xylosylrutinoside), cyanidin-3-rutinoside and peonidin-3-rutinoside and were present at concentrations of 147–204 mg/L and in a rather constant ratio of 72:3:22:3. Among aromatic substances, the secondary aroma arising during the fermentation process was dominant. The main components were ethyl esters of hexanoic acid, octanoic acid and decanoic acid, as well as the fruity esters, isoamyl acetate, butanoic acid ethyl ester, acetic acid butyl ester and acetic acid hexyl ester. The endogenous fruit aroma was mainly composed of acetic acid ethyl ester, phenylethyl alcohol, decanal, benzaldehyde, 1-hexanol, 1-octanol, nonanal, *trans*-nerolidol and linalool (Will *et al.*, 2005).

The mineral composition of different fruit wines was generally comparable with that of red wine, and potassium was the most abundant mineral found in all wine categories. However, the level of calcium was significantly higher in cranberry wine than in other wines. The biogenic amine histamine was present only in small amounts in non-traditional fruit wines compared with red wines (Rupasinghe & Clegg, 2007).

Mandarin wine obtained from clementines (*Citrus reticula* Blanco) was studied by Selli *et al.* (2004); 19 volatile compounds were identified including esters, higher alcohols, monoterpenes and furfural compounds. The major compounds were ethyl octanoate, ethyl decanoate, isoamyl alcohol, ethyl hexanoate and isoamyl acetate.

The composition of wines made from blackcurrants and cherries was studied by Czyzowska and Pogorzelski (2002, 2004). Blackcurrant musts contained 4800–6600 mg/L and cherry musts contained 3060–3920 mg/L total polyphenols. The fermentation

process caused a decrease in polyphenol content of approximately 25%. During the production of fruit wines, the method of treatment of the pulp had a considerable effect on the total polyphenol content. The highest extraction of polyphenols was obtained after enzymatic pectinolysis. In musts and wines, the presence of the following derivatives of hydroxycinnamic acid was determined: neochlorogenic, chlorogenic, caffeic, *para*-coumaric and ferulic acids. The content of neochlorogenic acid was the highest and amounted to 24.7–35.3 mg/L for blackcurrants and 44.5–71.4 mg/L for cherries. Furthermore, the flavan-3-ols, catechin, epicatechin, dimer B_2 and trimer C_1, were identified in cherry musts and wines. In the cherry wines studied, the variants subjected to pectinolysis and fermentation of the pulp contained smaller amounts of epicatechin than catechin whereas it was predominant in the wines subjected to thermal treatment. In the blackcurrant musts and wines, the flavanols, gallocatechin, catechin, epigallocatechin, dimer B_2, epicatechin and trimer C_1, were identified. In cherry musts and wines, the anthocyanin pigments, cyanidin 3-glucoside, cyanidin 3-rutinoside and cyanidin 3-glucosylrutinoside, have been identified, the last of which was the most abundant. Anthocyanins identified in blackcurrant musts and wines were delphinidine and cyanidine glycosides: delphinidin 3-glucoside, delphinidin 3-rutinoside, cyanidin 3-glucoside and cyanidin 3-rutinoside; their aglycones were also found.

The antioxidant effects of fruit wines were studied by Pinhero and Paliyath (2001). On the basis of specific phenolic content, summer cherry, blackberry and blueberry wines were 30–40% more efficient at scavenging superoxide radicals than red grape wine. From among several different fruit wines, elderberry, blueberry and blackcurrant wines were identified by Rupasinghe and Clegg (2007) as having the highest concentrations of phenolic compounds compared with red wine.

In contrast, Lehtonen *et al.* (1999) found that the amounts of phenolic compounds in berry and fruit wines were much smaller than those in red grape wines, which indicates that these compounds are more effectively extracted from red grapes than from berries and fruits. The total amount of phenolic compounds ranged from 18 to 132 mg/L in berry and fruit wines and liqueurs derived from apples, blackcurrants, bilberries, cowberries, crowberries, cherries, strawberries and arctic brambles. Anthocyanins and flavan-3-ols were the most abundant. The main anthocyanins were cyanidin and delphinidin in wine made from blackcurrants and black crowberries. Wines made from crowberries and from blackcurrants and strawberries were richest in flavan-3-ols and contained 79 and 76 mg/L, respectively. In addition, ellagic acid was found in strawberry and blackcurrant wines (44 mg/L) and in cherry liqueur (117 mg/L).

Fruit wines may also be manufactured from guava (Anderson & Badrie, 2005), peach (Joshi *et al*., 2005), banana (Brathwaite & Badrie, 2001; Jackson & Badrie, 2002; Akubor *et al.*, 2003; Jackson & Badrie, 2003), mango (Reddy & Reddy, 2005), cashew apples (Garruti *et al.*, 2006) or Brazilian jabuticaba fruit (Asquieri *et al.*, 2004) but their composition has not been studied in detail.

(c) Alcoholic beverages produced in Asia

In general, information on the composition of Asian alcoholic beverages is scarce but spirits produced in Japan and other East Asian countries have been reviewed (Minabe, 2004).

Shochu is a traditional Japanese distilled spirit. The category consists of two types of product. It is produced either from barley, maize or sugar cane by continuous distillation using a column still (the product is very similar to vodka) or from barley, rice or sweet potato using a pot-still. Saccharification in the second type is accomplished using fungi cultures (so-called koji—a mould grown on rice). The role of koji is analogous to that of malt in beer and whisky production (Iwami *et al.*, 2005). Barley shochu contains 20–30% vol alcohol. The flavour of shochu is closely associated with ethyl acetate, isoamyl acetate and ethyl caproate (Iwami *et al.*, 2006).

Another well known Japanese alcoholic beverage is sake. Despite its relatively high average alcoholic strength of 15% vol, sake is not a distilled beverage. It is manufactured from rice, koji and yeast. The koji degrades the starch to form glucose, which is immediately converted by yeast to form alcohol. Over 300 components have been identified in sake (Yoshizawa, 1999). Apart from ethanol, the main contributors to the flavour of sake are alcohols (1-propanol, isoamyl alcohol, 2-phenylethanol and isobutanol), esters (ethyl acetate, ethyl caproate and isoamyl acetate) and acids (succinic, malic, citric, acetic and lactic acids) (Bamforth, 2005).

Korean traditional lotus spirit made from lotus blossom and leaves contained 14% ethanol, 0.95% organic acids, 1.4% carbohydrate and polyphenol compounds (1063 mg/L) (Lee *et al.*, 2005).

An overview of alcoholic beverages from China was given by Chen and Ho (1989) and Chen *et al.* (1999). Alcoholic drinks from Nepal were discussed by Dahal *et al.* (2005).

In India, so-called 'Indian-made foreign liquors' are manufactured. They include the typical European spirit groups such as whisky, rum or brandy (Baisya, 2003). Due to problems of availability of cereals, Indian-made foreign liquors are generally manufactured from molasses, contrary to the practices followed in other countries (Sen & Bhattacharjya, 1991). In addition, 'country liquor' is manufactured in India, and is so named to indicate its local origin and to differentiate from the more expensive foreign liquor (Narawane *et al.*, 1998). Country liquors are the most popular alcoholic beverage consumed among low socioeconomic groups in India. It is either brewed locally or made in distilleries by distilling molasses supplied by sugar factories. A popular country liquor that is consumed by the lower socioeconomic group in South India is toddy, which is a non-distilled alcoholic beverage. It is obtained by natural fermentation of coconut palm (*Cocos nucifera*) sap, which is collected by tapping the unopened inflorescence of the coconut palm (Lal *et al.*, 2001). Several other types of country liquor are produced in India: for example, tharrah in Uttar Pradesh, chang in Punjab, arrack in Tamil Nadu, mahua in West Bengal, laopani in Assam and darru in Rajasthan. The

Bureau of Indian Standards had difficulty in identifying every type of country liquor and devising individual standards. However, requirements have been set for the three major types of distilled country liquor. Plain country liquor is an alcoholic distillate of fermented mash of different agricultural products (e.g. cereals, potatoes, fruit, coconut). Blended country liquor is a pot-still distillate, rectified spirit and/or neutral alcohol. Spiced country liquor is plain or blended country liquor that is flavoured and/or coloured (Sen & Bhattacharjya, 1991).

(d) Alcopops

Alcopops are also known as 'ready-to-drink' or 'flavoured alcoholic beverages'; they tend to be sweet, to be served in small bottles (typically 200–275 mL) and to contain between 5 and 7% vol alcohol.

In a recent study, the alcoholic strength of alcopops was in the range of 2.4–8% vol with an average of 4.7% vol. A significant deviation was detected in the volatile composition of alcopops that contain beer, wine and spirits. Alcopops derived from wine alcohol showed concentrations of volatile compounds (especially methanol, 1-propanol and 2-/3-methylbutanol-1) that were 10–100 times higher than those in products derived from spirits. However, this study noted the variability in alcopop composition, and the possibility of changes in recipes has to be taken into consideration even if the brand name of a given product has not been changed (Lachenmeier *et al.*, 2006c).

The recent practice of combined consumption of alcohol and so-called energy drinks has rapidly become popular. The main components of the marketed energy drinks are caffeine, taurine, carbohydrates, gluconolactone, inositol, niacin, pantenol and B-complex vitamins (Ferreira *et al.*, 2006). The levels of taurine in such alcoholic energy drinks were recently determined and large variations were detected. Ready-mixed energy drinks with spirits contained 223–4325 mg/L taurine (median, 314 mg/L), energy drinks with beer contained 112–151 mg/L taurine (median, 151 mg/L) and energy drinks with wine contained 132–4868 mg/L taurine (median, 305 mg/L) (Triebel *et al.*, 2007). However, valid scientific information on interactions between the ingredients of energy drinks (for example, taurine and caffeine) and alcohol was not available.

Another category of alcoholic beverages that is relatively similar to alcopops in their presentation is hemp beverages. Typical products are so-called hemp beers, which are flavoured with dried hemp (*Cannabis*) inflorescences, and hemp liqueurs. Δ9-Tetrahydrocannabinol, the main psychoactive substance found in the *Cannabis* plant, was not detected in hemp beers (Lachenmeier & Walch, 2005).

Table 1.12 Additives suitable for alcoholic beverages and maximum levels (mg/kg)

	Beer	Cider/ perry	Grape wine	Wines (other than grape)	Mead	Distilled spirituous beverages (>15% vol alcohol)	Aromatized alcoholic beverages
Benzoates	–	1000	–	1000	1000	–	1000
Carmines	100	200	–	200	–	200	–
Carotenes, vegetable	600	600	–	600	–	600	600
Colourants							
Brilliant Blue FCF	–	200	–	200	–	200	200
Caramel Colour, Class III	GMP	GMP	–[a]	GMP	–	GMP	GMP
Caramel Colour, Class IV	GMP	GMP	–	GMP	–	GMP	GMP
Fast Green FCF	–	–	–	–	–	100	100
Diacetyltartaric and fatty acid esters of glycerol	–	5000	–	5000	–	5000	10 000
Dimethyl dicarbonate	–	250	200	250	200	–	–
EDTA	25	–	–	–	–	25	–
Lysozyme		500	500	–	–	–	–
Polydimethylsiloxane	10	10	–	–	–	–	10
Polyvinylpyrrolidone	10	2	–	–	–	–	–
Riboflavins	–	300	–	300	–	–	100
Sulfites	50	200	350	200	200	200	–

From Codex alimentarius (2006) EDTA, ethylene diamine tetraacetate; GMP, good manufacturing practice (the quantity of the additive is limited to the lowest possible level necessary to accomplish its desired effect) [a] Additives are not suitable for this food category.

1.6.6 *Additives and flavourings*

(a) Additives

The Codex Standard for Food Additives includes several additives that are recognized as suitable for use in alcoholic beverages (*Codex alimentarius*, 2006) (Table 1.12). In addition, a list of 179 additives that are permitted for use in food in general is provided. These additives (including organic acids, alginates, salts, gases (e.g. carbon dioxide, nitrogen) and sugars) may be used in alcoholic beverages with the exception of grape wine that is excluded from the general conditions. The additives listed in this standard were determined to be safe by the Joint FAO/WHO Expert Committee on Food Additives.

Many countries provide stricter regulations on food additives than the *Codex alimentarius*. For example, the German beer purity law of 1516, which is still in force

today, states that only barley malt, hops, yeast and water are permitted in beer production (Donhauser, 1988). According to European law, no additives are permitted in most traditional spirits, e.g. rum, whisky, brandy, fruit spirits and many other types (European Council, 1989). In contrast, additives are regularly added to liqueurs (artificial colourings) or alcopops (artificial colourings, preservatives). Some national regulations also permit the use of additives other than those listed by the *Codex alimentarius*, e.g. a multitude of artificial colourings, sweeteners or further preservatives (e.g. sorbic acid). Caramel colouring is frequently used to ensure colour consistency of aged products (Boscolo *et al.*, 2002).

The most frequent additives in alcoholic beverages are sulfur dioxide and sulfites. Sulfite additives have been associated with allergic-like asthmatic responses in certain individuals (Vally & Thompson, 2003). For this reason, many countries require the labelling of sulfur dioxide and sulfites used as ingredients at concentrations of more than 10 mg/L (expressed as sulfur dioxide) (Lachenmeier & Nerlich, 2006).

In conjunction with added sulfite, natural sulfite may evolve in alcoholic beverages during fermentation by the metabolism of yeasts (Ilett, 1995).

Sulfite is a desirable component in beer because it has an antioxidative effect as a scavenger and binds to carbonyl compounds that cause a stale flavour. In contrast, during the early phases of fermentation, high concentrations of sulfite may cause an undesirable flavour (Guido, 2005). The formation of sulfite is strongly influenced by predisposition of the yeast and parameters that affect yeast growth during fermentation, such as the physiological state of the yeast and the availability of nutrients and oxygen (Wurzbacher *et al.*, 2005). The average residual quantities of sulfur dioxide were 7.5 mg/L in French beer and 25 mg/L in cider (Mareschi *et al.*, 1992). In a recent study, the average concentrations expressed as sulfur dioxide were 4.2 mg/L for beer (195 samples) and 1.0 mg/L for spirits (101 samples). The concentrations of sulfite in spirits were found to be significantly lower than those in beer ($P < 0.0001$) (Lachenmeier & Nerlich, 2006).

Generally higher levels of sulfur dioxide were determined in wine than in spirits or beer. However, during the last decade, a decrease in the sulfite content of wine has been detected that is probably due to new technological processes that improve the stability of wine using a smaller quantity of sulfite (Leclercq *et al.*, 2000). In a large survey of wines conducted in the 1980s, 3655 samples of Italian wine and 8061 samples of French wine that were analysed had mean sulfite contents of 135 mg/L and 136 mg/L, respectively (Ough, 1986). In later studies, an average of 92 mg/L sulfite was determined in 85 samples of wine in Italy (Leclercq *et al.*, 2000), whereas in France, the mean concentrations were 75 mg/L (Mareschi *et al.*, 1992).

(b) Flavourings

The *Codex alimentarius* (1987) provides general requirements for natural flavourings. Some flavourings contain biologically active substances for which maximum

Table 1.13 Maximum levels for biologically active substances contained in natural flavourings

Biologically active substance	Maximum level in alcoholic beverages (mg/kg)
Agaric acid	100
Aloin	50
β-Azarone	1
Berberine	10
Coumarin	10
Hydrocyanic acid, total (free and combined)	1 per % vol
Hypericine	2
Pulegone	100 (beverages in general) 250 (peppermint- or mint-flavoured beverages)
Quassine	50
Quinine	300
Safrole	2 (<25% vol) 5 (>25% vol)
Santonin	1 (>25% vol)
Thujones (α and β)	5 (<25% vol) 10 (>25% vol) 35 (bitters)

From Codex alimentarius (1987)

levels are specified (Table 1.13). It must be noted that the biologically active substances (with the exception of quinine and quassine) should not be added as such to food and beverages, and may only be incorporated through the use of natural flavourings, provided that the maximum levels in the final product ready for consumption are not exceeded.

Of the biologically active substances listed, the largest body of information available is on thujone. This derives from the fact that the prohibition of absinthe was overruled after adoption of the *Codex alimentarius* recommendation into European law in 1988. The thujone-containing wormwood plant (*Artemisia absinthium* L.) gave absinthe its name and is, together with alcohol, the main component of this spirit drink. Currently, more than 100 types of absinthe are legally available in Europe. Absinthe was recently reviewed by Lachenmeier *et al.* (2006d) and Padosch *et al.* (2006). The majority of 147 absinthe samples examined (95%) did not exceed the *Codex alimentarius* maximum level for thujone of 35 mg/kg for bitters. In fact, more than half of the samples examined (55%) contained less than 2 mg/kg thujone. This emphasized that thujone values in absinthes produced according to historical recipes can be conform to the *Codex alimentarius* maximum levels. Several studies on the experimental production of absinthes and the analyses of vintage absinthes consistently showed that they contained only relatively low concentrations of thujone (< 10 mg/L) (Lachenmeier

et al., 2006e). The thujone content of absinthe is irrespective of the quality of the spirit as there are several different wormwood chemotypes that have a large variance in thujone content (0–70.6% in essential oil) (Lachenmeier, 2007a). The easiest way to avoid thujone totally is to use the thujone-free wormwood herb, which is available in certain cultivation areas and appears to be perfect for use in the spirits industry. Some authors concluded that thujone concentrations of both pre-prohibition and modern absinthes may not cause detrimental health effects other than those encountered in common alcoholism (Strang *et al.*, 1999; Padosch *et al.*, 2006).

The Joint FAO/WHO Expert Committee on Food Additives has evaluated the safety of approximately 1150 individual flavouring agents (Munro & Mattia, 2004). Similarly, the expert panel of the Flavor and Extract Manufacturers' Association of the USA has evaluated the safety of nearly 1900 substances (Smith *et al.*, 2005). As a result of these evaluations, certain flavourings used in alcoholic beverages now have the status of 'generally recognized as safe' (GRAS).

In alcoholic beverages, the most prominent GRAS substance is (*E*)-1-methoxy-4-(1-propenyl)benzene (anethole). Anethole is a volatile substance that occurs naturally in several herbs and spices. Macerates, distillates or extracts of the plants star-anise (*Illicium verum* Hook. Fil.), aniseed (*Pimpinella anisum* L.) or fennel (*Foeniculum vulgar*e Mill.), the essential oils of which contain approximately 80–90% anethole, are used to flavour spirits. After extensive toxicological evaluations, anethole was determined to be GRAS (Newberne *et al.*, 1998, 1999). Certain spirits that contain anise, such as pastis, sambuca or mistrà, must contain minimum and maximum levels of anethole (usual range, 1–2 g/L) (Lachenmeier *et al.*, 2005a). Raki spirits from Turkey contained 1.5–1.8 g/L anethole (Yavas & Rapp, 1991). In arak from the Lebanon, levels of anethole varied from 1.2 to 3.8 g/L in commercial and from 0.5 to 4.2 g/L in artisanal samples. The variations in levels of anethole were found to be in direct relation to the amounts of aniseed used in the anization step of arak manufacture (Geahchan *et al.*, 1991). Twenty-one different brands of pacharán (a traditional Spanish beverage obtained by maceration of sloe berries (*Prunus spinosa L.*)) contained between 0.015 and 0.069 g/L anethole (Fernández-García *et al.*, 1998).

(c) Acetaldehyde

In addition to being an intermediate product of the metabolism of ethanol in humans and animals, acetaldehyde (ethanal) is a potent volatile flavouring compound found in many beverages and foods (Liu & Pilone, 2000). No current systematic surveys of acetaldehyde in alcoholic beverages were available. In general, the concentration of acetaldehyde in alcoholic beverages is below 500 mg/L and the flavour threshold varies between 30 and 125 mg/L (Liu & Pilone, 2000). During the production of spirits, acetaldehyde is enriched in the first fraction of the distillate, which is generally discarded due to its unpleasant flavour.

The levels of acetaldehyde in alcoholic beverages vary considerably. However, the acetaldehyde formed from the metabolism of alcohol in the oral cavity and the further digestive pathway is many times higher than the levels specified above.

Acetaldehyde at low levels gives a pleasant fruity aroma, but at high concentrations it possesses a pungent irritating odour (Miyake & Shibamoto, 1993). In alcoholic beverages, acetaldehyde may be formed by yeasts, acetic acid bacteria and coupled autooxidation of ethanol and phenolic compounds (Liu & Pilone, 2000). In other foods, acetaldehyde may be added as a flavouring substance. The JECFA included acetaldehyde in the functional class 'flavouring agent' and commented that there is no safety concern at current levels of intake when it is used as a flavouring agent (Joint FAO/WHO Expert Committee on Food Additives 1997). Acetaldehyde is formed in mild beer as a result of light oxidation. It is also a degradation product of poly(ethylene terephthalate), which is increasingly used as packaging choice for milk and beverages. The migration of acetaldehyde from the container into the product is an issue to be explored, particularly in the water industry, for which low acetaldehyde grades of poly(ethylene terephthalate) have been developed (van Aardt *et al.*, 2001).

Acetaldehyde is extremely reactive and binds readily to proteins, the peptide glutathione (GSH) or individual amino acids to generate various flavour compounds (Miyake & Shibamoto, 1993; Liu & Pilone, 2000).

(d) Illegal additives, adulteration and fraud

Occasionally, illegal additives, which may be very toxic and which are not permitted for use in commercial production in most countries, have been identified in alcoholic beverages. These include methanol, diethylene glycol (used as sweetener) and chloroacetic acid or its bromine analogue, sodium azide and salicylic acid, which are used as fungicides or bactericides (Ough, 1987). The fungicide methyl isothiocyanate has been added illegally to wine to prevent secondary fermentation (Rostron, 1992).

The authenticity of wine and detection of its adulteration have been reviewed (Médina, 1996; Arvanitoyannis *et al.*, 1999; Guillou *et al.*, 2001; Ogrinc *et al.*, 2003). Beet sugar, cane sugar or concentrated rectified must are added to grape must or wine before or during fermentation to increase the natural content of ethanol and therefore the value of the wine. Another type of economic fraud is mixing high-quality wines with low-quality wines that often originate from other geographical regions or countries. Nuclear magnetic resonance spectroscopy in combination with chemometric methods is a suitable approach to study the adulteration of wine in terms of varieties, regions of origin and vintage and also to detect the addition of undesirable or toxic substances (Ogrinc *et al.*, 2003). The $^{13}C/^{12}C$ isotope ratio of ethanol and the $^{18}O/^{16}O$ isotope ratio of water determined by isotopic ratio mass spectrometry can be used to detect adulteration of wine that involves the addition of cane sugar and watering (Guillou *et al.*, 2001). Wine differentiation is also possible using multivariate analysis of differ-

ent constituents such as minerals, phenolic compounds, volatile compounds or amino acids (Médina, 1996; Arvanitoyannis *et al.*, 1999).

The detection of illicit spirits has been reviewed (Savchuk *et al.*, 2001). The adulteration of spirits includes blending high-quality distillates with ethanol made from a cheaper raw material, adding synthetic volatile components to neutral alcohol or misleading labelling of the variety and origin of the raw material (Bauer-Christoph *et al.*, 1997). The classic approach to the authentication of spirits is gas chromatographic analysis of volatile compounds (congeners of alcoholic fermentation). However, the wide range of components in each type of spirit and the considerable overlap between them renders the unambiguous identification of many spirit types difficult. In addition, if a high degree of rectification takes place during distillation, the content of volatile components will be reduced and the application of gas chromatography for the identification of the raw material becomes inappropriate. In these cases, the natural isotope ratios may be used as discriminant analytical parameters (Bauer-Christoph *et al.*, 1997). For example, rums and corn alcohols from C_4 plants (cane and corn) can easily be distinguished from alcohols from C_3 plants such as grape, potato or beet or C_3 cereal alcohols (pure malt whisky). Isotopic criteria may also be used for short-term dating of brandies and spirits (i.e. the time of storage in casks) (Martin *et al.*, 1998).

Recently, infrared spectroscopy with multivariate data analysis was successfully applied for the authentication of fruit spirits and other spirits, (Lachenmeier, 2007b; Lachenmeier *et al.*, 2005b). Direct infusion electrospray ionization mass spectrometry was applied for chemical fingerprinting of whisky samples for type, origin and quality control (Moller *et al.*, 2005).

Another problem of premium spirits is the economic incentive to mix or completely substitute one brand with another less expensive brand. In such cases, the brand fraud can often be easily determined by analysing the composition of inorganic anions (Lachenmeier *et al.*, 2003). A mobile device that measures ultraviolet/visible absorption spectra was used for the authentication of Scotch whisky under field test conditions (MacKenzie & Aylott, 2004).

The same approaches as those in wine and spirit analysis were used for the authentication of beer. More recently, high-resolution nuclear magnetic resonance spectroscopy in combination with multivariate analysis was found to be adequate to distinguish beers according to their composition (e.g. differentiation between beers made with pure barley or adjuncts) or according to brewing site and date of production (Almeida *et al.*, 2006).

1.6.7 *Contaminants, toxins and residues*

For the purposes of this section of the monograph, the term ‘contaminant’ is used according to the definition given by the *Codex alimentarius*. A contaminant is any substance that is not intentionally added to food but which is present in such food as a result of the production, manufacture, processing, preparation, treatment, packing,

packaging, transport or holding of such food, or as a result of environmental contamination. The *Codex* definition of a contaminant implicitly includes naturally occurring toxicants such as those produced as toxic metabolites of certain microfungi that are not intentionally added to food (mycotoxins) (*Codex alimentarius*, 1997). Some of these contaminants have known toxic properties and, in some cases, carcinogenic effects (see Table 1.14).

(a) Nitrosamines

The chemical class of nitrosamines includes the Group 2A carcinogen *N*-nitrosodimethylamine (NDMA) (IARC 1978; IARC, 1987). The occurrence and formation of *N*-nitroso compounds in food and beverages have been reviewed (Tricker & Kubacki, 1992; Lijinsky, 1999).

In alcoholic beverages, NDMA was first found in German beers in 1978 (Spiegelhalder *et al.*, 1979), when concentrations of up to 68 μg/L caused worldwide concern. Subsequent research established that NDMA was a contaminant of malt that had been kilned by direct firing, which was the predominant production method at that time. Once the source of the contaminant and the mechanism of its formation had been elucidated, control was achieved by changing to indirect firing of the malt kiln. The possibilities for minimizing nitrosamine formation during malt kilning have been reviewed (Flad, 1989; Smith, 1994). As a result of the improvements in the quality of malt, a technical threshold value of 0.5 μg/kg NDMA in beer was established as a recommendation to the brewing industry. In Germany, this value was exceeded by 70% of all samples in 1978. In the most recent reports (2001–05), the technical threshold value was exceeded by only one of 363 German beers (0.2%) (Baden-Württemberg, 2006). Fig 1.5 demonstrates the decrease in levels of NDMA in German beers.

The concentrations of NDMA in beer that have been determined in different countries are summarized in Table 1.15. The data reflect the successful efforts of the malting and brewing industries to reduce the formation of NDMA.

Shin *et al.* (2005) analysed nitrosamines in a range of alcoholic beverages in the Republic of Korea in two surveys in 1995 and 2002, and included the first reports on the traditional Korean beverages chungju (fermented rice alcohol), takju (fermented cereal alcohol) and soju (distilled from fermented cereal alcohol). NDMA was detected in the 1995 survey in chungju (< 0.1 μg/kg) and soju (mean, 0.2 μg/kg) but in none of the samples in the 2002 survey. For domestic Korean beers, an average of 0.8 μg/kg and 0.3 μg/kg were reported in 1995 and 2002, respectively. Whisky and liqueurs contained an average of less than 0.1 μg/kg in both surveys.

Sen *et al.* (1996) noted that higher levels of NDMA might be present in beers in developing countries than in those in North America or Europe. The malt-drying techniques in various countries are unknown, and continuous monitoring and control of imported beers might therefore be necessary. As an example, high levels of nitrosamines were found in a survey of 120 Indian beers with an average of 3.2 μg/kg and a

Figure 1.5. Development of maximum concentration of N-nitrosodimethylamine (µg/kg) in German beer (data from Table 1.15)

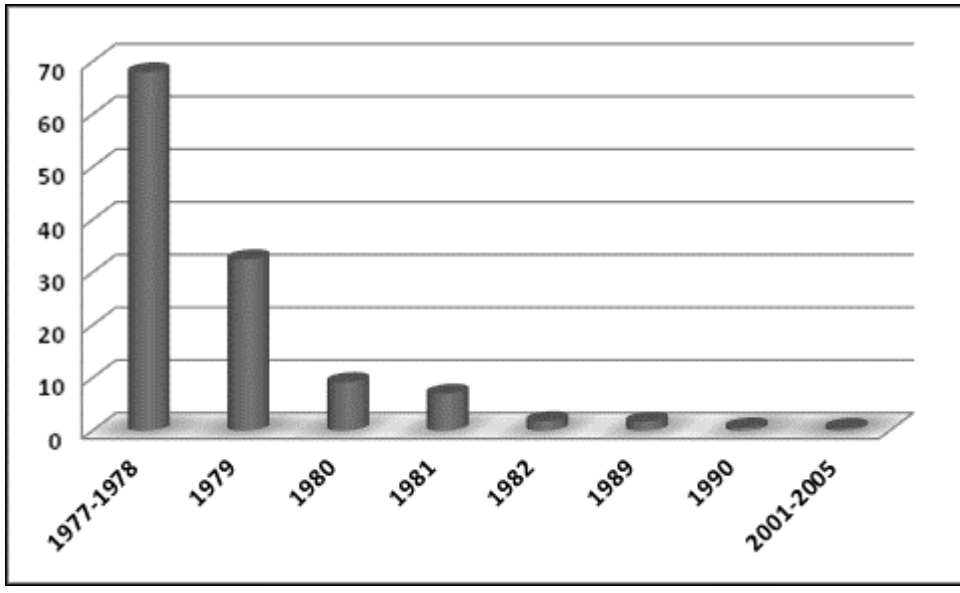


Table 1.14 Summary of carcinogens that may be present in alcoholic beverages

Agent	Amount in alcoholic beverages[a]	*IARC Monographs* evaluation of carcinogenicity			*IARC Monographs* volume, year
		In animals	In humans	IARC group	
Acetaldehyde	Lower mg/L range	Sufficient	Inadequate	2B	**71**, 1999
Acrylamide	Beer; <10 µg/kg	Sufficient	Inadequate	2A	**60**, 1994
Aflatoxins	Beer (Table 1.22)	Sufficient	Sufficient	1	**56**, **82**, 2002
Arsenic	(Table 1.25)	Sufficient	Sufficient	1	**84**, 2004
Benzene	(no sufficient data)	Sufficient	Sufficient	1	**Suppl. 7**, 1987
Cadmium	(Table 1.24)	Sufficient	Sufficient	1	**58**, 1993
Deoxynivalenol	Beer (Table 1.19)	Inadequate	Inadequate	3	**56**, 1993
Ethanol	(2–80% vol)	Inadequate	Sufficient	1	**44**, **96**, 2010
Ethyl carbamate (urethane)	See monograph in this volume	Sufficient	Inadequate	2A	**7**, **96**, 2010
Furan	Beer; <20 µg/kg	Sufficient	Inadequate	2B	**63**, 1995
Lead	(Table 1.23)	Sufficient	Limited	2A	**87**, 2006
N-Nitrosodimethylamine	Beer: <0.5 µg/kg (Table 1.16)	Sufficient	Inadequate	2A	**Suppl. 7**, 1987
Nivalenol	Beer (Table 1.20)	Inadequate	Inadequate	3	**56**, 1993
Ochratoxin A	Wine, beer (Table 1.17)	Sufficient	Inadequate	2B	**56**, 1993
Organolead compounds	Wine; limited data	Inadequate	Inadequate	3	**87**, 2006
Patulin	Apple cider	Inadequate	Inadequate	3	**Suppl. 7**, 1987

[a] Most carcinogens are contained at very different concentration ranges depending on the origin and different production technologies, so that no average concentration can be derived.

maximum of 24.7 µg/kg (Prasad & Krishnaswamy, 1994). [The Working Group noted the lack of data on nitrosamine contents of beer in developing countries.]

In a single study, volatile *N*-nitrosamines in mixed beverages containing beer (e.g. beer-cola, shandy) were reported. The contents were below 0.3 µg/kg in all samples. The formation of nitrosamines that might arise due to the low pH value of these beverages was not detected (Fritz *et al.*, 1998).

Tricker and Preussmann (1991) reviewed food surveys on NDMA. Dietary intake of NDMA was approximately 0.5 µg/day or less in most countries, which is about one-third of the intake in 1979–80. Previously, beer was the major source of NDMA in human nutrition (65% contribution). In 1990, beer was estimated to contribute to about 31% of total NDMA intake.

Table 1.15 *N*-nitrosodimethylamine in beer

Country	Year	No. of samples	Positive (%)	Concentration (µg/kg)		References
				Mean	Range	
Brazil	1997	60	43	0.09	0–0.32	Glória *et al*. (1997)
Canada	1978	13	100	1.4	0.60–4.9	Sen *et al*. (1982)
	1980	55	100	0.73	0.36–1.52	Sen *et al*. (1982)
	1982	24	No data	0.31	0–1.9	Sen *et al*. (1982)
	1989	46	59	0.095	0–0.59	Scanlan *et al*. (1990)
China	1981	26	77	2.7	0–6.5	Yin *et al*. (1982)
	1987	176	83	0.5	0–6	Song & Hu (1988)
Estonia	2003–04	158	No data	0.20	0–1.31	Yurchenko & Mölder (2005)
Former USSR	1980	165	53	No data	0–56	Kann *et al*. (1980)
Germany	1977–78	158	70	2.7	0–68	Spiegelhalder *et al*. (1979)
	1979	92	63	No data	0–32.5	Frommberger & Allmann (1983)
	1980	401	No data	0.28	0–9.2	Frommberger (1985)
	1981	454	24	0.44	0–7.0	Spiegelhalder (1983)
	1982	228	No data	0.075	0–1.8	Frommberger (1985)
	1989	514	41.2	0.16	0–1.7	Frommberger (1989)
	1990	14	No data	0.17	0–0.6	Tricker & Preussmann (1991)
	2001–05	363	No data	No data	0–0.5	Baden-Württemberg (2006)
India	1994	120	84	3.6	0–24.7	Prasad & Krishnaswamy (1994)
Italy	1982	6	67	0.4	0–0.79	Tateo & Roundbehler (1983)
	1986	15	87	0.3	0–0.71	Gavinelli *et al*. (1988)
Japan	1980	29	93	5.1	Tr–13.8	Kawabata *et al*. (1980)
	1982	12	0	0	–	Yamamoto *et al*. (1984)
Korea	1995	29	79	0.8	0.2–4.2	Shin *et al*. (2005)
	2002	18	56	0.3	0.1–0.7	Shin *et al*. (2005)
Netherlands	1978	32	No data	1.4	0–3.9	Ellen & Schuller (1983)
	1979	108	No data	2.0	0–7.4	Ellen & Schuller (1983)
	1980	86	No data	0.2	0–1.2	Ellen & Schuller (1983)
Poland	1989	12	83	0.2	0–0.3	Kubacki *et al*. (1989)
Spain	1994	21	52	0.11	0–0.55	Izquierdo-Pulido *et al*. (1996)
	2002	44	20	0.16	0–1.05	Cárdenes *et al*. (2002)

Table 1.15 (continued)

Country	Year	No. of samples	Positive (%)	Concentration (µg/kg)		References
				Mean	Range	
Sweden	1980–86	258	59	0.3	0–6.5	Österdahl (1988)
United Kingdom	1988–89	171	34	0.18	0.1–1.2	Massey *et al*. (1990)
USA	1979	6	100	3.1	0.9–7	Goff & Fine (1979)
	1980	52	No data	3.4	0.4–7.7	Fazio *et al*. (1980)
	1980	25	92	5.9	0–14	Scanlan *et al*. (1980)
	1988	10	100	0.28	0.03–0.99	Billedeau *et al*. (1988)
	1989	148	55	0.067	0–0.59	Scanlan *et al*. (1990)
	1997	28	50	0.07	0–0.50	Glória *et al*. (1997)

Tr, trace

(b) Mycotoxins

Mycotoxins are fungal secondary metabolites produced by many important phytopathogenic and food-spoilage fungi including *Aspergillus, Penicillium*, *Fusarium* and *Alternaria*. Various control strategies to prevent the growth of mycotoxigenic fungi and inhibit mycotoxin biosynthesis have recently been reviewed (Kabak *et al*., 2006). Mycotoxins survive ethanol fermentation to different degrees but are not carried over to distilled ethanol (Bennett & Richard, 1996). Therefore, alcoholic beverages manufactured without distillation (e.g. wine, cider, beer) are the main focus of research on mycotoxins.

(i) *Mycotoxins in wine*

Recent research on wine has been focused on ochratoxin A, which has been classified Group 2B—possibly carcinogenic to humans (IARC, 1993a). Human ochratoxicosis has been reviewed (Creppy, 1999). Ochratoxin A survives the fermentation process (Kabak *et al*., 2006) and is stable in wine for at least 1 year (Lopez de Cerain *et al*., 2002). It was indicated that fungi that produce ochratoxin A are already present on grapes in the vineyard before the harvest. Location of the vineyard has more influence on the levels of ochratoxin A than the variety of grape. Weather patterns also seem to influence these levels (Kozakiewicz *et al*., 2004). A study of Spanish wines reflected very different levels of contamination by ochratoxin A between 2 years of harvest: 85% of 1997 wine samples versus 15% of 1998 wine samples (Lopez de Cerain *et al*., 2002). The 1997 harvest was judged to be worse than that of 1998 probably because of differences in the weather conditions during the summer that led to lower production and several problems of contamination with fungi. On the contrary, in 1998, no sanitary problems were encountered during cultivation of the grapevines. The storage

conditions and subsequent processing of grapes were very similar in both cases. These results corroborate the notion that ochratoxin A is present in the grapes before the wine is produced and demonstrate the great importance of climate, which obviously depends on the latitude but also on the particular circumstances in any given year. The occurrence, legislation and toxicology of ochratoxin A have been reviewed (Höhler, 1998). Systematic surveys of ochratoxin A in wine are summarized in Table 1.16.

Otteneder and Majerus (2000) reported the results of a meta-analysis that evaluated more than 850 wine samples tested for ochratoxin A. According to these data, ochratoxin A is detected much more commonly and its concentration is remarkably higher in red wines than in rosé and white wines: it was detected in 25% of white, 40% of rosé and 54% of red wine samples. The same result was found when wines from southern and northern regions of Europe were compared. Red wine samples from the northern area showed a contamination of 12% in contrast to those from the southern area, which showed a contamination of about 95%. The differences were explained by wine-making procedures that are totally different with respect to red and white wines. White grapes are pressed out directly, whereas red grapes are left mashed for a certain length of time, which obviously permits fungal growth and production of the toxin (Höhler, 1998).

There is only limited information on the occurrence of other mycotoxins in wine. The occurrence of trichotecin from *Trichotecium roseum* in German wine was studied by Majerus and Zimmer (1995). Results showed that most samples were free from trichotecin. Low concentrations (~28 μg/L) were detected in a small proportion of samples from a vintage that was severely affected by fungal spoilage. Lau *et al.* (2003) reported the occurrence of alternariol from *Alternaria alternata* in a single wine sample (1.9 μg/L). In a limited survey of 66 wines on the Canadian market (Scott *et al.*, 2006), alternariol was found in 13/17 Canadian red wines at levels of 0.03–5.02 μg/L and in all of seven imported red wines at 0.27–19.4 μg/L, usually accompanied by lower concentrations of alternariol monomethyl ether. White wines (23 samples) contained little or no alternariol.

(ii) *Mycotoxins in apple cider*

Patulin, a mycotoxin produced in apples by several *Penicillium* and *Aspergillus* species, may be found in apple cider. To date, inadequate data are available for the classification of patulin (Group 3) (IARC, 1987). Although patulin is a fairly reactive compound in an aqueous environment, it is especially stable at low pH and survives the processes involved in the commercial production of apple juice. The complete destruction of patulin occurs during alcoholic fermentation of apple juice to cider (Moss & Long 2002). However, Wilson and Nuovo (1973) detected patulin in five of 100 samples of apple cider at levels of up to 45 mg/L. These very high levels were only found in cider that was produced when decayed apples had not been discarded or when apples had been stored in bins for very long periods. When these practices were changed, patulin was no longer detected. Tsao and Zhou (2000) found that infected apples may contain

Table 1.16 Ochratoxin A in wine

Country	Year	No. of samples	Positive (%)	Concentration (μg/L)		References
				Mean	Range	
Canada	1999–2002	79	19	0.012	0–0.393	Ng *et al*. (2004)
Europe	2003	38	34	0.032	0–0.057	Rosa *et al*. (2004)
Greece (dry)	1998–2000	242	61	0.28	0–2.69	Stefanaki *et al*. (2003)
Greece	1995–99	35	63	No data	0–3.2	Soufleros *et al*. (2003)
Imported to Canada	1999–2002	101	48	0.160	0–3.720	Ng *et al*. (2004)
Imported to Poland	2005	53	92	0.4775	0.0022–6.710	Czerwiecki *et al*. (2005)
Italy (red)	1995–97	96	85	0.419	0–3.177	Pietri *et al*. (2001)
Mediterranean	1999	31	100	No data	No data	Markaki *et al*. (2001)
Mediterranean	1999–2002	78	59	0.207	0–3.720	Ng *et al*. (2004)
Morocco	2001	30	100	0.65 median	0.028–3.24	Filali *et al*. (2001)
South Africa	2000–01	24	100	0.2	0.04–0.39	Shephard *et al*. (2003)
South America	2003	42	24	0.037	0–0.071	Rosa *et al*. (2004)
Spain	1997	20	85	0.195	0.056–0.316	Lopez de Cerain *et al*. (2002)
Spain	1998	20	15	0.153	0.074–0.193	Lopez de Cerain *et al*. (2002)
Swiss retail	1990–94	118	No data	No data	0–0.388	Zimmerli & Dick (1996)
Worldwide origin	1996	144	42	No data	0–7.0	Majerus & Otteneder (1996)
Worldwide origin	1997–99	420	48	0.177	0–3.31	Otteneder & Majerus (2000)
Worldwide origin	2000	281	40	No data	0–7.0	Majerus *et al*. (2000)
Worldwide origin	2001	942	12	No data	No data	Soleas *et al*. (2001)

extremely high concentrations of patulin (> 100 μg/L), and that one ‘bad’ apple could cause the maximal acceptable level of 50 μg/L in apple cider to be exceeded.

A recent study confirmed that patulin is a good indicator of the quality of apples used to manufacture cider. Patulin was not detected in cider pressed from culled tree-picked apples stored for 4–6 weeks at 0–2 °C, but was found at levels of 0.97–64.0 μg/L in cider pressed from unculled fruit stored under the same conditions. Cider from apples that were culled before pressing and stored in controlled atmospheres contained 0–15.1 μg/L patulin, while cider made from unculled fruit contained 59.9–120.5 μg/L. The washing of ground-harvested apples before pressing reduced levels of patulin in cider by 10–100%, depending on the initial levels and the type of wash solution used. The avoidance of ground-harvested apples and the careful culling of apples before pressing are good methods for reducing the levels of patulin in cider (Jackson *et al.*, 2003).

(iii) *Mycotoxins in beer*

Mycotoxins in beer have been reviewed (Odhav, 2005). Mycotoxins may be transmitted to beers from contaminated grains during brewing. Various surveys have indicated that a variety of mycotoxins reach the final product, but generally in limited concentrations (Odhav, 2005).

Advances in methodology have enabled detection and quantitation of much lower levels (< 1 μg/L) of important mycotoxins such as ochratoxin A and aflatoxins in beer. Consequently, in recent years, reported incidences of ochratoxin A have increased in European and North American beers (Table 1.17). The highest levels of contamination with mycotoxin in beer from these parts of the world is caused by deoxynivalenol. Local beer brewed in Africa may have high incidences and concentrations of aflatoxins and zearalenone (Scott, 1996).

Mycotoxins—aflatoxins, ochratoxin A, patulin, *Fusarium* toxins (zearalenone, fumonisins, trichlothecenes, nivalenol, desoxynivalenol)—that originate from barley or grain adjuncts survive malting and brewing processes to different extents (Scott, 1996; Dupire, 2003).

Deoxynivalenol, nivalenol and zearalenone are not classifiable as to their carcinogenicity to humans (Group 3) (IARC, 1993a). Surveys of the occurrence of deoxynivalenol and nivalenol in beer are summarized in Tables 1.18 and 1.19, respectively. Papadopoulou-Bouraoui *et al.* (2004) observed that the level of alcohol as well as the type of fermentation had a significant effect on the amount of deoxynivalenol in beer. In general, beers that contained higher levels of alcohol contained significantly larger amounts of deoxynivalenol. Spontaneously fermenting beers contained significantly higher levels of deoxynivalenol than top- or bottom-fermenting beers, while top-fermenting beers contained significantly higher concentrations than bottom-fermenting beers. A positive correlation between original gravity and levels of deoxynivalenol was reported by Curtui *et al.* (2005).

The most abundant naturally occurring fumonisin analogues produced by *Fusarium* species are fumonisins B_1, B_2 and B_3 (Rheeder *et al.*, 2002). Fumonisin B_1 was classified as a Group 2B carcinogen (IARC, 2002). Concentrations of fumonisin B_1 in beer are

Table 1.17 Ochratoxin A in beer

Country	Year	No. of samples	Positive (%)	Concentration (µg/L)		References
				Mean	Range	
Belgium	1998–2001	62	97	0.033	0.010–0.185	Tangni *et al*. (2002)
Canada (including 11 imports)	1995	41	63	0.06	0–0.2	Scott & Kanhere (1995)
Europe	1983	92	0	–	–	Majerus & Woller (1983)
Germany	1987–92	194	41	0.10	No data	Jiao *et al*. (1994)
Germany	1990–92	108	18	No data	0.1–1.5	Majerus *et al*. (1993)
Germany	1992	56	29	No data	0–1.53	El-Dessouki (1992)
Germany	1999	35	86	0.08	0–0.26	Degelmann *et al*. (1999)
Japan	1998	22	96	0.013	0.002–0.045	Nakajima *et al*. (1999)
South Africa	2002	35	31	No data	0–2340[a]	Odhav & Naicker (2002)
Worldwide origin	1998	94	92	0.010	0.001–0.066	Nakajima *et al*. (1999)
Worldwide origin	2001	107	2	No data	No data	Soleas *et al*. (2001)

[a] The Working Group was unable to verify this unusually high value with the authors.

shown in Table 1.20. Shephard *et al*. (2005) showed that fumonisin B_1 was the major fumonisin analogue present in South African home-brewed maize beer and accounted for a mean of 76% in samples that contained all three analogues. The amounts of fumonisin in maize beer were up to two orders of magnitude larger than those observed in beers from other parts of the world in which maize or maize products are not usual ingredients or are used merely as adjuncts. There is little information available on mycotoxin contamination of beer in Africa.

Naturally occurring aflatoxins are carcinogenic to humans (Group 1) (IARC, 2002). Studies on aflatoxins in beer are summarized in Table 1.21. Nakajima *et al*. (1999) conducted a worldwide survey of aflatoxins in beer. Aflatoxins were detected in beer samples from countries where aflatoxin contamination might be expected to occur because of the warm climate. Except for one sample, beers contaminated with aflatoxins were also contaminated with ochratoxin A. Generally, with the exception of a negative survey on 75 bottled Kenyan lager beers (Mbugua & Gathumbi, 2004), much higher concentrations of aflatoxins have been found in both commercial and home-brewed African beers (Scott, 1996; Odhav & Naicker, 2002). Mably *et al*. (2005) confirmed

Table 1.18 Deoxynivalenol in beer

Country	Year	No. of samples	Positive (%)	Concentration (µg/L)		References
				Mean	Range	
Argentina	1997	9	89	51	0–221	Molto *et al*. (2000)
Argentina	1998	26	31	7	0–43	Molto *et al*. (2000)
Argentina	1999	14	43	5	0–20	Molto *et al*. (2000)
Brazil	2001	72	5	No data	50–336	Garda *et al*. (2004)
Canada (and imported)	1993	50	29	No data	0–50	Scott *et al*. (1993)
Czech Republic	1994–95	77	77	13–25	0–70	Ruprich & Ostrý (1995)
Europe	2000–01	51	6	No data	0–41	Schothorst & Jekel (2003)
Germany	2001–04	794	90	7	0–353	Curtui *et al*. (2005)
Japan	2005	17	No data	No data	0.5–1.4	Suga *et al*. (2005)
Kenya	2004	75	100	3.42	1.56–6.40	Mbugua & Gathumbi (2004)
Korea (and imported)	1996	54	26	No data	No data	Shim *et al*. (1997)
Turkey	2002–03	39	0	–	–	Omurtag & Beyoglu (2007)
Worldwide origin	2000–02	313	87	13.5	4.0–56.7	Papadopoulou-Bouraoui *et al*. (2004)

in a large worldwide survey that beers from warmer countries such as Mexico have a higher median concentration of aflatoxin B_1. The highest incidence and concentrations of aflatoxins B_1 and B_2 occurred in beer from India. Other countries where aflatoxin

Table 1.19 Nivalenol in beer

Country	Year	No. of samples	Positive (%)	Concentration (µg/L)		References
				Mean	Range	
Argentina	1997–99	14	0	–	–	Molto *et al*. (2000)
Canada (and imported)	1993	50	6	No data	0–0.84	Scott *et al*. (1993)
Europe	2000–01	51	0	–	–	Schothorst & Jekel (2003)
Korea (and imported)	1995	54	80	4	0–38	Shim *et al*. (1997)

Table 1.20 Fumonisin B_1 in beer

Country	Year	No. of samples	Positive (%)	Concentration (µg/L)		References
				Mean	Range	
Canada (and imported)	1995	41	20	No data	0–59	Scott & Lawrence (1995)
Canada (and imported)	1996	46	48	No data	0–64.3[a]	Scott *et al*. (1997)
Kenya	2004	75	72	0.3	0–0.78	Mbugua & Gathumbi (2004)
South Africa (home-brewed maize beer)	1991–2004	18	100	281	38–1066	Shephard *et al*. (2005)
Spain	1996–97	32	44	No data	0–85.5	Torres *et al*. (1998)
USA (and imported)	1998	29	86 (total fumonisins)	4.0	0–12.7	Hlywka & Bullerman (1999)

[a] The higher incidence of fumonisin B_1 was a bias towards brands that were manufactured from corn grits or cornflakes.

B_1 was detected in beer were Mexico, Spain and Portugal, but levels found in positive samples were much lower. Beers from Canada and the USA were negative for aflatoxins in a reasonably large sampling from these countries.

(c) Ethyl carbamate (urethane)

Ethyl carbamate is evaluated in detail in a separate Monograph in this Volume.

(d) Inorganic contamination

The mineral content of wine depends on many factors, including the type of soil, variety of grape, climate conditions, viticultural practices and pollution (Frías *et al*., 2003). The mineral content of beer was found to be reduced during beer production by about 50–80% (lead, cadmium, copper and zinc). Primarily, the main fermentation and the absorption capacity of beer yeast are responsible for the reduction in the lead, cadmium and zinc contents. In contrast, the amount of copper is reduced during the filtration phase (Mäder *et al*., 1997).

(i) *Lead*

Metallic lead is considered to be a possible carcinogen (Group 2B) (IARC, 1987) whereas inorganic lead compounds are probably carcinogenic to humans (Group 2A) (IARC, 2006). Lead in wine has been reviewed (Eschnauer, 1992; Eschnauer & Scollary, 1996). The concentrations of lead in alcoholic beverages are given in Table 1.22.

Table 1.21 Aflatoxins in beer

Country	Year	No. of samples	Positive (%)	Concentration (μg/L)		References
				Mean	Range	
Canada (and imported)	1998–2002	304	4	0.002	0–0.230	Mably *et al.* (2005)
Czech Republic	1990	34	0	–	–	Fukal *et al.* (1990)
Europe	1982	174	0	–		Woller & Majerus (1982)
Japan	1998	22	9	No data	0.0005–0.0008	Nakajima *et al.* (1999)
Kenya	2004	75	0	–	–	Mbugua & Gathumbi (2004)
South Africa	2000	33	9	No data	12–400	Odhav & Naicker (2002)
Worldwide origin	1998	94	11	No data	0.0005–0.0831	Nakajima *et al.* (1999)

Many authors ascribed the main sources of contamination by lead in wine to winery equipment (Kaufmann, 1998; Rosman *et al.*, 1998), lead capsules (Eschnauer, 1986; Pedersen *et al.*, 1994), lead crystal wine glasses (Hight, 1996) and atmospheric pollution (Lobiński *et al.*, 1994; Teissedre *et al.*, 1994; Médina *et al.*, 2000). The levels of lead were significantly raised by pesticide treatment with azoxystrobin and sulfur (Salvo *et al.*, 2003). The *Codex alimentarius* recommends a maximum level of 0.20 mg/kg lead in wine (*Codex alimentarius*, 2003).

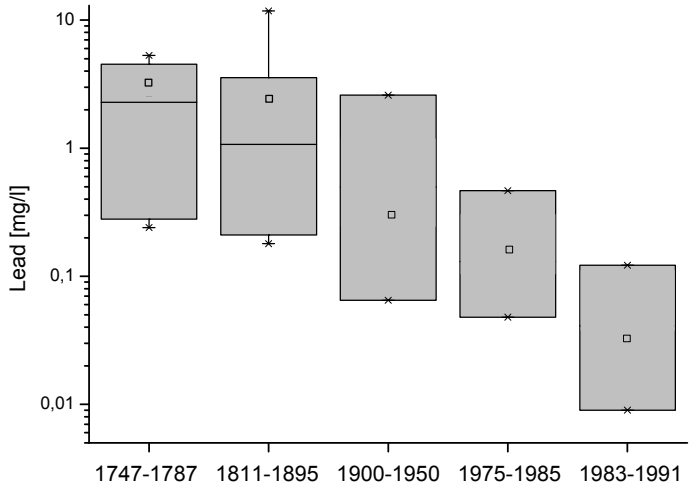
In a recent study, the contents of lead in wine were found to be very low (< 87 μg/L) in all samples. The mean values of lead in red wines (30 μg/L) were higher than those in white wines (22 μg/L), but there was no significant difference in lead content between red and white wines (Kim, 2004). Tahvonen (1998) reported means of 33 μg/L in white wines and of 34 μg/L in red wines. Previous studies have shown higher values of lead in wines (Sherlock *et al.*, 1986) compared with more recent results; the mean concentrations of lead in red wines were 106 μg/L, while those in white wines were 74 μg/L. Significant differences between red (65.7 μg/L), rosé (49.5 μg/L) and white (38 μg/L) wines were also determined by Andrey *et al.* (1992).

The lead content of wine has tended to decrease over the last few decades. Eschnauer and Ostapczuk (1992) detected a significant reduction in the content of lead in wines of various vintages between the eighteenth and twentieth centuries (see Fig. 1.6). A reduction was also detected in vintages of French wine between 1950 and 1991 (Rosman *et al.*, 1998).

Table 1.22 Lead in alcoholic beverages

Product Country	Year	No. of samples	Concentration (µg/L)		References
			Mean	Range	
Wine					
Argentina	1996	59	69	0–190	Roses *et al*. (1997)
Finland (and imported)	1994	19	No data	7–43	Tahvonen (1998)
France	1747–87	6	2680	240–5290	Eschnauer & Ostapczuk (1992)
France	1811–95	11	2610	180–11800	Eschnauer & Ostapczuk (1992)
France	1900–50	25	497	65–2600	Eschnauer & Ostapczuk (1992)
Germany	1975–85	250	130	48–467	Eschnauer & Ostapczuk (1992)
Germany	1983–91	56	41	9–122	Eschnauer & Ostapczuk (1992)
Germany	1993–94	150	50	4–254	Ostapczuk *et al*. (1997)
Greece	1989	113	230	50–560	Lazos & Alexakis (1989)
Italy	2002	68	No data	10–350	Marengo & Aceto (2003)
Canary Islands, Spain	1995–96	148	28.74	3.89–159.53	Barbaste *et al*. (2003)
Worldwide origin	1975–90	2500	No data	10–785	Kaufmann (1993)
Worldwide origin	1992	867	57.1	3–326	Andrey *et al*. (1992)
Worldwide origin	2000	60	29.16	5.26–87.04	Kim (2004)
Beer					
Brazil	2002	63	37	0–290	Valente Soares & Monteiro de Moraes (2003)
Finland (and imported)	1994	16	No data	2–7	Tahvonen (1998)
Germany	1987	100	1.6	0–15	Donhauser *et al*. (1987)
India	1994	5	13.2	10,4–15,7	Srikanth *et al*. (1995)
United Kingdom	1982–83	201	20	<5–330	Sherlock *et al*., (1986); Smart *et al*. (1990)
United Kingdom	1985–86	146	9.8	<5–85	Smart *et al*. (1990)
Spirits					
Cachaças and international	1998	100	No data	0–600	Nascimento *et al*. (1999)
Sherry brandies, Spain	2000	20	58	8–313	Cameán *et al*. (2000)
Whisky, Scotland	2002	35	3	0–25	Adam *et al*. (2002)

Figure 1.6. Lead concentrations in wine since the eighteenth century (data from Eschnauer & Ostapczuk, 1992)



Médina *et al.* (2000) showed a decrease from about 250 µg/L in the early 1950s to less than 100 µg/L. Kaufmann (1998) reported that the average wine in vintage 1990 contained 55 µg/L lead while the concentration in vintage 1980 was 109 µg/L. Statistical analysis revealed that the vintage and the colour but not the age of the wine were the most significant factors that correlated with the lead content.

The code of practice for the prevention and reduction of lead contamination in foods recommends that lead foil capsules should not be used on wine bottles because this practice may leave residues of lead around the mouth of the bottle that can contaminate wine upon pouring (*Codex alimentarius*, 2004). Currently, wine capsules are made from other materials.

Before leaded gasoline was banned in the 1990s, atmospheric deposition was a main source of lead in wines (Teissedre *et al.*, 1994; Médina *et al.*, 2000). During this period, organolead species from automotive sources were recorded in a series of wine collected in southern France (Lobiński *et al.*, 1994). At present, the contribution of road traffic to the levels of lead in the atmosphere is much smaller than in the past due to the reduction of natural lead content of the combustibles used in car engines (Kim, 2004). Kaufmann (1998) reported that brass (a lead alloy that was widely used in traditional wine cellars) was also a main source of lead contamination of wines. The gradual replacement of brass by stainless steel has resulted in a steady decrease in levels of lead in wine. Nevertheless, the wines produced at present still contain significant amounts of lead, and it is important that all of the sources of this metal be known to enable their removal or minimization (Kim, 2004). Almeida and Vasconcelos (2003) confirmed that marked reductions in the lead content of wines would occur if the sources of lead were removed from the tubes and containers used in the vinification system, particularly by using lead-free welding alloys and small fittings.

The lead contents of beers were negligible, and low values for beer were also reported in earlier studies (Tahvonen, 1998). Donhauser *et al.* (1987) found a mean content of 1.6 µg/L in 100 beer samples. Only three-piece tinplate cans with a soldered body seam, which must have been damaged, contained beer with higher lead values of up to 15 µg/L. The tin-coating of welded cans may also contribute some of the lead. According to Jorhem and Slorach (1987), foods packed in unlacquered welded cans contained substantially more lead than foods conserved in lacquered welded cans. Previously, old equipment was found to be a source of lead in draft-beer samples (Smart *et al.*, 1990). After the elimination of sources of lead contamination such as bronze and brass fittings, successful reduction was observed between two surveys in the United Kingdom (Sherlock *et al.*, 1986; Smart *et al.*, 1990).

(ii) *Cadmium*

Cadmium and cadmium compounds are carcinogenic to humans (Group 1) (IARC, 1993b). In a recent study, the mean contents of cadmium in red wines were higher than those in white wines but without statistically significant differences (Kim, 2004). The data (average, 0.5 µg/L) were in accordance with those reported previously (Table 1.23).

There was no significant difference in lead and cadmium contents of wines with different countries of origin (Kim, 2004). In contrast, Barbaste *et al.* (2003) reported significant differences in the mean cadmium content among the three types of wine: the lowest and the highest mean content were found for red and white wines, respectively. These differences may be related to variations in the wine-making process. The wide variability of these data may result from different factors, both natural and exogenous. Natural factors include soil composition and grape variety. Exogenous factors are the fermentation process, the wine-making system, processing aids (filter materials) or different types of contamination (Kim, 2004). The high concentration of cadmium found in some wine samples could be due to the use of pesticides or fertilizers that contained salts of this metal (Mena *et al.*, 1996).

In the samples of beer analysed by Mena *et al.* (1996), the mean concentration of cadmium was 0.21 μg/L. Canned beers contained the highest levels, probably due to the fact that low-quality cans had been used, with values that varied from 0.50 to 0.80 μg/L; lower concentrations were found in draft beers, with a mean value of 0.20 μg/L. In the other alcoholic beverages that were analysed, the highest concentrations were found in brandy (5.31 μg/L) and whisky (3.20 μg/L) samples; the lowest values were found in samples of liquor and anisette (0.13 and 0.04 μg/L, respectively) (Mena *et al.*, 1996).

(iii) *Arsenic*

Arsenic is included in the Group 1 of carcinogens (IARC, 1987).

The mean arsenic content of red wines was significantly lower than that of rosé and white wines (Barbaste *et al.*, 2003). These differences were attributed by Aguilar *et al.* (1987) to the different methods of vinification used for rosé and red wines. Typical arsenic concentrations in alcoholic beverages are shown in Table 1.24.

(iv) *Copper*

The copper contents of alcoholic beverages are summarized in Table 1.25.

Copper may occur in wine because copper alone or formulated with other agrochemicals is an important substance for the prevention of the outbreak of fungal diseases. During fermentation, the concentration of copper in wine may decrease due to sedimentation as insoluble sulfides together with yeasts and lees (García-Esparza *et al.*, 2006). The contents of metals were increased in samples treated with organic or inorganic pesticides. In particular, the use of quinoxyfen, dinocap-penconazole and dinocap considerably increased the copper(II) and zinc(II) contents of white and red wines (Salvo *et al.*, 2003).

In whisky, copper can be traced to two major sources: the copper stills used for distillation and the barley from which the spirit is distilled. However, the use of copper stills mainly determines the amount of copper, and the influence of the raw material can virtually be ignored (3%) (Adam *et al.*, 2002). In Brazilian sugar-cane spirits, the copper content was correlated with the acidity of the distillate and was higher in

Table 1.23 Cadmium in alcoholic beverages

Product Country	Year	No. of samples	Concentration (µg/L)		References
			Mean	Range	
Beer					
Brazil	2002	63	1.6	0–14.3	Valente Soares & Monteiro de Moraes (2003)
Germany	1987	100	0.2	0–6.5	Donhauser *et al*. (1987)
Wine					
Germany	1993–94	150	0.63	0.003–0.98	Ostapczuk *et al*. (1997)
Greece	1989	113	3	0–30	Lazos & Alexakis (1989)
Greece	2000	39	0.3	0.1–0,6	Karavoltsos *et al*. (2002)
Italy	2003	68	No data	0.01–0.95	Marengo & Aceto (2003)
Canary Islands, Spain	1995–96	146	0.63	0.20–1.73	Barbaste *et al*. (2003)
Spain	1995	70	No data	0.1–15.38	Mena *et al*. (1996)
Worldwide origin	1992	219	No data	0.3–6	Andrey *et al*. (1992)
Worldwide origin	2000	60	0.47	0.01–3.44	Kim (2004)
Spirits					
Sherry brandies, Spain	2000	20	6	0–40	Cameán *et al*. (2000)

the tail fractions. Therefore, the copper content may be reduced if the distillation is stopped at a higher alcoholic grade (Boza & Horii, 2000). Another possibility to reduce the copper levels in Brazilian sugar-cane spirits is storage in oak barrels. A significant reduction in copper levels of 74% was observed during 6 months of ageing (Ferreira Lima Cavalheiro *et al.*, 2003).

(v) *Chromium*

The amounts of chromium in Spanish wines varied widely, and differences in the chromium contents of red (32.5 g/L) and white (19.5 µg/L) wines have been reported (Lendinez *et al.*, 1998). Cabrera-Vique *et al.* (1997) found levels of chromium that ranged from 6.6 to 90.0 µg/L in French red wines (mean, 22.6 µg/L), from 6.6 to 43.9 µg/L in French white wines (mean, 21.3 µg/L) and from 10.5 to 36.0 µg/L in champagne (mean, 25.1 µg/L). On the basis of analyses of different vintage wines from the same vineyard and winery, it was suggested that concentrations of chromium significantly increase with the age of the wine. Italian wines contained 20–50 µg/L chromium (Marengo & Aceto, 2003) and Greek wines contained 0.01–0.41 mg/L chromium (Lazos & Alexakis, 1989).

Table 1.24 Arsenic in alcoholic beverages

Product Country	Year	No. of samples	Concentration (µg/L)		References
			Mean	Range	
Beer					
Croatia	1988–93	70	1	0–8	Sapunar-Postružnik *et al.* (1996)
Germany (and imported)	1987	100	6.4	0–102.4	Donhauser *et al.* (1987)
Spain	1999	21	8.3	1.5–28.4	Herce-Pagliai *et al.* (1999)
Wine					
Croatia	1988–93	82	0.8	0–6	Sapunar-Postružnik *et al.* (1996)
Italy	2003	68	No data	0.04–0.80	Marengo & Aceto (2003)
Spain	1995–96	148	3.13	0.58–8.45	Barbaste *et al.* (2003)
Spain	2002	45	8.3	2.1–14.6	Herce-Pagliai *et al.* (2002)
Spirits					
Sherry brandies, Spain	2000	20	13	0–27	Cameán *et al.* (2000)

Table 1.25 Copper in alcoholic beverages

Product Country	Year	No. of samples	Concentration (mg/L)		References
			Mean	Range	
Wine					
Germany	1993–94	150	0.250	0.050–0.394	Ostapczuk *et al.* (1997)
Greece	1989	113	0.23	0–1.65	Lazos & Alexakis (1989)
Italy	2002	68	No data	0.001–1.34	Marengo & Aceto (2003)
Italy	2003	34	0.71 (red) 1.01 (white)	No data	García-Esparza *et al.* (2006)
Worldwide origin	1992	250	0.228	No data	Andrey *et al.* (1992)
Spirits					
Cachaças and international	1998	100	No data	0–14.3	Nascimento *et al.* (1999)
Sherry brandies, Spain	2000	20	1.42	0.30–5.31	Cameán *et al.* (2000)
Sugar-cane, Brazil	2001	20	2.56	0.04–9.2	Bettin *et al.* (2002)
Whisky, Scotland	2002	35	0.48	0.1–1.7	Adam *et al.* (2002)

Significant differences were also observed among beer samples; in which the chromium content ranged from 3.94 to 30.10 µg/L. Canned and draft beers had the highest values, and lower concentrations were found in bottled beers. Among other alcoholic beverages, mean concentrations of chromium ranged from 7.50 µg/L in rum to 24.45 µg/L in anisette. The highest values were obtained for beverages that contained sugar (Lendinez *et al.*, 1998). The average chromium content of 100 German beers was given as 7.5 µg/L (range, 1–42 µg/L) (Donhauser *et al.*, 1987). Danish beers had a mean chromium concentration of 9 µg/L (range, < 2–32 µg/L) (Pedersen *et al.*, 1994). Fifty-two samples of Brazilian cachaça contained chromium at concentrations of 0.64–1.53 µg/L (Canuto *et al.*, 2003). A large variation in chromium levels from undetectable to 520 µg/L was reported in an international selection of beverages (Nascimento *et al.*, 1999).

(vi) *Other metals*

Selenium was determined in sweet and dry bottled wines from Spain; the concentration varied between 1.0 and 2.0 µg/L in sweet wines and between 0.6 and 1.6 µg/L in dry wines (Frías *et al.*, 2003). Another survey of Spanish beverages showed 0.15–0.38 µg/L selenium in wine (mean, 0.26 µg/L) and 0.89–1.13 µg/L in beer (mean, 1.007 µg/L) (Díaz *et al.*, 1997). The mean selenium concentration of 100 German beers was 1.2 µg/L (range, < 0.4–7.2 µg/L) (Donhauser *et al.*, 1987).

Concentrations of *mercury* ranged from 2.6 to 4.9 µg/L in sweet Spanish wines and from 1.5 to 2.6 µg/L in dry Spanish wines (Frías *et al.*, 2003). Mercury was detected in only two of 100 German beers at concentrations of 0.4 and 0.8 µg/L (Donhauser *et al.*, 1987). In wine and beer on the Danish market, all samples analysed for mercury were below the detection limit of 6 µg/L (Pedersen *et al.*, 1994).

Antimony levels in 52 samples of cachaça from Brazil varied from undetectable to 39 µg/L (Canuto *et al.*, 2003). Italian wines contained antimony at concentrations in the range of 0.01–1.00 µg/L (Marengo & Aceto, 2003).

Nickel concentrations in beverages on the Danish market have been reported. Average nickel contents were 49 µg/L in red wine, 42 µg/L in white wine, 93 µg/L in fortified wine and 23 µg/L in beer (Pedersen *et al.*, 1994). Italian wines contained 15–210 µg/L nickel (Marengo & Aceto, 2003) and Greek wines contained 0–0.13 mg/L (Lazos & Alexakis, 1989). Whisky contained 0.002–0.6 mg/L nickel (Adam *et al.*, 2002).

Iron concentrations in sugar-cane spirits from Brazil ranged between 0.01 and 0.78 mg/L with an average of 0.21 mg/L (Bettin *et al.*, 2002). The iron concentration in whisky varied considerably between 0.02 and 28 mg/L (Adam *et al.*, 2002). The large variance in iron levels in spirits was confirmed by Nascimento *et al.* (1999) (range, 0.009–2.24 mg/L) and Cameán *et al.* (2000) (range, not detected–2.03 mg/L). Wine contained concentrations of iron in a range of 1.35–27.8 mg/L (Marengo & Aceto, 2003) or 0.70–7.30 mg/L (Lazos & Alexakis, 1989).

Zinc was determined in 251 wine samples on the Swiss market, with a mean concentration of 614 µg/L (Andrey *et al.*, 1992), in Italian wine which had a range of

0.135–4.80 mg/L (Marengo & Aceto, 2003) and in Greek wines which had a range of 0.05–1.80 mg/L (Lazos & Alexakis, 1989). The concentrations of zinc in whisky ranged between 0.02 and 20 mg/L (Adam *et al.*, 2002). Various spirits contained concentrations of zinc between not detectable and 0.573 mg/L; manganese, cobalt and nickel were found in ranges of 0.002–0.657 mg/L, 0.003–0.063 mg/L and 0.001–0.684 mg/L, respectively (Nascimento *et al.*, 1999). Sherry contained zinc (0–0.829 mg/L), manganese (0–0.157 mg/L) and aluminium (0.02–1.37 mg/L) (Cameán *et al.*, 2000).

Thallium was regularly found in very low quantities in wine; red wines contained 0.2 μg/L, which was about half that in white wine (Eschnauer *et al.*, 1984). With a detection limit of 10 μg/L, thallium could be detected in none of 700 wines of worldwide origin (Kaufmann, 1993). More sensitive analyses showed a range of 10–95 ng/L thallium in Italian wine (Marengo & Aceto, 2003).

Only limited data are available on alkali metals and alkaline earth metals in alcoholic beverages. Wine was found to contain lithium (0.008–0.045 mg/L), sodium (3.4–200 mg/L), potassium (750–1460 mg/L), calcium (30–90 mg/L) and magnesium (70–115 mg/L) (Marengo & Aceto, 2003). Another study of wine reported the presence of lithium (0–0.09 mg/L), sodium (5.5–150 mg/L), potassium (955–2089 mg/L), calcium (14–47.5 mg/L) and magnesium (82.5–122.5 mg/L) (Lazos & Alexakis, 1989). Sodium (2–24 mg/L), calcium (0.5–4 mg/L) and magnesium (0.02–4 mg/L) were determined in whisky by Adam *et al.* (2002). In a survey of 100 spirits, lithium (0.004–1.26 mg/L), sodium (0.612–94.3 mg/L), potassium (0.34–31.3 mg/L), magnesium (0.40–80.7 mg/L) and calcium (1.36–44.6 mg/L) were detected (Nascimento *et al.*, 1999). Sherry brandies contained sodium (17.8–635 mg/L), potassium (0.11–70.06 mg/L), calcium (0–14.8 mg/L) and magnesium (0.19–11.2 mg/L) (Cameán *et al.*, 2000).

Further elements determined in Italian wines include aluminium, boron, iodine, phosphorus, rubidium, silicone, strontium and tin in the milligram per litre range, barium, beryllium, cerium, cesium, cobalt, gallium, germanium, lanthanum, neodymium, palladium, tellurium, tungsten, vanadium, yttrium and zirconium in the microgram per litre range and dyprosium, erbium, europium, gadolinium, hafnium, holmium, molybdenum, nobelium, praseodymium, rhodium, samarium, terbium, thorium, thulium, titanium, uranium and ytterbium in the nanogram per litre range (Marengo & Aceto, 2003).

(vii) *Inorganic anions*

The fluoride content of alcoholic beverages was found to be very variable. The mean concentration ranged from 0.06 to 0.71 mg/L in beer available in the United Kingdom. Ciders contained a mean of 0.086 mg/L fluoride and wines a mean of 0.131 mg/L fluoride (Warnakulasuriya *et al.*, 2002).

(viii) *Organometals*

Organolead compounds are not classifiable as to their carcinogenicity to humans (Group 3) (IARC, 2006).

As mentioned previously, organolead contamination in wine from automotive sources has rapidly decreased due to the use of unleaded fuel since the 1980s (Lobiński *et al.*, 1994; Teissedre *et al.*, 1994); only limited information is available on the presence of organometals in other alcoholic beverages. Organotin residues in wine and beer could result from the use of organotin pesticides, contaminated irrigation water or the use of non-food-grade polyvinyl chloride products in storage or production facilities (Forsyth *et al.*, 1992a,b). A preliminary survey of wines and beers on the Canadian market indicated that butyltins are the principal organotin contaminants present in these products. Very low levels of phenyl- and cyclohexyltin compounds were detected in both wine and beer (Forsyth *et al.*, 1992a). In a larger survey, 29 of 90 wines (32%) came out positive for organotin compounds. Dibutyltin (23%) and monobutyltin (16%) were the predominant species. Tributyltin, monooctyltin and dioctyltin were found in single instances (Forsyth *et al.*, 1994). In 44 samples of Chinese and international alcoholic beverages, the amounts of monobutyltin and dibutyltin ranged from < 0.016 to 5.687 and from < 0.0022 to 33.257 μg/L, respectively. Tributyltin concentrations were much lower, with a highest level of 0.269 μg/L (Liu & Jiang, 2002).

Organic arsenic species were studied in beer and wine (Herce-Pagliai *et al.*, 1999, 2002). In table wines and sherry, the percentages of total inorganic arsenic were 18.6 and 15.6% lower than those of the organic species; dimethylarsinic acid and monomethylarsonic acid were the predominant compounds, respectively. In most wine samples, dimethylarsinic acid was the most abundant species, but the total fraction of inorganic arsenic was considerable, and represented 25.4% of the total concentration of the element. In beer, a predominant occurrence of organic arsenic species was determined; the contribution of monomethyl arsonic acid was more significant in alcoholic beers than in alcohol-free beers.

(e) Pesticides

Pesticide residues in grapes, wine and their processing products have recently been reviewed (Cabras & Angioni, 2000). The principal parasites of vines in Mediterranean countries are the grape moth (*Lobesia botrana*), downy mildew (*Plasmopora viticola*), powdery mildew (*Uncinula necator*) and grey mould (*Botrytis cinerea*). To control these parasites, insecticides and fungicides were used and, at harvest time, pesticide residues were found on grapes and could pass into the processed products, depending on the technological processing and the concentration factor of the fruit. The application rates of fungicide were only a few tens of grams per hectare and, consequently, fungicide residues on grapes (cyproconazole, hexaconazole, kresoximmethyl, myclobutanil, penconazole, tetraconazole and triadimenol) were very low after treatment and were not detectable at harvest. Pyrimethanil residues were constant up to harvest, whereas fluazinam, cyprodinil, mepanipyrim, azoxystrobin and fludioxonil showed different disappearance rates (half-lives of 4.3, 12, 12.8, 15.2 and 24 days, respectively). The decay rate of organophosphorus insecticides was very fast with a half-life ranging

between 0.97 and 3.84 days. The residue levels of benalaxyl, phosalone, metalaxyl and procymidone on sun-dried grapes equalled those on fresh grapes, whereas residue levels were higher for iprodione (1.6 times) and lower for vinclozolin and dimethoate (one-third and one-fifth, respectively). In the oven-drying process, benalaxyl, metalaxyl and vinclozolin showed the same residue value in fresh and dried fruit, whereas iprodione and procymidone residues were lower in raisins than in fresh fruit.

The wine-making process begins with the pressing of grapes where pesticides on the grape surface come into contact with the must. After fermentation, pesticide residues in wine were always smaller than those on the grapes and in the must, except for those pesticides that did not show a preferential partition between the liquid and solid phase (azoxystrobin, dimethoate and pyrimethanil) and were present in wine at the same concentration as that on the grapes. In some cases (mepanipyrim, fluazinam and chlorpyrifos), no detectable residues were found in the wines at the end of fermentation. Comparison of residues in wine obtained by vinification with and without skins showed that their values generally did not differ. Among the clarifying substances commonly used in wine, charcoal completely eliminated most pesticides, especially at low levels, whereas the other clarifying substances were ineffective. The use of pesticides according to good agricultural practice guaranteed no residues, or levels lower than maximum residue limits at harvest.

Wine and its by-products (cake and lees) are used to produce alcohol and alcoholic beverages by distillation. Fenthion, quinalphos and vinclozolin passed into the distillate from the lees only if present at very high concentrations, but with a very low transfer percentage (2, 1 and 0.1%, respectively). No residue passed from the cake into the distillate, whereas fenthion and vinclozolin passed from the wine, but only at low transfer percentages (13 and 5%, respectively) (Cabras & Angioni, 2000).

The status of pesticide residues in grapes and wine in Italy has been reviewed (Cabras & Conte, 2001). The Italian Ministry of Health reported that, of 1532 grape samples analysed from 1996 to 1999, 1.0, 0.9, 1.8 and 1.9% in each year, respectively, were contaminated. The Italian National Residue Monitoring Programme found that, of 481, 1195 and 1949 grape samples analysed in 1996, 1998 and 1999, 7.9, 6.5 and 2.5%, respectively, were contaminated, while no residues were detected in 259 wine samples. Of the 846 grapes samples and 190 wine samples collected by the National Observatory on Pesticide Residues in 1998 and 1999, a total of 6.1 and 2.1%, respectively, of grapes and 0% of all wine samples were found to contain residues. The low incidence of pesticides in wine was explained by the combined effect of technological processes that lead to a decrease in residues and the fact that large wineries collect grapes from farmers who use different pesticides. Mixing these different grape batches causes a decrease in residues by dilution.

A total of 92 commercial Greek and Yugoslavian wine samples were screened for residues of 84 pesticides. No residues were detected in any of the wine samples from either country (Avramides *et al.*, 2003).

A total of 51 samples of wines imported in Germany (from Spain, Chile and South Africa) were analysed for residues of 27 pesticides. Overall, vinclozolin was detected in 80%, methidathion, captan, quintozene, iprodione and dichlofluanid were detected in 33–61% and tetradifon was found in 6% of the samples. Other pesticides were not detected in any sample. The wine samples from Spain contained no iprodione, but often contained quintozene and methidathion. South African wines contained no methidathion. All Spanish and South African wines, but only 68% of Chilean wines, contained vinclozolin. Most pesticides occurred more commonly in red than in white wines (Pietschman *et al.*, 2000).

A recent survey of pesticide residues in wines on the Swiss market was reported by Edder and Ortelli (2005); 176 wines from conventional cultures were analysed and residues were found in 95% of the samples, which indicated that pesticide treatments were frequently used. Approximately 25 active substances used as fungicides or insecticides were detected. For example, the fungicide fenhexamid was present in 61% of the samples at a maximum concentration of 0.59 mg/L and a Swiss maximum residue level of 1.5 mg/L. The following pesticides were found in less than 5% of the samples: spiroxamine, procymidone, diethofencarb, benodanil, chlorothalonil, cyproconazole, tebufenozide, metalaxyl, spinosad, dimethoate, fuberidazole, oxadixyl, pyrifenox and thiabendazol. The total pesticide residues measured ranged between 1 and 700 μg/L. All samples complied with the legal requirements and none exceeded the maximum residue level. It was observed that Swiss wines are generally more heavily contaminated than imported wines. This was explained by the fact that the climate in Switzerland is more favourable to fungal diseases than that in southern countries. The high level of pesticide residue in Swiss wines was mainly caused by one fungicide, fenhexamide, which is currently one of the fungicides most frequently used in vineyard protection.

Edder and Ortelli (2005) also reported results from 70 organic wines sold on the Geneva area market. Unlike conventional culture, the use of synthetic pesticides is totally forbidden in organic wine growing. Most of the samples were Swiss wines (52), particularly from Geneva producers, and the rest were mostly from France and Italy. Approximately half of the organic wines (33 samples) contained no detectable traces of pesticide residues and 29 samples contained only very low levels (below 10 μg/L). Traces were found, in eight samples, in concentrations ranging between 10 and 34 μg/L. The levels of pesticide residues found in organic wines were much lower than those in conventional wines. Traces below 10 μg/L in organic wines were probably due to environmental contamination.

In beer, pesticide residues may be present in the hops, barley or other cereals that are used as raw materials, and may remain in beer produced from contaminated ingredients. During the first steps (malting, mashing and boiling), pesticides on the barley can pass into the wort in various proportions, depending on the process used, although the removal of material in the form of trub and spent grain tends to reduce the level of contaminants, especially pesticides, that are often relatively insoluble in water. Recent research showed that dinitroaniline herbicide residues (pendimethalin and trifluralin)

practically disappeared (< 0.3%) after boiling the wort, whereas the percentages of the remaining insecticides (fenitrothion and malathion) ranged from 3.5 to 4.3%, respectively. No residues of dinitroaniline compounds were detected in young beer, whereas there was a significant reduction in fenitrothion (58%) and malathion (71%) residues during fermentation. Lagering and filtering processes also reduced the content of organophosphorus insecticides (33–37%). After the storage period (3 months), the content of fenitrothion was reduced by 75%, and malathion residues were below the limit of detection (Navarro *et al.*, 2006).

Miyake *et al.* (1999) showed that none of the agrochemicals spiked into hop pellets were detected in beer because of their loss during boiling and fermentation; however, the levels of these agrochemicals were sufficiently high to be detected in beer when they were not lost through these processes. The same was shown for commercially treated hops. Pesticide residues were not found to carry over into the beer at an appreciable level, except for dimethomorph. Nevertheless, the level of residue was still very low relative to the high levels found on the raw commodity. The potential risk of exposure to pesticide from the consumption of beer produced from hops treated with the agrochemicals studied is low (Hengel & Shibamoto, 2002).

(f) Thermal processing contaminants

In recent years, several heat-generated contaminants have been detected in food, including the chloropropanols, acrylamide and furan. The most probable alcoholic beverage to contain these substances is beer because malt, the main ingredient of beer, is manufactured through heating processes (e.g. kilning or roasting). All three groups of contaminants readily dissolve in aqueous foodstuffs such as beer (Baxter *et al.*, 2005a).

The most abundant chloropropanol found in foodstuff is 3-monochloropropane-1,2-diol (3-MCPD) and, to a lesser degree, 1,3-dichloropropan-2-ol; they have been the centre of scientific, regulatory and media attention as they are considered to be carcinogens (Tritscher, 2004). [3-MCPD is genotoxic *in vitro*, but there is no evidence of its genotoxicity *in vivo* (reviewed by Lynch *et al.* (1998).] The Scientific Committee on Food of the European Commission considered a level of 2 µg/kg bw as an allowable daily intake for 3-MCPD (Scientific Committee on Food, 2001).

3-MCPD is not present in lager or ale malts, but is formed when raw or malted cereals are exposed to temperatures above about 120 °C. 3-MCPD is soluble in water, is readily extracted during mashing and can persist into the beer. However, because of the relatively small proportions of specialty products used in the grist, most beers do not contain detectable levels of 3-MCPD. The precursors for 3-MCPD are lipid and chloride, which occur naturally in raw barley in sufficient quantities to allow the formation of 3-MCPD when the grain is heated; no other inputs are involved (Dupire, 2003).

3-MCPD was found in nine of 24 malt products analysed from food suppliers in the United Kingdom at concentrations above 0.01 mg/kg. Significantly, 3-MCPD was only found in coloured malts, and the highest levels were found in the most intensely

coloured samples. Additional heat treatments, which include heavy kilning or roasting, were assumed to be a significant factor in the formation of 3-MCPD in malt (Hamlet *et al.*, 2002). Breitling-Utzmann *et al.* (2003) analysed a series of German pale and dark brewing malts and malt flours. In the malt flours and the pale brewing malts, only trace amounts of 3-MCPD could be detected, whereas dark brewing malt contained 247 µg/kg 3-MCPD. However, 3-MCPD was not found at levels above 10 µg/kg in lightly or darkly coloured types of beer. The fact that 3-MCPD can react with other food ingredients such as alcohol, aldehydes or acids was given as the reason for the low concentrations in beer. Recent tests by Baxter *et al.* (2005a) found no 3-MCPD in 55 beers in the United Kingdom, with a quantification limit of 10 µg/L.

3-MCPD can occur in foods and food ingredients either as a free compound or esterified with higher fatty acids. Svejkovská *et al.* (2004) reported concentrations of free and bound 3-MCPD in Czech malts. A light malt sample (Pilsner type) contained a free 3-MCPD level of about 0.01 mg/kg and a bound 3-MCPD level of less than 0.05 mg/kg. A sample of dark malt had a free 3-MCPD level of about 0.03 mg/kg, while the bound 3-MCPD level reached 0.58 mg/kg.

Similar to 3-MCPD, highest levels of acrylamide were found in specialty malts. Acrylamide is formed in association with Maillard reactions that occur at two main stages in the malting and brewing process: during wort boiling and in the manufacture of specialty malts, which are made by the caramelization of green malts (Baxter *et al.*, 2005a).

Acrylamide is probably carcinogenic to humans (Group 2A) (IARC, 1994). Precursors of acrylamide formation (free sugars and amino acids) are generated during the 'stewing' phase of crystal malt manufacture, and acrylamide has been detected in these types of specialty malt (Baxter *et al.*, 2005a). Studies using a pilot scale roaster have identified heating conditions that produce crystal malts with significantly lower concentrations of acrylamide without increasing levels of 3-MCPD (Baxter *et al.*, 2005b).

There are only few reports on acrylamide contents in beer. Spiking experiments revealed that acrylamide remained stable in beer (Hoenicke & Gatermann, 2005). Tareke *et al.* (2002) analysed three beer samples from the Swedish market. All samples had acrylamide concentrations below the detection limit of 5 µg/kg. Gutsche *et al.* (2002) analysed 11 German beers and found that only one wheat beer had a detectable acrylamide concentration of 72 µg/kg. Dupire (2003) reported that acrylamide is found in many beers although at much lower concentrations than in other foods. There was a pronounced association with beer colour; little or no acrylamide was detected in either the very palest or the darkest beers, but higher levels were found in beers of intermediate colour. No beers tested contained more than 10 µg/kg. No acrylamide could be detected in ale or lager malt, or in very dark roasted barleys or malts. However, specialty products such as amber and crystal malts did contain significantly higher levels. It appeared that acrylamide is degraded or lost at higher roasting temperatures.

Furan, a very volatile and colourless liquid, has been classified by the IARC as a possible human carcinogen (Group 2B) (IARC, 1995).

EFSA (2004) reported furan concentrations between 5 and 13 μg/kg in six beer samples. Baxter *et al.* (2005a) found equally low levels in a range of beers; the maximum concentration detected was below 20 μg/L. The low levels of furan in beer, together with a lack of correlation with beer colour, suggest that much of the furan present in the raw materials is lost during brewing due to its high volatility.

Despite the relatively low concentrations of all three classes of thermal processing contaminants in beer, Baxter *et al.* (2005a) observed that beer could still make a significant contribution to dietary exposure because of the high volume of its consumption.

(g) Benzene

Benzene is carcinogenic to humans (Group 1) (IARC, 1987). Benzene has been reported in carbonated drinks due to contaminated industrial carbon dioxide. Because relatively low levels of carbonation are used in beer and since there is an indigenous source of carbon dioxide from the fermentation process, the average level of benzene found in products due to the use of contaminated gas was below 10 μg/L and did not exceed 20 μg/L (Long, 1999). In the presence of ascorbic acid and the preservative sodium benzoate, benzene might be formed under certain conditions (Gardner & Lawrence, 1993). Contamination of soft drinks with benzene was recently reported (Hileman, 2006). In mixtures of alcoholic beverages and soft drinks (e.g. alcopops, shandy), contamination with benzene may occur; however, the Working Group noted an absence of studies on this topic.

(h) Miscellaneous contaminants

Several contaminants have been found in single cases in alcoholic beverages. Due to a lack of systematic surveys, the relevance of these contaminants cannot be evaluated.

Monostyrene that may derive from polyester tanks was determined in 168 wines originating from 12 countries. The maximum level found was 7.8 μg/L. In 29% of all products, no monostyrene could be detected (Hupf & Jahr, 1990).

Contamination with polydimethylsiloxanes (0.15–0.35 mg/kg) was detected in four brands of Italian wine (Mojsiewicz-Pieńkowska *et al.*, 2003).

Traces of halogenated acetic acids in beers and wines may arise if the equipment is not cleaned diligently after use of such disinfectants (Gilsbach, 1986; Fürst *et al.*, 1987).

Analysis of nine beer and two wine samples showed the presence of the polycyclic aromatic hydrocarbons (PAH) benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, benzo[*a*]pyrene, benz[*ghi*]perylene and indeno[1,2,3-*cd*]pyrene and, in some cases, traces of fluoranthene, benz[*a*]anthracene and dibenz[*a*,*h*]anthracene. Total contents of PAHs ranged from trace amounts to 0.72 μg/kg (Moret *et al.*, 1995). PAHs were also present in 18 brands of whisky. Concentrations of the indicator carcinogen benzo[*a*]pyrene were 0.3–2.9 ng/L (Kleinjans *et al.*, 1996). The sum of the analysed PAH concentrations

in 26 aged alcoholic beverages ranged from zero for a white wine to 172 ng/L for a 'brandy de Jerez solera'. Benzo[*a*]pyrene was found at concentrations below 10 ng/L (García-Falcón & Simal-Gándara, 2005).

1.7 Biomarkers, biomonitoring and aspects of survey measurement

In the following, two aspects of the measurement of alcohol are highlighted that are particularly relevant to epidemiological assessment of alcoholic beverage consumption: the use of biomarkers and the assessment of lifetime exposure. For a recent overview of other aspects of measurement, see Gmel and Rehm (2004).

1.7.1 *Biomarkers and biomonitoring*

(a) Blood alcohol concentration

No laboratory test is sufficiently reliable alone to support a diagnosis of alcoholism. Sensitivities and specificities vary considerably and depend on the population concerned. The merits and limitations of traditional and newer biomarkers for alcohol abuse (and abstinence) have been examined critically and reviewed (Sharpe, 2001; Musshoff, 2002).

Some conventional biomarkers are described briefly below (Sharpe, 2001).

(b) Ethanol in body fluids

Measurement of alcohol concentrations in blood, urine and breath has a limited, but important role. The results provide no information regarding the severity of alcohol drinking but, when positive, do give objective evidence of recent drinking and can identify increased tolerance.

(c) Serum γ-glutamyl transferase

Serum γ-glutamyl transferase (γGT) activity is increased in the serum of patients with hepatobiliary disorders and in individuals with fairly heavy consumption of alcohol. Serum levels of γGT have been found to be elevated in about 75% of individuals who are alcohol-dependent, with a range in sensitivity of 60–90%. In the general population, progressively higher serum γGT activities are associated with levels of alcohol consumption. Elevated serum γGT is found in 20% of men and 15% of women who consume ~40 g alcohol per day and in 40–50% of men and 30% of women who drink more than 60 g/day. γGT is primarily an indicator of chronic consumption of large amounts of alcohol and is not increased by binge drinking in non-alcohol abusers, unless there is concomitant liver disease. The half-life of γGT is between 14 and 26 days and its level usually returns to normal in 4–5 weeks after drinking ceases. As well as low sensitivity in some clinical situations, one of the major drawbacks to γGT as a marker of excessive alcohol consumption is its lack of specificity, which can vary

from 55 to 100%. Numerous other disorders and drugs can elevate γGT and produce false-positive results, including biliary tract disease, non-alcoholic liver disease, obesity, smoking, *diabetes mellitus*, inflammation and antidepressants. Although γGT is not an ideal screening marker, it is useful in the confirmation of a clinical suspicion of alcoholism.

(d) Serum transaminases

Aspartate aminotransferase (AST) and alanine aminotranferase (ALT) concentrations in serum are often higher in patients who are alcoholics, although generally not more than 2–4 times the upper normal limits; sensitivities are 25–60% for AST and 15–40% for ALT. Serum levels depend markedly on the degree of liver damage and how recently alcohol has been consumed. Acute alcohol intakes of 3–4 g/kg body weight (bw) can lead to a moderate transient increase in AST in healthy subjects within 24–48h. The AST:ATL ratio improves the test: a ratio > 1.5 strongly suggests, and a ratio > 2.0 is almost indicative of, alcohol-induced damage of the liver. One study has shown that the AST:ALT ratio is the best of several markers to distinguish between alcohol-induced and non-alcoholic liver diseases.

(e) Mean corpuscular volume

An increased mean corpuscular volume (MCV) follows chronic heavy alcohol drinking and correlates with both the amount and frequency of alcohol ingestion, but it may take at least 1 month of drinking more than 60 g alcohol daily to raise the MCV above the reference range. It then takes several months of abstinence for MCV to return to normal. The main weakness of MCV is its low sensitivity (40–50%), but its specificity is high (80–90%) and very few abstainers and social drinkers have elevated MCV values.

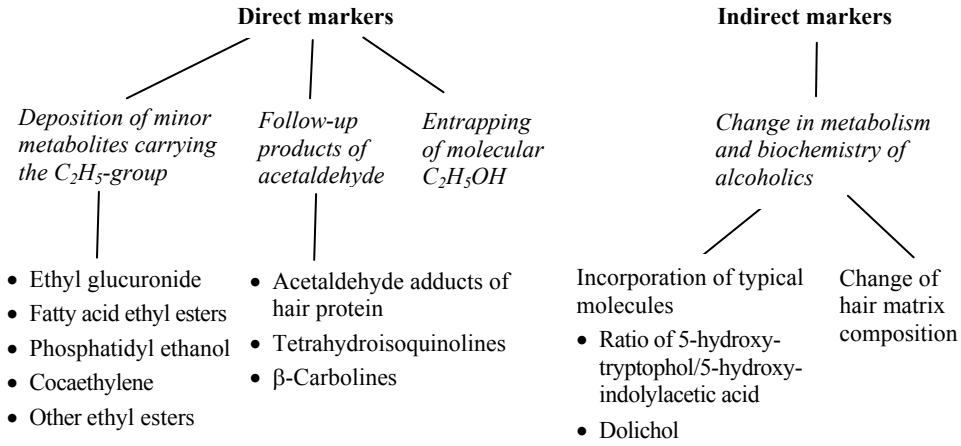
(f) Lipids

Although increased high-density lipoprotein cholesterol or triglycerides can raise suspicion of excessive alcoholic beverage consumption, neither has sufficient sensitivity or specificity to be of use in diagnosis and monitoring.

The conventional marker γGT continues to be the test that combines greatest convenience and sensitivity. Its diagnostic accuracy can be enhanced by combination with other traditional markers such as AST, ALT and MCV (Sharpe, 2001).

The development in chromatographic techniques has enhanced the possibilities for the determination of new and innovative biomarkers of alcohol abuse. New tests have been shown to be useful not only to indicate previous ethanol ingestion, but also to approximate intake and the time when ethanol ingestion has occurred. For such purposes, the determination of ethyl glucuronide in serum or urine samples, the analysis of 5-hydroxytryptophol in urine or the analysis of fatty acid ethyl esters appear to be useful (Musshoff, 2002). These new markers could also be detected in hair (Fig. 1.7).

Figure 1.7. Possible markers of chronically elevated alcohol consumption in hair



From Pragst *et al*. (2000)

A well known advantage of hair analysis is that compounds with a relative short lifetime in blood can be entrapped and are detectable for a long time and at a relatively high concentration in this sample material; hair analysis could provide a good test for the measurement of alcohol consumption (Pragst *et al.*, 2000)

1.8 Regulations on alcohol

1.8.1 *Regulations on the composition of alcoholic beverages*

The *Codex alimentarius* was created in 1963 by FAO and WHO to develop international food standards and guidelines. For alcoholic beverages, the Codex Standards for food additives (*Codex alimentarius*, 2006), for natural flavourings (*Codex alimentarius*, 1987) and contaminants (*Codex alimentarius*, 1997) are of special interest. These standards are discussed in detail in Sections 1.6.6 and 1.6.7. In general, the standards provide some information about suitable additives for alcoholic beverages with maximum levels for certain substances. Maximum levels are also given for certain biologically active substances in natural flavourings. Due to advances in food production and surveillance, the concentrations of some contaminants (e.g. nitrosamines in beer, lead in wine) have been significantly reduced over the past years (see Section 1.6.7 for details). The standards have been incorporated into the national legislation of the majority of countries. However, some countries may impose more specific or more stringent regulations. For example, the European Union has published detailed regulations for food additives and even defines certain categories of spirits such as whisky, rum and vodka (European Council, 1989).

1.8.2 *Regulations on alcoholic beverage consumption*

The available data on regulations for alcoholic beverages for the majority of the WHO Member States have been reviewed by the Global Status Report: Alcohol Policy (WHO, 2004), and the following brief discussion relies mainly on that report.

Regulations for alcoholic beverages are often referred to as alcohol policy or alcohol control policy. Alcohol policy can be defined as measures put in place to control the supply and/or affect the demand for alcoholic beverages, minimize alcohol-related harm and promote public health in a population. This includes education and treatment programmes, alcohol control and harm-reduction strategies. To alleviate or mitigate the burden of alcoholic beverages on societies, most countries have employed some strategies across time to limit or regulate alcoholic beverage consumption and the distribution of alcoholic beverages. Some of these measures have been due to public health concerns, and others have been based on religious considerations or quality control of products, or have been introduced to eliminate private-profit interest or increase government revenue. The different measures can be broadly divided into three main groups: population-based policies, problem-directed policies and direct interventions. The first group are policies that are aimed at altering levels of alcoholic beverage consumption among the population as a whole. They include taxation,

advertising, availability controls (from prohibition to state monopolies, regulations on density of outlets, hours and days of sale), drinking locations, minimum drinking age limits, health-promotion campaigns and school-based education. The second group of policies are aimed at specific alcohol-related problems such as drinking and driving (e.g. promoting random breath testing) or alcohol-related offences. The third group are interventions that are aimed at individual drinkers and include brief interventions, treatment and rehabilitation programmes.

Countries emphasize various policies differently, since each country is unique in its needs and requirements, but there is mounting evidence that strategies are available which clearly impact levels and patterns of alcoholic beverage drinking in a population when implemented with sufficient popular support and continuously enforced. Over the past 20 years, considerable progress has been made in the scientific understanding of the relationship between alcohol policies, levels of alcoholic beverage consumption and alcohol-related harm. The existing evidence ideally should be the basis for formulating polices that protect health, prevent disability and address the social problems associated with alcoholic beverage consumption.

A study of the alcohol policies of 117 WHO Member States looked at the following areas of alcohol policy: restrictions on availability, drink–driving, price and taxation, advertising and sponsorships, and alcohol-free environments. The following gives some examples of the measures implemented, but it should be noted that the study does not cover all countries (WHO, 2004).

About 15% of countries have retail state monopolies, while 74% have alcoholic beverage licensing requirements to sell or serve alcohol. For off-premises sales, many countries also have restrictions on places of sale (59%) and hours of sale (46%) and, to a lesser degree, on days of sale (27%) and density of the outlets (19%).

Only 18% of countries do not have any age requirements for the purchase and consumption of alcoholic beverages. In the majority of countries, the age limit is set at 18 years (61%).

Seven per cent of countries do not have a legal drink–driving limit in place, while most countries (39%) fall in the middle category of having a blood alcohol concentration level of 0.04–0.06 g/100 mL. Of the countries that have existing drink–driving legislation, 46% have no testing or only test rarely for the sobriety of drivers through random breath testing.

With regard to the pricing of alcoholic beverages, the 118 countries showed great differences; however, with regard to median values of relative prices across the countries, a bottle of wine would cost the same as two bottles of beer and a bottle of spirits the same as two bottles of wine. In general, relative price seems closely related to economic development—the more developed a country is, the lower are the prices relative to the average income. In addition, countries that have large domestic production of a beverage tend to have lower prices for this product.

Countries have banned or restricted the advertisement of alcoholic beverages in different media to a varying degree. Television and radio are more controlled than print

media and billboards, and advertising of spirits is more strictly controlled than that of beer and wine. About 24% of countries restrict sponsorship of youth or sports events by the alcohol industry. In countries where advertising of alcohol is allowed, 33% require a health warning of some sort on the advertisement.

Many countries ban drinking in different public domains such as in educational buildings (58%), health care facilities (55%), government offices (48%), workplaces (47%) and public transport (45%). Less controlled are sporting events (26%), parks/streets (24%) and leisure events such as concerts (16%).

Regulations on alcohol are occasionally beverage-specific. Some countries regulate and tax beer according to its strength—the stronger the beer, the higher the tax and the more strict are regulations, for example, on advertising. In a mainly European context, so called alcopops have received special attention. Media, politicians and public health advocates have called for legal restrictions specifically on alcopops, which have been introduced through increased prices, e.g. in France, Germany and Switzerland. The beverage industry avoids the legal restriction on alcopops by creating new designer drinks such as beerpops that do not fall under the special tax (Wicki *et al*., 2006). In Germany, solid alcopops in powder form were developed to evade the alcopop tax. The alcohol is bound to a sugar matrix and, after dissolution in water, the product contains about 4.8% vol alcohol (Bauer-Christoph & Lachenmeier, 2005).

1.9. References

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2. Studies of Cancer in Humans

The available knowledge on the relationship between the consumption of alcoholic beverages and a variety of human cancers is based primarily on epidemiological evidence. The cancers considered to be causally related to alcoholic beverage consumption in the previous *IARC Monographs* on alcohol drinking (IARC, 1988) included those of the upper aerodigestive tract (oral cancer and cancers of the oropharynx, hypopharynx, larynx and oesophagus), liver, colon, rectum and possibly breast. Since 1988, many cohort and case–control studies on the relationship between consumption of alcoholic beverages and these and other cancers have been conducted in many different countries. The most comprehensive evidence has been obtained from several large cohort studies that investigated different cancer sites and, when available, different types of alcoholic beverage consumed. These cohort studies are described briefly in Section 2.1. The case–control studies are described in the sections pertaining to particular cancer sites. Additionally, two meta-analyses (Bagnardi *et al.*, 2001; Corrao *et al.*, 2004) found significantly increased risks for cancer at all of the aforementioned sites associated with alcohol drinking. Meta odds ratios less than 1.00 were found for melanoma, cervical cancer and kidney cancer. A positive dose-response relationship was observed for most of these sites. [The Working Group noted that the Bagnardi *et al.*, 2001 study appears to be more comprehensive than Corrao *et al.*, 2004, although a detailed list of the studies included in both meta-analyses is not given].

In reviewing these epidemiological studies, the Working Group took particular note of those that adequately considered issues related to bias and confounding. In this respect, since much of the evidence relates to cancers known to be caused by tobacco smoking, confounding by the effects of tobacco smoking is critical for many sites. Thus, the few studies that considered the risks from alcoholic beverage consumption in lifelong nonsmokers are particularly important.

The terminology and methods used to characterize the combined effects of two or more agents have been poorly standardized. For the purposes of this monograph, interdependence of effects is called ‘effect modification’, and the terms ‘synergism’ and

'antagonism' are used to describe the consequences of the interdependence of disease when both risk factors are present (Rothman & Greenland, 1998).

The effect of a risk factor for a disease may be estimated on an absolute (additive) scale or a relative (multiplicative) scale. In general, epidemiological studies use the relative risk scale, and present ratio measures (e.g. the relative risk that compares risk in the exposed group to that in a referent, typically unexposed, group). In those studies in which the findings depart (in either direction) from this scale, lack of synergy in the multiplicative scale (i.e. similar relative risks in low and high incidence groups) can imply synergy in the additive scale, and thus have important public health implications.

The Working Group did not evaluate studies of precancerous lesions, e.g. adenomas and polyps of the rectum, precursor lesions of the oral cavity or intraepithelial neoplasia of the cervix uteri for several reasons: firstly, many studies considered invasive cancers, secondly, precancerous lesions do not necessarily progress to cancer during the subjects' lifetime and thirdly, the implications of studies on lesions that have a high propensity not to progress to invasive cancer are uncertain.

In this respect, the pooling of results from many small studies and meta-analyses provide an opportunity to evaluate sites for which relatively few cases accrue. The Working Group placed substantial weight on the findings for cancer sites for which studies had been pooled.

Assessment of alcoholic beverage intake in case–control and cohort studies

In cohort studies, it may be difficult to obtain lifetime estimates of exposure to alcoholic beverages, especially for those studies that only collected data at baseline, since there is a risk that individuals may change their drinking habits during the period of observation. Even in case–control studies, in which, theoretically, there is an opportunity to collect exposure data up to the date of interview, problems of recall, including difficulties in recollection and classical recall bias, may result in complications in the development of reliable estimates of cumulative exposure. In general, the Working Group felt that the classification of subjects as current drinkers (light and heavy), former drinkers and never drinkers is valid and that data on amounts drunk per day (or per week for light or occasional drinkers) are also sufficiently reliable. However, estimates of various patterns of exposure to alcoholic beverages, especially binge drinking, are not available in most studies. Nevertheless, in spite of the differences in the quality and reliability of data on exposure between cohort and case–control studies, when data were available that produce findings that are congruent from both types of study, the Working Group placed much weight upon such evidence.

Alcoholic beverage intake in epidemiological studies has usually been assessed by interviews or questionnaires regarding usual intake over a period of months or years. Two main methods have been used: semiquantitative questionnaires (e.g. how often on average do you consume a bottle of beer?) or frequency–quantity questionnaires (e.g. how many days per week do you drink beer? And, on the days you drink, how many

bottles of beer do you drink?). These questions can refer to consumption of either alcoholic beverages in general or specific beverages (e.g. beer, wine and liquor), which can then be summed to compute total intake of alcohol. Total alcohol intake is calculated by assuming (based on knowledge of the contents in the population studied) a specific amount of alcohol for each type of beverage (e.g. 12 g of alcohol per glass of wine, 13 g per bottle of beer and 15 g for one glass of liquor). Alcoholic beverage consumption can also be assessed by diet diaries or 24-hour recalls, but multiple days of intake are usually required because intake in many populations can vary considerably from day to day or over a year. Because these methods impose a substantial burden on the participant and/or investigator, they have rarely been used in cohort studies and, in case–control studies, they are not appropriate because alcoholic beverage consumption may have changed due to the occurrence of disease. However, these methods provide a quantitative measure of intake that can serve as a criterion of validity in subsamples of a study population.

Multiple sources of error can contribute to imperfect measurement of alcoholic beverage consumption. These include errors in reporting the frequency of intake, which can be influenced by many factors including inaccurate memory, social norms of desirability and subtle indications of judgment by the interviewers. Also, serving size and alcohol content of the same serving size can vary over time for the same person and between people. However, some of these sources of variation are tempered by averaging over time; for example, although serving size may vary from drink to drink over time for an individual, the average intake for one person compared with that of another may vary to a much lesser degree. Also, the differences among individuals in alcoholic beverage intake are large, and errors in serving sizes are usually minor in relation to the overall range of alcoholic beverage intake.

The validity of alcoholic beverage intake as assessed in typical epidemiological studies has been evaluated by comparisons with daily diaries or recalls, by associations with biological variables that reflect alcoholic beverage intake and by their ability to predict well established relationships such as those between alcoholic beverage consumption and risks for cirrhosis. Correlations between alcoholic beverage intake assessed by standardized questionnaire and diaries or 24-hour recalls have been evaluated in many studies and are high, generally ranging from 0.7 to 0.9 (Kaaks *et al*., 1997; Willett, 1998; Lee *et al*., 2007). Although the mean reported intakes in these studies are usually well below that of the average population, based on production or sales of alcoholic beverages, these comparisons are misleading because a larger percentage of alcoholic beverages is consumed by a small group of heavy drinkers (Greenfield & Rogers, 1999), who are less likely to participate in epidemiological studies.

The relationship between alcoholic beverage intake assessed by a questionnaire and that assessed by detailed recording can be used to adjust relative risks for measurement error in epidemiological studies (Rosner, 1995; Willett, 1998); several variations of this approach have been used, but they basically consist of two steps: first a regression calibration is conducted by assessing intake using a detailed method in a

sample of the study population; then the true intake (intake assessed by the detailed method) is regressed on the 'surrogate method' (intake assessed by the questionnaire). The relationship between surrogate intake and true intake, expressed by the regression slope, is then used to correct the observed relative risk for error. Refinements of this method allow the calculation of confidence intervals (CIs) and adjustment for errors in covariates (Rosner, 1995). This approach to measurement error has been used in large cohort studies of alcoholic beverages and cancer, and the adjustments have been small (less than 5% change in relative risks) (Smith-Warner *et al*., 1998; Cho *et al*., 2004; Lee *et al*., 2007).

Studies on biomarkers, such as HDL (Giovannucci *et al*., 1991), provided strong evidence that alcoholic beverage consumption assessed by questionnaire has high validity.

The evidence described above suggests that the questionnaires commonly used in epidemiological studies provide reasonably accurate quantitative assessments of alcoholic beverage intake over the time period considered, typically a few months or a year. In a cohort study with long follow-up, repeated measures of exposure over time may provide a more accurate measure of long-term intake and allow a more detailed examination of temporal relationships (Willett, 1998). In both case–control and cohort studies, it may be useful to ask about alcoholic beverage intake during past periods of life (for example between the ages 20 and 30 years) because, for some cancers, that may be the period of maximal susceptibility. Few data are available of the validity of reported remote intake.

In summary, evidence based on comparisons with detailed assessments of alcoholic beverage intake using diaries or recalls and non-specific biomarkers indicate that recent alcoholic beverage consumption assessed by the questionnaires typically used in epidemiological studies has a high degree of validity within the ranges of consumption in the general population, and that important associations will not be missed. Further, the results of correction analysis of measurement error suggest that estimates of quantitative dose–response relationships for recent intake are reasonably accurate. However, with long follow-up, repeated measures of intake may be useful. The assessment of intake at remote periods of life may be useful, but the validity of these measures has not been well quantified.

2.1 Description of cohort studies

Information on cohort studies of cancer and alcoholic beverage consumption in general populations and special populations is given in Tables 2.1a and 2.1b, respectively.

2.1.1 *Studies in general populations (Table 2.1a)*

These studies are classified by the country in which the study was conducted.

Table 2.1a. Cohort studies of cancer and alcoholic beverage consumption in general populations

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Asia/Oceania								
Australia								
Melbourne Collaborative Cohort Study	1990–94	Baglietto *et al*. (2005, 2006)	1990–2003	Cohort of 41 528 men and women, aged 27–75 years	Interview	Cases/ deaths	Breast, prostate	
China								
Zoucheng/ Shandong Study	1982	Zhang *et al*. (1997)	1982–94	7809 men and 7994 women from probabilistic sample of general population in three counties, aged ≥20 years	Baseline questionnaire		Lung	No dose–response found for frequency, amount or duration of drinking; lung cancer mortality found in crude analyses
Linxian Nutrition Intervention Trial	1986	Guo *et al*. (1994); Tran *et al*. (2005)	1986–2001	Nested case–control study; a cohort of 29 584 adults in a randomized intervention trial, aged 40–69 years	Structured interview	Cases	Oesophagus, stomach	Drinking alcoholic beverages was relatively uncommon in Lin Xian residents, but was reported by 22% of the cancer patients.

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Shanghai Men's Study	1986–89	Yuan *et al.* (1997)	1986–95	18 244 male residents of Shanghai, aged 45–64 years	Structured interviewed	Deaths	Upper aerodigestive tract, stomach, colon, rectum, liver, lung	Joint effects of alcohol and smoking examined
Jiashan County Screening Study	1989–90	Chen *et al.* (2005a)	1989–2001	31 087 men and 33 256 women screened for colorectal cancer in 1989–90, aged ≥30 years	Interviewer-administered standardized questionnaire	Deaths	Colon, rectum	No differences in risk for men and women; among only one case among former drinkers
Yunnan Tin Corporation Miners Cohort	1992	Lu *et al.* (2000a)	1992–97	7965 miners, aged ≥40 years; 10 years of high-risk professional activity	Interviewer-administered questionnaire		Lung	
Japan								
Japanese Physicians' Study	1965	Kono *et al.* (1985, 1986, 1987)	1965–83	5130 male Japanese physicians, aged 27–89 years	Self-administered questionnaire	Deaths	Upper aerodigestive tract, oesophagus, stomach, large bowel, liver, lung	Joint effects of alcohol and tobacco examined

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Six Prefecture Study	1965	Hirayama (1989, 1992); Kinjo *et al*. (1998)	1966–82	122 261 male and 142 857 female, Japanese adults aged 40–69 years at the baseline of 1965, from 29 public health districts in six prefectures of Japan	Interviewer-administered standardized questionnaire	Deaths	Mouth, pharynx, oesophagus, stomach, proximal colon, rectum, sigmoidcolon, upper and lower digestive tract, liver, prostate	Joint effect of alcohol and tobacco examined
Life Span Study	1979–81	Goodman *et al*. (1997a)	1979–89	Analytical cohort of 22 000 residents of Hiroshima and Nagasaki in 1945 [age range not stated]	Self-administered questionnaire	Cases	Breast	No association in women who drank beer, sake or other alcoholic beverages
Chiba Center Association Study	1984	Murata *et al.* (1996)	1984–93	Nested case–control study; cohort of 17 200 men part of a gastric mass screening survey	Self-administered questionnaire	Cases	Oral cavity, pharynx, oesophagus, stomach, colon, rectum, liver, pancreas, biliary tract, larynx, lung, prostate urinary bladder	The effect of tobacco smoking was examined.

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Aichi Cancer Center Hospital Study	1985	Kato *et al*. (1992a)	1985–89	3 914 subjects who underwent gastroscopic examination	Self-recorded questionnaire, cancer registry and death certificate	Cases	Stomach	Non-significant increase for risk in stomach cancer among past and daily drinkers
Aichi Prefecture Study	1986	Kato *et al*. (1992b)	1986–91	9 753 Japanese men and women, aged ≥40 and ≥30 years, respectively	Baseline survey using a mailed questionnaire; death certificate	Cases	Stomach	Association between alcohol intake and stomach cancer slightly weakened when smoking status, diet and family history of stomach cancer were included in the multivariate analysis.
Japanese Collaborative Cohort Study (JACC)	1988–90	Lin *et al*. (2002, 2005); Sakata *et al*. (2005), Wakai *et al*. (2005); Nishino *et al*. (2006)	1988–99	110 792 (46 465 men, 64 327 women), aged 40–79 years	Self-administered questionnaire	Cases/ deaths	Oesophagus, colon, rectum, breast, pancreas, lung,	Relative risks by smoking status reported

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Hospital-Based Epidemiologic Research Program at the Aichi Chiba Center (HERPACC)	1988–99	Inoue *et al.* (2003)	1988–2000	Nested case–control study of 78 755 hospital patients, aged 32–85 years	Self-administered questionnaire	Cases	Pancreas	Increased risk in men and women, separately; the increased risk in former drinkers may be due to ill-health
Japan Public Health Center Study Cohort I	1990	Sasazuki *et al.* (2002)	1990–99	27 063 men, 27 435 women born in 1930–49, aged 40–59 years at baseline	Self-administered questionnaire, death certificates, cancer registry	Cases	Stomach	Data for women collected but not presented
Takayama City Cohort	1992	Shimizu *et al.* (2003)	1993–2000	Analytic cohort of 13 392 men and 15 695 women, aged ≥35 years	Self-administered standardized questionnaire	Cases	Colon, rectum	Significant dose–response relationship between alcohol consumption and colon cancer in both sexes

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Japan Public Health Center Study Cohort II	1993	Otani *et al.* (2003)	1993–99	42 540 male and 47 464 female Japanese, aged 40–69 years	Self-administered standardized questionnaire	Cases	Colon, rectum	In men, no interaction of smoking with alcoholic beverage consumption for colon, rectal or colorectal cancer; no associations for colorectal cancer in women
North America								
Canada								
Nutrition Canada Survey Cohort	1970–72	Ellison (2000)	1970–93	12 795 respondents to a population survey, aged 50–84 years	Interviews	Cases	Prostate	
National Breast Screening Study	1980–85	Friedenreich *et al*. (1993); Jain *et al.* (2000a,b); Rohan *et al*. (2000); Navarro Silvera *et al.* (2005)	1980–93	Total 89 835 women, aged 40–59 years; 56 837 women, aged 40–59 years	Self -administered lifestyle questionnaire	Cases	Breast, endometrium, thyroïd	

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
USA								
American Registry of Radiologic Technologists	1926–82	Boice *et al*. (1995); Freedman *et al*. (2003)	1926–89	146 022 radiologic technologists, aged 23–90	Self-administered questionnaire	Cases	Melanoma, breast	Nested case–control study
University of Pennsylvania Alumni Study	1931–40	Whittemore *et al*. (1985)	1931–78	13 356 male and 4 076 female students examined at the University of Pennsylvania in 1931–40	College physical examination, questionnaires	Cases/ deaths	Buccal cavity, oesophagus, stomach, small intestine, colon, rectum, liver, biliary tract, pancreas, larynx, trachea, bronchus, lung, melanoma, other skin, breast, urogenital organs, prostate, testis, urinary bladder, kidney, brain, thyroid, Hodgkin disease, non-Hodgkin lymphoma, leukaemia, other cancer	Data on collegiate alcohol consumption limited

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Minnesota Breast Cancer Family Study	1944–52	Vachon *et al*. (2001)	1944–90	Breast cancer patients from the Tumor Clinic of the University of Minnesota; 544 families representing 4418 family members	Telephone interviews (surrogate and self-reported)	Cases	Breast	Higher risk in first-degree relatives for daily versus never drinkers; validation study verified 136 of 138 breast cancers through medical and pathology records
US Army Veterans Study	1944–45	Robinette *et al*. (1979)	1946–74	4401 chronic alcoholic male veterans, hospitalized in 1944–45	Death certificates	Deaths	Buccal cavity, pharynx, nasopharyngitis, oesophagus, stomach, large intestine, rectum, pancreas, larynx, trachea, bronchus, lung, prostate, testis, penis, urinary bladder, kidney, malignant lymphoma, lymphatic and haematopoeitic leukaemia, ureter	Compared with age-matched male veterans hospitalized for nasopharyngitis; no individual exposure data; no information on potential confounders

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Framingham Study (1948) and Framingham Offspring (1971)	1948, 1971	Gordon & Kannel (1984); Zhang *et al*. (1999); Djoussé *et al*. (2002, 2004)	1948–present	In 1948, 5209 subjects, aged 28–62 years at first examination; in 1971, 5124 children of the original cohort participated	Questionnaire, physical examination	Cases	Colon, lung, breast, urinary bladder	
Western Electric Company Cohort Study	1957	Garland *et al.* (1985)	1957–76	1954 men, aged 40–55 years, employed for at least 2 years at the Western Electric Company	28-day diet history and interview	Cases	Colorectal	Compared alcoholic beverage intake reported at initial examination; no information regarding the exposure or relative risk given

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
American Cancer Society Prevention Study I (CPSI)	1959–60	Garfinkel *et al.* (1988); Boffetta & Garfinkel (1990)	1960–72	Analytical cohort of 581 321 women across the USA, aged >30 years; 276 802 white men, aged 40–59 years, volunteers for the American Cancer Society in 25 states	Self-administered questionnaire	Deaths	Buccal cavity, oesophagus, larynx, breast,	Based on mortality only
Tecumseh Community Health Study	1959–60	Simon *et al.* (1991)	1959–87	Analytical cohort of 1954 women, aged >21 years	Interview-administered questionnaire	Cases	Breast	No difference in risk by menopausal status (but low numbers)

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Harvard Alumni Study	1962, 1966	Whittemore *et al*. (1985); Sesso *et al*. (2001)	1988–93	7612 male Harvard alumni	Questionnaire	Cases/ deaths	Buccal cavity, oesophagus, stomach, small intestine, colon, rectum, liver, biliary tract, pancreas, larynx, trachea, bronchus, lung, melanoma, other skin, breast, prostate, testis, urogenital organs, urinary bladder, kidney, thyroid, Hodgkin disease, non-Hodgkin lymphoma, leukaemia, brain, other cancer	Relative risk adjusted for smoking.
Kaiser Permanente Medical Care Program Study	1964	Klatsky *et al*. (1981, 1988); Hiatt *et al*. (1988, 1994); Iribarren *et al*. (2001); Efird *et al*. (2004)	1964–88	Original cohort contained 182 357 Kaiser Foundation Health Plan members	Self-administered questionnaire	Deaths/ cases	Colon, rectum, pancreas, prostate, brain, thyroid	

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
American Men of Japanese Ancestry Study/ Honolulu Heart Study	1965–68	Pollack *et al.* (1984); Kato *et al.* (1992c); Nomura *et al.* (1990, 1995); Stemmermann *et al.* (1990); Chyou *et al.* (1993, 1995, 1996)	1965–93	6701 American men of Japanese ancestry, born from 1900–19, and residing on the Hawaiian island of Oahu, 8 006 subjects for the Honolulu Heart Study	Structured interview	Cases	Oral cavity, pharynx, oesophagus, upper aerodigestive tract, stomach, colon, rectum, liver, biliary tract, pancreas, larynx, lung, prostate, urogenital organs, urinary bladder, renal, lymphoma, leukaemia	SEER Registry used as a reference
Lutheran Brotherhood Insurance Study	1966	Hsing *et al.* (1990, 1998a); Kneller *et al.* (1991); Chow *et al.* (1992); Zheng *et al.* (1993)	1966–86	17 633 male white policy holders, aged ≥35 years, of the Lutheran Brotherhood Insurance Society	Questionnaire	Deaths	Stomach, colorectum, pancreas, lung, prostate	Relative risk for total alcoholic beverage consumption and risk for lung cancer not available

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
[name not given] Hawaiian Cohort Study	1968	Le Marchand *et al*. (1994)	1968–89	41 400 persons in the State of Hawaii, (20 316 men), aged >18 years	Lifestyle questionnaire	Cases	Prostate	Data recorded on current drinking status, age when drinking started, amount and frequency of intake of beer, wine, saké and hard liquor.
NHANES I Epidemiologic Follow-up Study	1971–75	Schatzkin *et al*. (1987); Yong *et al*. (1997); Breslow *et al*. (1999); Su & Arab (2004)	1971–93	14 407 men and women, aged 25–74 years, who completed a medical examination	Interviewer-administered questionnaire	Cases	Colon, lung, breast, prostate	Joint effects of tobacco and alcohol examined (Yong *et al*, 1997)

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Nurses' Health Study	1976	Willett et al. (1987a,b); Fuchs *et al*. (1995); Garland *et al*. (1999); Colditz & Rosner (2000); Michaud *et al*. (2001); Chen *et al*. (2002a); Wei *et al*. (2004); Lee *et al*. (2006)	1976–2004	121 700 female nurses aged 30-55; cohort size after exclusions: 80 253	Questionnaire	Cases	Colon, rectum, pancreas, breast, renal	Relative risk adjusted for smoking; joint effects of tobacco and alcohol examined
Breast Cancer Detection and Demonstration Project (BCDDP)	1979–81, 1987–89	Flood *et al*. (2002)	1993–98	45 264 women, aged 40–93 years, participated in a breast cancer screening programme	Mailed, self-administered standardized questionnaire	Cases	Colon, rectum	Interaction with smoking where the association of alcoholic beverages with colorectal cancer observed only in nonsmokers
New York State Cohort	1980	Bandera *et al*. (1997)	1980–87	27 544 men and 20 456 women long-term residents of New York State	Mailed questionnaire	Cases	Lung	Relative risk adjusted for smoking

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Leisure World Study	1981–83, 1985	Shibata *et al.* (1994)	1982–90	Analytical cohort of 13 976 men and women 65–80 years	Self-administered questionnaire	Cases	Pancreas	
	1981–82	Wu *et al.* (1987)	1981–85	11 888 residents of a retirement community	Mailed, self-administered standardized questionnaire	Cases	Colorectum	For men, results similar for right and left colon, but with lower statistical significance for left colon; for women, association was apparent but not significant for the left colon.
American Cancer Society, Cancer Prevention Study-II (CPS II)	1982	Boffetta *et al.* (1989); Thun *et al.* (1997); Coughlin *et al.* (2000); Feigelson *et al.* (2003)	1982–96	Analytical cohort of 1.2 million men and women, recruited 1982, aged >30 years	Self-administered questionnaire	Cases/ deaths	Mouth, pharynx, oesophagus, colon, rectum, liver, pancreas, larynx, breast, multiple myeloma, lymphatic and/or haematopoietic	Cases not verified, nested case–control design (Boffetta *et al.*, 1989)
Iowa 65+ Rural Health Study	1982	Cerhan *et al.* (1997)	1982-93	3673 residents (1420 men), aged >65 years, from two rural counties in Iowa	Interview	Cases	Prostate	

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Second Cancers Following Oral and Pharyngeal Cancers Study	1984–85	Day *et al.* (1994a)	1984–89	1090 first primary cancers of the oral cavity and pharynx included in a multicentre population-based case–control study from 4 areas of the USA	Interviewer-administered questionnaire	Cases	Oral cavity, pharynx, oesophagus, larynx, lung	Information on alcoholic beverage type and cessation of alcoholic beverage drinking
Iowa Women's Health Study	1985–86	Potter *et al*. (1992); Gapstur *et al*. (1993); Harnack *et al*. (1997, 2002); Chiu *et al*. (1999); Kushi *et al*. (1999); Folsom *et al*. (2003); Kelemen *et al*. (2004)	1986–2001	99 826 randomly selected women, aged 55–69 years, from Iowa driver's licence list	Mailed questionnaire	Cases	Colon, rectum, pancreas, lung, breast, endometrium, ovary, kidney, non-Hodgkin lymphoma, lymphatic/ haematopoietic cancers	Nested case–control study; odds ratio for total alcoholic beverage consumption not available; joint effect of smoking and alcohol examined (Potter *et al.*, 1992)

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Cohort of Iowa Men	1986–89	Cantor *et al.* (1998) Putnam *et al.* (2000)	1986–1995	Analytical cohort of 1572 men, aged ≥65 years	Mailed, self-administered standardized questionnaire and supplemental telephone interview	Cases	Prostate, urinary bladder	
Health Professionals Follow-up Study (HPFS)	1986	Giovannucci *et al.* (1995); Michaud *et al.* (2001); Platz *et al.* (2004); Wei *et al.* (2004); Lee *et al.* (2006)	1986–2000	HPFS: 51 529 men, aged 40–75 years	Self-administered standardized questionnaire	Cases	Colon, rectum, pancreas, prostate, renal,	Combined analysis of NHS and HPFS, performed by Lee *et al.* (2006), Wei *et al.* (2004), Michaud *et al.* (2001), relative risk adjusted for smoking.
Study of Osteoporotic Fractures	1986–88	Lucas *et al.* (1998)	1986–89	Analytical cohort of 8015 white women, aged ≥65 years	Self-administered questionnaire	Cases	Breast	No association in women with a positive family history, but few cases (n=20)

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
National Health Interview Survey (NHIS)	1987	Breslow *et al.* (2000)	1987–95	Sub-cohort of 20 195 adults, aged 18 years or older, who completed the Cancer Epidemiology Supplement	Cancer Epidemiology Supplement questionnaire (in-home interview)	Cases	Lung	Deaths arising within the first year of follow-up excluded; relative risk adjusted for smoking
The β-Carotene and Retinol Efficacy Trial (CARET)	1988	Omenn *et al.* (1996)	1988–1995	4060 male asbestos workers and 14 254 smokers	Questionnaire	Cases	Lung	Intervention trial
Prostate Lung, Colorectal and Ovarian Cancer Screening Trial (PLCOCST)	1993–2001	Stolzenberg-Solomon *et al.* (2006)	1993–2003	Analytical cohort of 25 400 women, aged 55–74 years	Self-administered questionnaire	Cases	Breast	
California Teachers Study	1995–96	Horn-Ross *et al.* (2004); Chang *et al.* (2007)	1995–2003	Analytical cohort of 103 460 women, aged 21–84 years	Self-administered questionnaire	Cases	Breast, ovary	
Scandinavia								
Denmark								
Copenhagen City Heart Study	1964	Prescott *et al.* (1999); Petri *et al.* (2004)	1964–96	Analytical cohort of 13 074 women, aged 20–91 years	Self-administered questionnaire	Cases	Breast, lung	Relative risk adjusted for smoking (Prescott *et al.*, 1999)

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Glostrup Population Study	1964–86	Høyer & Engholm (1992); Petri *et al*. (2004)	1964–90	Analytical cohort of 5207 women; aged 30–80 years	Self-administered questionnaire	Cases	Breast	
Copenhagen Male Study	1970	Gyntelberg (1973); Hein *et al*. (1992); Suadicani *et al*. (1993)	1970–88	Cohort of 5249 men aged 40–59 years	Danish Central Population Register and Quetsionnaire		Colon, rectum, lung	
Danish Diet, Cancer and Health Study	1993–97	Tjønneland *et al*. (2003, 2004)	1993–2000	Analytical cohort of 23 778 women; aged 50–64 years	Self-administered questionnaire	Cases	Breast	
Finland								
α-Tocopherol β Carotene Cancer Prevention (ATBC) Study	1985–88	Glynn *et al*. (1996); Woodson *et al*. (1999); Stolzenberg-Solomon *et al*. (2001); Mahabir *et al*. (2005); Lim *et al*. (2006)	1985–93	29 133 white male smokers, aged 50–69 years in southwestern Finland	Self-administered questionnaire	Cases/ deaths	Colon, rectum, pancreas, lung, renal, non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma	Relative risk by type of alcoholic beverage and by smoking categories reported (Woodson *et al*., 1999; Mahabir *et al.,* 2005)

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Norway								
Norwegian Cohort of Waitresses	1932–1978	Kjaerheim & Andersen (1994)	1959–91	5314 waitresses organized in the Restaurant Workers Union	Employers lists from Restaurant Workers Union	Cases	Tongue, mouth, pharynx, oesophagus, stomach, colon, rectum, liver, gall bladder, pancreas, larynx, lung, melanoma, breast, cervix uteri, other female genital, urinary bladder, kidney, brain, leukaemia	No individual exposure data. Estimates not adjusted for smoking.
Norwegian Cohort	1960	Heuch *et al*. (1983)	1960–73	Analytical cohort of 16 713 men and women, aged 45–74 years	Self-administered questionnaire	Cases	Pancreas	Joint effects of tobacco and alcohol examined
	1968	Kjaerheim *et al*. (1998)	1968–92	10 960 men born in 1893–1929	Mailed survey	Cases	Oral cavity, pharynx, oesophagus, larynx	Relative risk adjusted for smoking
	1984–86	Lund Nilsen *et al*. (2000)	1984–96	22 895 men (≥ 40 years) with no history of any cancer	Questionnaire	Cases	Prostate	Relative risks adjusted for smoking

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
HUNT-1 Cohort Study	1984–1986	Sjödahl *et al.* (2007)	1984–2002	69 962 inhabitants of the country of Nord-Trondelag, at least 20 years of age; follow-up by linkage to the Norwegian Cancer Registry and the Norwegian Central Person Registry	Health survey	Cases	Stomach	
Norwegian Women and Cancer Study (NOWAC)	1991–97	Dumeaux *et al.* (2004)	1991–2001	Analytical cohort of 86 948 women, aged 30–70 years	Self-administered questionnaire	Cases	Upperaerodigestive tract, pancreas, breast	Relative risk not adjusted for smoking
Sweden								
Swedish Twin Registry Study	1967	Grönberg *et al.* (1996); Terry *et al.* (1998, 1999); Isaksson *et al.* (2002)	1967–92	Analytical cohort of 21 884 men and women recruited in 1961, aged 36–75 years	Questionnaire	Cases	Stomach, pancreas, endometrium, prostate	No adjustment for smoking (Terry *et al.*, 1999)

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Swedish Mammography Cohort	1987–90	Holmberg *et al*. (1995); Rashidkhani *et al*. (2005); Suzuki *et al*. (2005); Larsson *et al*. (2007)	1987–2004	66 651 Swedish women, aged 40–76 years, living in the counties of Västmanland and Uppsala, who responded to a questionnaire	Self-administered questionnaire	Cases	Stomach, endometrium, breast, renal	Nested case-control design (Holmberg *et al*., 1995)
Malmö Diet and Cancer Cohort	1991–96	Mattisson *et al*. (2004)	1991–2001	Analytical cohort of 11 726 women; aged ≥ 50 years	Interview-administered diet history	Cases	Breast	Relative risk adjusted for smoking
Western Europe								
France								
Supplementation and Vitamins and Minerals Antioxidant Study (SU.VI.MAX)	1994	Hirvonen *et al.* (2006)	1994–2002	Analytical cohort of 4 396 women, aged 35-60 years	Telephone-administered 24-h recalls	Cases	Breast	

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Netherlands								
Netherlands Cohort Study	1986	Goldbohm *et al*. (1994); Schuurman *et al*. (1999); Zeegers *et al*. (2001); Schouten *et al*. (2004); Balder *et al*. (2005); Loerbroks *et al*.(2007)	1986–97	58 279 men and 62 573 women from 204 municipal population registries, aged 55–69 years	Mailed self-administered standardized	Cases	Colon, rectum, lung, endometrium, ovary, prostate, urinary bladder	Case–cohort design; for colon cancer, possible limitation: misclassification of alcohol consumption; no adjustment for smoking (Schuurman *et al*. 1999)
United Kingdom								
British Doctor's Study	1978	Doll *et al*. (1994, 2005)	1978–2001	Male physicians born between 1900 and 1930	Mailed questionnaire	Deaths	Large bowel, rectum, lung, other cancers,	Relative risk for alcohol use on lung cancer mortality not given; no adjustment for smoking
Oxford Vegetarian Study	1980–84	Sanjoaquin *et al*. (2004)	1980–99	10 998 vegetarian and non-vegetarians (4162 men, 6836 women), aged 16–89 years; no personal history of cancer	Self-administered standardized questionnaire	Cases	Colorectum	Association between alcohol partially confounded by smoking

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
General Practitioner Research Database Study	1994	Lindblad *et al.* (2005)	1994–2001	287 oesophageal adenocarcinomas and 10 000 controls, aged 40–84 years	Interview	Cases	Oesophagus, stomach	Nested case–control study
Multi-Country								
European Prospective Investigation into Cancer and Nutrition (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, Netherlands, UK)	1992	Boeing (2002); Rohrmann *et al.* (2006); Tjønneland *et al.* (2007);	1992–2004	521 457 from 10 European countries; most study centres recruited from the general population; other sources of recruitment included members of insurance plans, blood donors, mammographic screening, employees of enterprises, civil servants	Dietary instruments developed specifically for each country	Cases	Oral cavity, pharynx, oesophagus, lung, breast	Relative risks reported by histological type and by smoking status

Table 2.1a (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Multicentric European Study of Second Primary Tumours Italy, Spain, Switzerland	1979–82	Dikshit *et al.* (2005)	1979–2000	A cohort of 928 cases of laryngeal cancer from a multicentric population-based case–control study from, Italy, Spain and Switzerland	Interviewer-administered questionnaire	Cases	Oral cavity, pharynx, oesophagus, lung	

HERPACC, Hospital-based Epidemiologic Program at Aichi Cancer Center; HUNT, Helseundersøkelsen i Nord-Trøndelag; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses Health Study; PLCOCST, Prostate Lung, Colorectal and Ovarian Cancer Screening Trial

(a) Asia/Oceania

(i) *Australia*

Melbourne Collaborative Cohort Study

This cohort was recruited in 1990–94 from the Melbourne metropolitan area, using the electoral rolls, advertisements and community announcements in the local media. The cohort comprised 41 528 people (17 049 men) aged 27–75 years. A structured interview included alcoholic beverage consumption for those who had ever drunk 12 alcoholic drinks in a year. Cancer cases were ascertained from the Victoria Cancer Register through to 31 December 2003 (Baglietto *et al*., 2005, 2006).

(ii) *China*

Zoucheng/Shandong Study

A 12.5-year prospective cohort study was carried out in a rural area of Zoucheng city. A probabilistic sample from three townships, aged 20 years and older, was identified in 1982 and consisted of 7809 men and 7994 women. An individual case card was created for each of the villagers and their smoking and drinking habits were recorded. Data concerning their death and change in health were collected annually. Mortality follow-up was to 1994 (Zhang *et al*., 1997).

Lin Xian Nutrition Intervention Trial Study

In the frame of an intervention trial for micronutrients, approximately 30 000 residents of the Lin Xian region, aged 40–69 years, were interviewed in 1985 to obtain information on usual dietary intake, tobacco use, alcoholic beverage consumption, family history of cancer and other factors. The cohort was followed-up from 1986 through to May 1991, with little loss to follow-up. Information on cause of death and incidence of cancer was collected from local hospitals or a study medical team. Relative risks were adjusted for potential confounders as well as the vitamin/mineral intervention group (Guo *et al*., 1994; Tran *et al*., 2005).

Shanghai Men's Study

A cohort of 18 244 male residents of four small geographically defined communities from a wide area of Shanghai, aged 45–64 years, were enrolled between January 1986 and September 1989 (80% of eligible subjects). A structured questionnaire was completed at a face-to-face interview. The information obtained included level of education, history of tobacco use and alcoholic beverage consumption, current diet and medical history. Cancer incidence was ascertained through the population-based Shanghai Cancer Registry and vital status was ascertained by inspection of the Shanghai death-certificate records. Only 108 subjects were lost to follow-up, which continued until February 1993 (Yuan *et al*., 1997).

Jiashan County Screening Study

Screening for colorectal cancer was initiated in May 1989–April 1990 when all residents, aged 30 years and over, in 10 small towns in Jiashan County, Zhejiang Province, China, were invited for screening and a face-to-face questionnaire was completed

by professional interviewers including information on alcoholic beverage drinking and smoking habits. Of 75 842 eligible individuals, 31 087 men and 33 256 women responded, about 70% of whom were farmers. Subjects were followed through the Cancer Registration System and a rapid reporting system from the Colorectal Registry, that was documented to be 95% complete. Deaths were ascertained through the Jiashan County Death Registration System through to 2001. Out-migration was estimated to be less than 1% annually (Chen *et al*., 2005a).

Yunnan Tin Corporation Miners Cohort

A cohort of 7965 Yunnan Tin Corporation miners aged 40 years and over was established in 1992. Cumulative radon exposure for each subject was obtained by adding-up the estimated working level months, for each job held at the Yunnan Tin Corporation before baseline screening. A questionnaire was administered by interviewers at baseline which included data on alcoholic beverage consumption. Follow-up continued until 1997 (Lu *et al*., 2000a).

(iii) *Japan*

Japanese Physicians' Study

A survey of smoking habits and alcoholic beverage consumption among physicians in western Japan was carried out using self-administered questionnaires in 1965. From 6815 male respondents in nine prefectures (51% response rate), a cohort of 5477 male physicians was established. Vital status was followed until 1983 and was confirmed by various medical associations. Copies of death certificates were obtained from the District Legal Affairs Bureau and the cause of death was coded with the ICD-8. After exclusions, the analysies were performed on 5130 men. Statistical analysis was performed using the Cox proportional hazards model (Kono *et al*., 1985, 1986, 1987).

Six Prefecture Study

In 1965, 122 261 men and 142 857 women, aged 40–69 years (95% of the census population), in 29 health centre districts from six prefectures in Japan were interviewed. The six prefectures were selected as being representative of the entire country. The one-page questionnaire administered at baseline included questions on smoking, alcoholic beverage consumption and dietary habits, occupation and marital status. A record linkage system was established for the annual follow-up. During the 16-year follow-up period, 8% of the cohort migrated from the original health districts. Deaths among cohort members were monitored by linkage to vital statistics kept at each public health centre (Hirayama, 1989; 1992; Kinjo *et al*., 1998).

Life Span Study

The Life Span Study cohort originally consisted of 100 000 survivors [sex distribution not reported] of the atomic bomb blasts in Hiroshima and Nagasaki. The cohort was expanded in 1968 and 1985 by adding approximately 10 000 survivors each time. The total cohort included approximately 120 000 individuals, of whom approximately 27 000 were non-exposed controls. Information on smoking was obtained from three interview surveys conducted on a subgroup of the entire cohort in 1963–64, 1964–68

and 1968–70, and four postal surveys conducted on various subgroups in 1965, 1969, 1979 and 1980.

The cancer incidence in 61 505 survivors for whom smoking data were available was reported. For 42% of this group, information on smoking was available from at least two surveys. Information on cancer incidence and mortality was obtained from the Radiation Effects Research Foundation tumour registry and mortality database. Poisson regression models were used to fit log-linear relative risk and linear excess relative risk models (Akiba, 1994; Land *et al.*, 1994; Goodman *et al.*, 1995).

Chiba Center Association Study

The Chiba Center Association Study was a nested case–control study based on a cohort population of 17 200 male participants in a mass screening for gastric cancer by the Chiba Cancer Association in Japan in 1984. Cancer cases in cohort members were detected by record linkage to the Chiba Cancer Registry. The participants were followed from 1984 until 1993. For each cancer case, two controls were selected from the cohort population by matching on sex, birth year and area of residence (Murata *et al*., 1996).

Aichi Cancer Center Hospital Study

The relation of atrophic gastritis, other gastric lesions and lifestyle factors to stomach cancer risk was prospectively studied among 3,914 subjects who underwent gastroscopic examination and responded to a questionnaire survey at the Aichi Cancer Center Hospital. During 4.4 years of follow-up on average, 45 incident cases of stomach cancer were identified at least three months after the initial examination. If the baseline endoscopic findings indicated the presence of atrophic gastritis, the risk of developing stomach cancer was increased 5.73-fold, compared with no indication at the baseline. The risk further increased with advancing degree of atrophy and increasing extension of atrophy on the lesser curvature. These trends in the relative risks were statistically significant ($P = 0.027$ and $P = 0.041$, respectively). The risk for stomach cancer was statistically significantly increased among subjects with gastric polyps, but not among those with gastric ulcer. Stomach cancer cases tended to consume more cigarettes, alcohol, rice, pickles and salted fish gut/cod roe and less fruits and vegetables and to have more family histories of stomach cancer than noncases, although these differences were not statistically significant. The results of the present study provide additional evidence on the relation between atrophic gastritis and stomach cancer and suggest a need for intensive follow-up of patients with atrophic gastritis and gastric polyps (Kato *et al.,* 1992a).

Aichi Prefecture Study

Stomach-cancer mortality was prospectively studied among 9753 Japanese men and women who first responded to a mailed questionnaire in 1985 and were then followed through May 31, 1991. During this follow-up period, 57 stomach-cancer deaths were identified. Current smokers had an increased risk of death from stomach cancer compared with never-smokers (relative risk (RR) = 2.29, 95% confidence interval (CI): 1.15-4.56), but there was no dose-response to number of cigarettes smoked.

Daily alcohol drinkers who consumed 50 ml or more of alcohol per day also had a greater risk than nondrinkers (RR = 3.05, 95% CI: 1.35-6.91). There was no association between stomach-cancer mortality and individual food consumption except a positive association with fruit intake. However, frequent use (greater than or equal to 3-4/week) of meat broiling and traditional style Japanese salad preparation in their cooking procedures were positively associated with stomach-cancer mortality. The RR values compared with infrequent use (less than or equal to 1-2/month) were 2.27 (95% CI: 1.06-4.85) and 3.10 (95% CI: 1.40-6.85), respectively. A positive family history of cancer, especially stomach cancer, significantly increased the risk for stomach-cancer death (RR = 2.01, 95% CI: 1.12-3.63). The effects of these variables remained after adjustment for other variables (Kato *et al.,* 1992b).

Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risk

A baseline survey was conducted in 45 areas throughout Japan from 1988 through to 1990 by investigators from 25 centres. At the end of 1990, a total of 127 500 (125 760) inhabitants were enrolled in this cohort. Among them, 110 792 subjects (46 465 men, 64 327 women aged between 40 and 79 years at baseline) were followed-up through to the end of 1997 and subsequently to 1999. The baseline data, which included details on alcoholic beverage consumption and tobacco use were collected using a self-administered questionnaire. Population registers were used to identify subjects who had moved out of a study area. The date and cause of death were confirmed annually or biannually by reviewing death certificates with the approval of the Prime Minister's office. In one analysis of 38 600 women participants in the cohort, follow-up was to 31 December 1997 (Lin *et al*., 2002; 2005; Sakata *et. al*., 2005; Wakai *et al*., 2005; Nishino *et al*., 2006).

The Hospital-based Epidemiological Research Program at the Aichi Cancer Center (HERPACC)

A database was established in 1988 in the Aichi Cancer Center that included all outpatients on a first visit who completed a self-administered questionnaire on lifestyle factors which included information on alcoholic beverage consumption. The database was routinely linked with the hospital cancer-registry to identify cases of cancer. Between January 1988 and December 1999, 78 755 subjects were included. Cases were frequency-matched by age to cancer-free subjects, selected at random from the database, and the study was analysed as a nested case–control study (Inoue *et al*., 2003).

The Japan Public Health Center Study Cohorts (I and II)

A population-based cohort of 27 063 men and 27 435 women was established in 1990 from subjects who registered their addresses in 14 administrative districts of four Public Health Center areas. All subjects were born between 1930 and 1949 (40–59 years of age at baseline). Subjects were asked to reply to a lifestyle questionnaire, which included information on alcoholic beverage consumption. A total of 43 149 subjects (20 665 men (76%), 22 484 women (82%)) returned their questionnaires. All subjects were followed from 1 January 1990 to 31 December 1999. All deaths of cohort subjects were based on death certificates from each Public Health Center. Newly diagnosed cases of

cancer were reported by hospitals in and around the study areas when the birth date and residence fulfilled the criteria for inclusion into the cohort. (Sasazuki *et al*., 2002).

A second cohort was established in 1993, and included six Public Health Centers in six prefectures, which comprised all residents aged 40–69 years (except for Osaka, which included other ages and was excluded from this cohort). By combining the first with the second cohort and excluding subjects deemed to be ineligible, a study population of 42 540 men and 47 464 women was defined for analysis. Mortality data were obtained from the Ministry of Health, Labour and Welfare; those who moved to other areas were identified from residential registers; cancer cases were identified through local major hospitals and population-based cancer registries. Follow-up was until 31 December 1999 (Otani *et al.,* 2003).

Takayama City Cohort

A cohort was established in September 1992 among 36 990 residents of Takayama City, aged 35 years or older, who were asked to complete a questionnaire that included data on alcoholic beverage consumption. A total of 34 018 (92%) subjects responded. Details on patients with colon and rectal cancer were obtained from the two major hospitals in Takayama City, which cover about 90% of the colorectal cases in the city. Details of subjects who moved away from the city during the study were obtained from the residential registers. Follow-up was until 31 December 2000. After excluding those with incomplete data and non-melanoma skin cancer, the analysis cohort comprised 13 392 men and 15 659 women (Shimizu *et al*., 2003).

(b) North America

(i) *Canada*

Nutrition Canada Survey Cohort

The Nutrition Canada Survey was conducted beween September 1970 and December 1972, and incorporated 12 795 people from all 10 provinces in Canada who responded to the invitation to participate (a 47% response rate), together with 3295 unsolicited volunteers who participated. A retrospective cohort study was performed by linking the records for those aged 50–84 years to the Canadian Cancer Registry and the Canadian National Mortality Data Base to the end of 1993. Data on alcoholic beverage consumption had been collected at baseline by a 24-hour diet recall and a 1-month food-frequency questionnaire (Ellison, 2000).

National Breast Screening Study

The National Breast Screening Study is a multicentre, randomized controlled trial of mammography screening for breast cancer. Between 1980 and 1985, 89 835 women aged 40–59 years were randomized. In 1982, a semiquantitative diet questionnaire, which included data on alcoholic beverage consumption, was distributed to new attendees and previously enrolled women returning to the screening centres for further screening. A total of 56 837 women returned the dietary questionnaires. Reports on the diet cohort are based mainly on a case–cohort analysis, with a 10% subsample selected

at random from the cohort as controls. The National Breast Screening Study diet cohort is included in the Pooling Project (Friedenreich *et al*., 1993; Jain *et al*., 2000a,b; Rohan *et al*., 2000; Navarro Silvera *et al*., 2005).

(ii) *USA*

American Registry of Radiologic Technologists

The cohort was based upon 143 517 radiological technologists certified by the American Registry of Radiologic Technologists for at least 2 years during 1926–1982. A questionnaire was mailed to 132 519 who were known to be alive and data on cancers diagnosed were obtained from that questionnaire, with 79 016 female respondents. Thus, this study was essentially of factors associated with the prevalence of breast cancer among those still alive at the time of the questionnaire, and was analysed as a nested case–control study (Boice *et al*., 1995; Freedman *et al*., 2003).

University of Pennsylvania Alumni Study

Physical and social characteristics recorded at college physical examination and reported in subsequent questionnaires to alumni in 1962 or 1966 by 50,000 former students from Harvard University and the University of Pennsylvania were reviewed for their relationship to major site-specific cancer occurrence. The records of 1,359 subjects who died with a major site-specific cancer in a 16- to 50-year follow-up period and of 672 subjects who reported such a cancer by mail questionnaire in 1976 or 1977 were compared with those of 8,084 matched classmates who were known to be alive and free of cancer at the time subjects with cancer had died or had been diagnosed. Cigarette smoking, as reported both in student years and years as alumni, predicted increased risk for cancers of the respiratory tract, pancreas, and bladder. Student coffee consumption was associated with elevated risk for leukemia, but it was unrelated to cancers of the pancreas and bladder. Male students with a record of proteinuria at college physical examination experienced increased risk for kidney cancer, and those with a history of tonsillectomy experienced increased risk for prostate cancer. Students who at college entrance reported occasional vague abdominal pain were at elevated risk for pancreatic and colorectal cancers in later years. Increased body weight during college was associated with increased risks for kidney and bladder cancers, whereas for alumni this index was associated only with kidney cancer. Increased weight-for-height during college (but not in 1962 or 1966) predicted increased occurrence of female breast cancer. Jewish students experienced elevated risk for subsequent cancers of the female breast, colon, and combined colorectum. These and other findings are presented as clues deserving further exploration for any etiologic significance that they may hold for the cancer sites studied (Whittemore *et al*., 1985).

Minnesota Breast Cancer Family Study

A family study on breast cancer was initiated between 1944 and 1952, including a total of 544 families and data on 4418 family members. Information was obtained from interviews, medical history questionnaires and death certificates. Follow-up of this cohort was initiated in 1990; families in which the proband was diagnosed with breast

cancer before 1940 were excluded. Telephone interviews were completed with 6194 living women and 2974 surrogates from 426 multigeneration families; after excluding those with missing data, data on 9032 women were available for analysis (Vachon *et al*., 2001).

US Army Veterans Study

A cohort of 4401 US Army service men hospitalized for chronic alcoholism in 1944-45 was drawn as a sample from records of the US Department of Defense and the Veterans' Administration. Of these, 98% were <40 years of age at the time of hospitalization. They were matched for age with an equal number of enlisted men hospitalized for acute nasopharyngitis during the same period. Deaths in these groups were ascertained through the Veterans' Administration Beneficiary Identification and Records Locator Subsystem, and death certificates were obtained to code for cause of death. Follow-up for death was estimated to be 90-98% complete. No information was available on the drinking habits of individual members of the cohort or on average consumption by the cohort members. It was noted that only 7.5% of the chronic alcoholics had been discharged from military service for medical disability, including alcoholism. The mortality experience of the cohort was compared with that of the matched cohort of nasopharyngitis patients, and the mortality of both cohorts was compared with that of US males for selected causes of death. Overall mortality was approximately 80% higher in the alcoholics group than in the nasopharyngitis group (SMR, 1.9) (Robinette *et al.,* 1979).

Framingham Study and Framingham Offspring Study

The Framingham Study began in 1948. The original cohort included 5209 persons (2873 women) aged 28–62 years at the first examination, who were examined biennially thereafter. In 1971, examination was begun on many of the children of the original cohort and their spouses. Of 5124 subjects aged 12–60 years enrolled in the Framingham Offspring Study, 2641 were women, and have been followed at 4-year cycles. Information on alcoholic beverage consumption was obtained at the examinations. Cancer cases have been identified by self reports and, for non-respondents, by linkage with the National Death Index and a cancer registry, with confirmation of diagnosis by searching for medical records. The median follow-up was 34.3 years (range, 0.2–42.5 years) for the original cohort and 19.3 years (range, 0.2–22.6 years) for the offspring cohort (average for the total cohort of 9821 subjects, 27.3 years) (Gordon & Kannel, 1984; Zhang *et al*., 1999; Djoussé *et al*., 2002, 2004).

Western Electric Company Cohort Study

In 1957, 3102 men were randomly selected from the population of 5397 men aged 40-55 years who had been employed for at least 2 years at the Western Electric Company's Hawthorne Works in Chicago; 2080 (67.1%) agreed to participate in a long-term, prospective, epidemiological study (Western Electric Health Study). Another 27 men served as a pilot group, bringing to 2107 the total number initially examined from October, 1957 to December, 1958. Approximately 65% were first and second generation Americans, predominantly of German, Polish, or Bohemian ancestry; most of the

others were descendants of earlier emigrants from the British Isles. The men worked at various occupations associated with the manufacture of telephones and related products (Garland et al., 1985).

American Cancer Society Cancer Prevention Study I (CPS-I)

Between October 1959 and February 1960, volunteers for the American Cancer Society in 25 states recruited more than one million subjects, aged 30 years and over, from among their friends, neighbours and acquaintances. Families were enrolled, with the condition that there be at least one person aged over 45 years in the family. All family members over 30 years of age were requested to fill out a detailed four-page questionnaire. Vital status was checked yearly to 1965 and again in 1971 and 1975. Death certificates of deceased participants were obtained from state health departments. For 581 321 women, deaths were ascertained for 12 years (Garfinkel *et al*., 1988). For 276 802 white men in the cohort aged 40–59 years, enrolled in 1959 and followed for 12 years, 9293 deaths from all cancers were observed and related to alcoholic beverage consumption obtained at baseline (Boffetta & Garfinkel, 1990).

Tecumseh Community Health Study

A community health study was initiated in the town of Tecumseh, MI, through interviews and medical examinations in 1959–60. Information on alcoholic beverage consumption was obtained by trained interviewers. Follow-up was for up to 28 years by mailed questionnaires, with review of death certificates to confirm cause of death. The cohort included in the analysis totalled 1954 women (Simon *et al*., 1991).

Harvard Alumni Study

A cohort of undergraduates who had entered the University of Harvard between the years of 1916 and 1950 was identified when they responded to a health questionnaire sent out in 1962 or 1966. Updated information was obtained from 13 905 cohort members from periodic surveys that assessed lifestyle habits and medical history. The questions asked for information on daily amount of cigarette smoking, age at start and cessation of cigarette smoking, weight, height and physical activity. In surveys conducted in 1988 and 1993, participants were asked whether a cancer had been diagnosed by a physician. Deaths that occurred up to 1992 were traced using information from the alumni office to obtain death certificates. The authors claimed that mortality follow-up was virtually complete (Whittemore *et al.,* 1985; Sesso *et al.,* 2001).

Kaiser Permanente Medical Care Program Study

The first cohort for this study was selected from 87 926 white or black men and women who underwent at least one multi-phasic health check-up within the Kaiser Permanente Medical Care Program from July 1964 and August 1968 and who were followed through to 1976. From data in the baseline questionnaire, four groups were extracted, each of 2015 persons, matched for age, race and cigarette smoking, according to the usual number of alcohol-containing drinks/day (0, ≤2, 3.5 and ≥6). Mortality was ascertained by a search of California death indexes (Klatsky *et al*., 1981).

An expansion of this cohort comprised 94 549 men and 110 425 women, aged 10–89 years at baseline in 1964–73, who underwent at least one multi-phasic health

check-up within the Kaiser Permanente Medical Care Program and were followed through to 1997 (Iribarren *et al*., 2001). Cancer incidence was ascertained from the first health examination through the San Francisco–Oakland Surveillance, Epidemiology and End Result (SEER) programme and the Northern California Kaiser Permanente Medical Care Program. Attrition due to termination of health plan coverage and death was of the order of 2% per year; the median follow-up time was 19.9 years (range, <1–33 years) (Klatsky *et al*., 1981; Iribarren *et al*., 2001).

Between 1978 and 1985, a similar cohort was established, which included 122 894 (for one study 106 203) men and women who received a multi-phasic health examination during 1978–84. Cancer cases were ascertained as for the first cohort (see above). Follow-up was eventually to 31 March 1999 (Klatsky *et al*., 1988; Hiatt *et al*., 1988, 1994; Efird *et al*., 2004).

American Men of Japanese Ancestry Study and Honolulu Heart Study

A cohort of 8006 American men of Japanese ancestry, born during the years 1900–19 and who resided on the Hawaiian island of Oahu, were interviewed and examined clinically from 1965 to 1968. Information obtained at the interview included age, smoking history, usual occupation, type of housing, education and religion. A food-frequency questionnaire and a 24-hour dietary recall was also administered. Newly diagnosed cases of cancer were identified through continuous surveillance of Oahu hospitals and linkage with the Hawaii Tumor Registry through to 1994 (Pollack *et al*., 1984; Nomura *et al*., 1990, 1995; Stemmermann *et al*., 1990; Kato *et al*., 1992c; Chyou *et al*., 1993, 1995, 1996).

Lutheran Brotherhood Insurance Study

A cohort of 26 030 white male life insurance policy holders of the Lutheran Brotherhood Insurance Society was identified in 1966, of whom 17 633 responded to a mailed food-frequency questionnaire and were followed for 20 years. Little difference was observed between responders and non-responders with regard to age, urban or rural residence, policy status and cancer mortality at 11.5 years of follow-up. The questionnaire included questions on tobacco use and the longest held occupation, frequency of consumption of 35 food items and the consumption of coffee, beer and spirits. Death certificates were coded for underlying and contributory causes of death. Person–years were accumulated up to death, loss to follow-up or the end of the study in 1986. The age-adjusted relative risks for cancer mortality resulting from exposure to alcoholic beverages were computed using Poisson regression. Statistical interaction between smoking and other risk factors was also examined. About 23% of the cohort members were lost to follow-up due to maturation or lapse of their policies (Hsing *et al*., 1990, 1998a; Kneller *et al*., 1991; Chow *et al*., 1992; Zheng *et al*., 1993).

Hawaiian Cohort Study

In this study, the consumption of high-fat animal products, raw vegetables, and fresh fruits, as well as obesity, smoking, and drinking was evaluated in relation to subsequent occurrence of prostate cancer. Data from a cohort of 20,316 men of various ethnicities were collected between 1968-1989 in Hawaii. A total of 198 incident

cases with invasive prostate cancer were identified by computer-assisted linkage of this cohort to the statewide Surveillance, Epidemiology, and End Results registry. Weight was not consistently associated with prostate cancer, but there was an association with height. These associations were stronger in men diagnosed before age 72.5 years. The risk estimates for raw vegetable and fresh fruit intakes were close to 1.0. Smoking and alcohol drinking appeared to be unrelated to risk (Le Marchand *et al*., 1994)

The National Health and Nutrition Examination Survey (NHANES) I Epidemiological Follow-up Study

The first NHANES was performed in 1971–75, based on a probability sample of the civilian non-institutionalized population of the USA. Follow-up surveys were conducted and, by the end of 1992, 96% of the cohort was traced, and death certificates were traced for 98% of decedents. The analytical cohort comprised 3968 men and 6100 women aged 25–74 years at baseline (Schatzkin *et al*., 1987; Yong *et al*., 1997; Breslow *et al*., 1999; Su & Arab, 2004).

Nurses' Health Study

In 1976, a cohort of 121 700 female registered nurses was assembled in the USA. At enrolment, the nurses completed a mailed questionnaire on risk factors for cancer and heart disease. Responses to food-frequency questionnaires were also collected in 1980, when 98 462 nurses responded, and in 1984, 1986 and 1990. The response rate to follow-up questionnaires was almost 96% through to 1990. Family members were the main source of information on vital status for non-respondents but the National Death Index was also used. Multiple logistic regression models were used to compute odds ratios, after controlling for age, total energy intake and other potentially confounding variables. A subset of 89 538 women who reported alcoholic beverage consumption in 1980 were assessed by follow-up questionnaires in 1982 and 1984, and cases of cancer were identified (Willett *et al*., 1987a). A subsequent report on 85 709 women who reported alcoholic beverage consumption in 1980 and were followed for 12 years considered mortality related to alcoholic beverage consumption (Fuchs *et al*., 1995). A second cohort of 116 671 women was established from women who completed a more detailed dietary questionnaire in 1989, and were followed by questionnaires every 2 years to 1995 (Garland *et al*., 1999). This study is included as two cohorts (those initially assembled and followed to 1986, and those who completed a more detailed dietary questionnaire in 1986 and were followed subsequently) in the Pooling Project (Willett *et al*., 1987b; Fuchs *et al*., 1995; Garland *et al*., 1999; Colditz & Rosner, 2000; Michaud *et al*., 2001; Chen WY *et al*., 2002a; Wei *et al*., 2004; Lee *et al*., 2006).

Breast Cancer Detection Demonstration Project (BCDDP)

A cohort was established based upon the participants in the US Breast Cancer Detection Demonstration Project, which was established between 1973 and 1980 at 29 screening centres in 27 cities and involved 283 222 women. A follow-up cohort was established in 1979 from a subset of the participants, which included 4275 women who had been diagnosed with breast cancer, 25 114 women who had biopsies indicating benign breast disease, 9628 women who were recommended for biopsy but did not have

the procedure and an additional 25 165 women not recommended for biopsy, matched with the other subjects on age, time of entry into the programme, ethnicity, screening centre and length of participation in the Project and comprised a total of 64 182 women. Between 1979 and 1981, 61 433 of the women completed a baseline food-frequency questionnaire, which included questions related to alcoholic beverage consumption. A follow-up questionnaire was sent between 1993 and 1995 in which self-reports of cancer occurrence were made. Medical records confirmed the diagnosis for 80% of these. Non-respondents were contacted by telephone. Women with prevalent colorectal cancers (reported at baseline) were excluded. The final analytical cohort comprised 45 264 women, of whom 40 865 had complete follow-up through to 1995–98. This cohort is included in the Pooling Project (Flood *et al*., 2002).

The New York State Cohort

A 45-item food-frequency questionnaire was sent to 265 000 residentially stable subjects selected from a private sampling frame in New York State in 1980 and was returned by 57 968 (32 689 men, 25 279 women). Follow-up was passive through to December 1987 from the records of the New York State Department of Health's vital statistics section and cancer registry. A second questionnaire was sent to the subjects who responded in 1980 who were not listed as dead or diagnosed with cancer. Assessment of the validity of follow-up was conducted in a nested case–control study, with each case matched by age, race, gender and country of residence to one control subject randomly selected from a pool of controls alive at the time of diagnosis of the case. The analytical cohort comprised 27 544 men and 20 456 women (Bandera *et al*., 1997).

Leisure World Study

A detailed health questionnaire was mailed to all residents of a retirement community in California in 1981, and to new residents in 1982, 1983 and 1985. A response rate of 62% was achieved overall (11 888 participants initially, and 13 979 later). Almost all of the residents were Caucasians of the upper-middle class, about two-thirds were women, and 80% were aged 65–86 years. Histological diagnosis of cancer was obtained from local hospitals. All participants were sent a follow-up questionnaire every 2 years. The latest follow-up reported (Shibata *et al*., 1994) was to 30 June 1990 (Wu *et al*., 1987; Shibata *et al*., 1994).

American Cancer Society Cancer Prevention Study II (CPS-II)

The CPS-II is a nationwide prospective mortality cohort study of nearly 1.2 million adults, aged 30 years or more, enrolled by volunteers of the American Cancer Society in 1982. As in CPS-I, enrolment was based on families and excluded persons in institutions and military service and others who would be difficult to trace. Each participant completed a four-page postal questionnaire on tobacco and alcoholic beverage use and diet. Deaths were ascertained from the month of enrolment until 31 December 1996 through personal enquiries made by the volunteers in 1984, 1986 and 1988 and later through linkage with the National Death Index. In one analysis (Thun *et al*., 1997), 490 000 men and women were followed from 1982 through to 1991, after

excluding those with unquantified smoking and alcoholic beverage use, those missing all data on wine, beer and spirit consumption, and former drinkers who were non-drinkers. In another analysis, 66 561 postmenopausal women were followed for mortality from 1992 to 1997–98 (Boffetta *et al*., 1989; Thun *et al*., 1997; Coughlin *et al*., 2000; Feigelson *et al*., 2003).

Iowa 65+ Rural Health Study

In late 1981 and 1982, 80 percent of the non-institutionalized residents aged 65 years and older who lived in Iowa and Washington counties, Iowa (US), were enrolled into the Iowa 65+ Rural Health Study (n = 3,673), which was one of the four Established Populations for Epidemiologic Studies of the Elderly (EPESE) sites. These two counties are primarily rural, with several small towns. Of the 1,420 men enrolled into the cohort, only the 1,155 men completing the full-form baseline interview were eligible for inclusion into this report. The full-form baseline interview was conducted in the respondent's home by a trained interviewer, and included data on a variety of demographic, health, and social characteristics (Cerhan *et al.,* 1997).

Second Cancers Following Oral and Pharyngeal Cancers Study

The cohort comprised 1090 first primary cancers of the oral cavity and pharynx included in a multicentre population-based case–control study in four areas of the USA in 1984–85, and followed to 1989. Information on alcoholic beverage consumption and tobacco use was obtained at the time the subjects were originally enrolled, and was updated for 80 cases with second cancers and 189 sex-, study area- and survival-matched cancer patients free of second cancers, with analysis as a nested case–control study (Day *et al*., 1994a).

Iowa Women's Health Study

The Iowa Women's Health Study was conducted on a cohort of women selected randomly from the Iowa Department of Transportation Driver's License list of whom 41 837 completed a postal questionnaire (response rate, 42.7%) sent in 1986. The questionnaire covered information on age, smoking history, physical activity and level of education. The Harvard semiquantitative food-frequency questionnaire was used to assess diet and alcoholic beverage consumption. Incident cases of cancer were ascertained through the Health Registry of Iowa, which is a population-based cancer registry in the SEER Program of the National Cancer Institute. The Iowa Women's Health Study is included in the Pooling Project (Gapstur *et al*., 1992, 1993; Potter *et al*., 1992; Harnack *et al*., 1997, 2002; Chiu *et al*., 1999; Kushi *et al*., 1999; Folsom *et al*., 2003; Kelemen *et al*., 2004).

Cohort of Iowa men

A retrospective cohort was formed from the controls in a population-based case–control study of six cancer sites conducted 1986–89 in Iowa (Cantor *et al*., 1998). These controls were randomly selected from the Iowa population using driver's licence records for men aged 40–64 years and from the files of the US Health Care Financing administration for men aged 65 years and older. Of 1989 men invited, 1601 (81%)

agreed to participate. Follow-up was through to 1995. Incident cases of cancer were identified by linkage with the Iowa State Cancer Registry (Putnam *et al*., 2000).

Health Professionals' Follow-up Study (HPFS)

In 1986, a cohort of 51 529 male dentists, optometrists, osteopaths, podiatrists, pharmacists and veterinarians in the USA were asked to respond to a mailed semi-quantitative food questionnaire. The questionnaire included questions on age, current and past tobacco use, marital status, height and weight, ancestry, medications, disease history, physical activity and diet. Only men who completed the diet questionnaire adequately at baseline and who reported no cancer other than non-melanoma skin cancer were included in the analysis. After all baseline exclusions, 47 931 men, 40–75 years old in 1986 and followed for 6 years comprised the first analysis cohort (Giovannucci *et al*., 1995); subsequently, follow-up was extended to 31 January 1998 (Platz *et al*., 2004). Follow-up questionnaires were sent in 1988, 1990 and 1992 to ascertain new cancer cases. Family members and the National Death Index were the main source of information on vital status of non-respondents. This study is included in the Pooling Project (Giovannucci *et al*., 1995; Michaud *et al*., 2001; Platz *et al*., 2004; Wei *et al*., 2004; Lee *et al*., 2006).

Study of Osteoporotic Fractures

This cohort was based upon a multicentric prospective study of white women aged 65 years and over who were recruited from population-based listings and followed for the occurrence of osteoporotic fractures. One year after the baseline examination, participants completed a questionnaire. Incident cancers were identified by follow-up at year 3, and verified by perusal of medical records. Those who had died were excluded, leaving 8 015 for analysis (Lucas *et al*., 1998) .

National Health Interview Survey (NHIS)

The 1987 National Health Interview Survey included a core questionnaire completed by 47 240 households containing 122 859 persons. One adult, aged 18 years and over, from each household who completed the core questionnaire was randomly selected to complete a cancer-control or cancer-epidemiology supplement, the latter comprising 22 080 individuals. The response rate for the core questionnaire was 95% and that for the cancer epidemiology supplement was 86%. Records from this cohort were linked to the National Death Index to provide a mortality follow-up through to 31 December 1995. Usable data were available for 20 195 participants (Breslow *et al*., 2000).

The β-Carotene and Retinol Efficacy Trial (CARET)

This trial of the potential chemopreventive effects of β-carotene and retinol began as a pilot study of 816 asbestos-exposed male workers and 1029 male and female heavy smokers and became a full-blown efficacy trial in 1988, with a total of 4060 male asbestos-exposed workers and 14 254 smokers (44% women) after 3 years of randomization. The trial was stopped 21 months before the planned cessation of the intervention; detailed results of associations with risk factors ascertained at baseline

(including alcoholic beverage consumption) considered cancers ascertained through to 15 December 1995 (Omenn *et al*., 1996).

Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

A cohort of 25 400 women participated in a study that investigated the association between dietary folate, alcohol consumption, and postmenopausal breast cancer. Dietary data were collected at study enrollment between 1993 and 2001. Folate content was assigned on the basis of pre-fortification (i.e., pre-1998) databases. Of the 25 400 women participants with a baseline age of 55-74 years and with complete dietary and multivitamin information, 691 developed breast cancer between September 1993 and May 2003. Cox proportional hazard models with age as the underlying time metric were used to generate hazard ratios (HRs) and 95% CIs (Stolzenberg-Solomon et al., 2006).

California Teachers Study

This cohort was established in 1995–96 when 133 479 active and retired female teachers and administrators participating in the California State Retirement System returned a 16-page questionnaire that included data on alcoholic beverage consumption. Women who moved out of state or who died contributed person–months to the analysis up to the date of these events. Incident cancer cases are identified by annual linkage to the California Cancer Registry. Follow up was to January 2001 (Horn-Ross *et al*., 2004; Chang *et al*., 2007).

(c) Scandinavia

(i) *Denmark*

Pooled Copenhagen cohort studies

The data from three cohort studies—the Copenhagen City Heart Study, the Glostrup Population Study and the Copenhagen Male Study—were pooled. The Copenhagen City Heart study was initiated in 1976; participants were selected from 90 000 persons living in a defined area around the University Hospital of Copenhagen. An age-stratified sample of subjects aged 20 years or more was selected at random. Seventy-four per cent of those invited to participate (14 223 subjects) attended, and the subjects were followed-up until 1989. The Glostrup Population Studies Cohort (see above) comprised a total of 10 162 subjects (including men and women). The Copenhagen Male Study followed 5246 men, aged 40–59 years, from 14 large workplaces who were examined four times between 1970 and 1985. The combined study cohort included 18 602 men and 14 662 women. Information on smoking and intake of wine, beer and spirits was collected using self-administered questionnaires. Cancer cases were identified by record linkage to the Danish Cancer Register. Vital status was determined from the national Central Person Register. Cox regression was used to adjust for confounding by cigarette smoking, in a model that included six categories of current smoking and eight 10-year bands of duration of smoking. The cohort was eventually followed through to 1998, when 15 491 men and 13 641 women were included (Grønbaek *et al*., 1998;

Prescott *et al*., 1999; Albertsen & Grønbaek, 2002; Pedersen *et al*., 2003). Details concerning the pooled results from these studies are not provided in the Table.

Glostrup Population Study

The Glostrup Population Study was established primarily to investigate cardiovascular disease, and comprised subjects from several birth cohorts (1897–1962) examined between 1964 and 1992, drawn from a study area Southwest of Copenhagen. A study population of 5207 women aged 30–80 years at baseline was considered for the analysis of breast cancer risk factors. Cases of cancer were identified by linkage to the Danish Cancer Register (Høyer & Engholm, 1992; Petri *et al*., 2004).

Danish Diet, Cancer and Health Study

Between December 1993 and May 1997, 79 729 women aged 50–64 years, who were born in Denmark and living in the greater Copenhagen and Aarhus area, were selected from the Central Population Register and invited to participate in this study. Participants completed a detailed 192-item food-frequency questionnaire that they received by mail before a visit to one of the two study clinics. Information was obtained on alcoholic beverage consumption from the food-frequency questionnaire and on drinking patterns from a lifestyle questionnaire completed at the clinic visit. The study cohort comprised 23 778 women whose records were linked to the Central Population Register for information on vital status and migration and to the Danish Cancer Register for diagnostic details of cancer. Follow-up was to 31 December 2000. This cohort was also included in the EPIC study (Tjønneland *et al*., 2003, 2004).

(ii) *Finland*

α-Tocopherol β-Carotene (ATBC) Cancer Prevention Study

A cohort of 29 133 white Finnish men, aged 50–69 years, who smoked five or more cigarettes per day and who participated in the ATBC randomized trial, were recruited beween 1985 and 1988 and followed for 5–8 years; 27 101 completed the baseline questionnaire. Incident cancers were identified by linkage with the Finnish Cancer Register. Alcoholic beverage consumption was ascertained through a food-use questionnaire administered before randomization in the trial. Deaths were identified from the Register of Causes of Death in Finland. Trial assignment was available [but does not seem to have been incorporated into the analysis] (Glynn *et al*., 1996; Woodson *et al*., 1999; Stolzenberg-Solomon *et al*., 2001; Mahabir *et al*., 2005; Lim *et al*., 2006).

(iii) *Norway*

Norwegian Cohort of Waitresses

The cohort consisted of 5,314 waitresses organized in the Restaurant Workers' Union between 1932 and 1978. The follow-up period was from 1959 to 1991. The standardized incidence ratio (SIR) for all causes of cancer was 1.0 (95 percent confidence interval [CI] = 0.9-1.1), based on 430 observed cases. Cancers of the tongue, mouth, pharynx, larynx, esophagus, and liver were grouped together as alcohol-associated cancers. SIR for these cancers combined was 1.1 (CI = 0.5-2.2). For lung cancer, SIR

was 2.3 (CI = 1.6-3.1). Cervical cancer was also more frequent than expected, and breast cancer less frequent than expected. The larger excess of lung cancer and cervical cancer appeared in the sub-cohort working in restaurants with a license to serve alcohol. No excess risk of alcohol-associated cancers could be detected in this cohort of Norwegian waitresses (Kjaerheim & Andersen, 1994)

Norwegian Cohort Study

A cohort of Norwegian men born between 1883 and 1929, who completed a self-administered dietary questionnaire in 1967, was followed from 1968 (Heuch *et al*., 1983) through to 1992. The target population was initially drawn from three sources: approximately 19 000 persons randomly drawn from lists of residents of Norway from the 1960 population census, approximately 5200 drawn from four selected counties and approximately 13 000 from a cohort of Norwegians living in Norway who had siblings living in the USA (Kjaerheim *et al*., 1998). The study population for the Heuch *et al*. (1983) analysis comprised 16 713 men and women aged 45–74 years who responded to a questionnaire on dietary habits (which included alcoholic beverage consumption) and were followed to 31 December 1968. The study population for the Kjaerheim *et al*. (1998) analysis comprised 10 960 men who were alive and living in Norway on 1 January 1968, and who had no diagnosis of cancer before that date. Information on cancer incidence in both analyses was obtained through the population-based Norwegian Cancer Register (Heuch *et al*., 1983; Kjaerheim *et al*., 1998; Lund Nilsen *et al*., 2000).

HUNT-1 Cohort Study

All inhabitants of the county of Nord-Trondelag who were at least 20 years of age were invited by mail to participate in a health survey, 'Helseundersokelsen i Nord Trondelag 1' (HUNT-1), in 1984. Of 85 100 adults invited, 75 043 attended and were subsequently followed. Those who attended were examined and completed detailed questionnaires including information on alcoholic beverage consumption and tobacco smoking. After exclusions of persons followed for less than 3 years, 69 962 persons were included in the study. Follow-up to 2002 was by linkage to the Norwegian Cancer Register and the Norwegian Central Person Register (Sjödahl *et al*., 2007).

Norwegian Women and Cancer Study (NOWAC)

Between January 1991 and January 1997, 179 388 women aged 30–70 years, sampled according to birth years from the national population register at Statistics Norway, were invited to participate in a study. Mailing was conducted in 24 sets over 7 years; 102 443 women responded. The questionnaire included detailed information on alcoholic beverage consumption and diet. Cancer incidence was determined by linkage to the Norwegian Cancer Register (Dumeaux *et al*., 2004).

(iv) *Sweden*

Swedish Twin Register Study

A cohort of 12 889 twin pairs of the same sex, identified from the Swedish Twin Register, was asked to complete a questionnaire in 1961; 10 942 responded initially. Zygosity was based on questions of childhood similarity. In 1967, a 107-item

questionnaire regarding lifestyle factors including alcoholic beverage consumption was mailed to registrees. Mortality in twins was followed-up by record linkage to the Swedish Cancer and Death Registers through to 1997. Information from death certificates and hospital records and other data were collected for the period up to 1981; the underlying cause of death was determined according to the ICD 8th revision. For the period after 1981, the underlying cause of death as stated on the death certificate was used (Grönberg *et al*., 1996; Terry *et al*., 1998, 1999; Isaksson *et al*., 2002).

Swedish Mammography Cohort

The Swedish Mammography Cohort was established between 1987 and 1990, when all women who were born between 1914 and 1948 and resided in Uppsala and Vastmanland counties in central Sweden were invited to undergo a mammography and complete a mailed questionnaire on diet (67 items), including alcoholic beverage consumption, weight, height and education. A total of 66 651 women (74% of those approached) who returned the questionnaire formed the cohort. A second 96-item questionnaire was mailed in 1997 and was returned by 39 227 women. Follow-up was by record linkage to the National Swedish Cancer Register, the Regional Cancer Register and the Swedish Death and Population registers at Statistics Sweden. An initial report was conducted as a nested case–control study and included cases detected at the first screen (Holmberg *et al*., 1995). After various exclusions, the final cohort for analysis comprised 61 433 women for the first questionnaire and 36 664 for the second. This cohort was included in the Pooling Project (Holmberg *et al*., 1995; Rashidkhani *et al*., 2005; Suzuki *et al*., 2005; Larsson *et al*., 2007).

Malmö Diet and Cancer Cohort

The population for this cohort was defined in 1991 as all persons who lived in the city of Malmö and were born during 1926–45, and was expanded in May 1995 to include all women born during 1923–50 and all men born during 1923–45. On completion of the baseline examinations in October 1996, 28 098 persons were regarded as the base cohort, with a subsample of 11 726 postmenopausal women. Exposure data on alcoholic beverage consumption were collected by an interview-based modified diet history, including a 7-day menu book that recorded details of alcoholic beverage consumption. Cancer cases were identified by linkage to the National Swedish Cancer Register and the Southern Swedish Tumour Register (Mattisson *et al*., 2004).

(d) Western Europe

(i) *France*

Supplémentation en Vitamines et Minéraux Antioxydants Study

The objective of the study was to evaluate the relation between antioxidant-rich beverages and the incidence of breast cancer. This prospective study consisted of 4396 women without a history of cancer who were participants in the French Supplémentation en Vitamines et Minéraux Antioxydants Study. Beverage consumption was estimated by using three nonconsecutive 24-hour recalls. Incident cancer cases were identified

through clinical examinations performed every other year, including, e.g., a screening mammogram, and through a monthly health questionnaire. Participants were followed for a median 6.6 years (Hirvonen *et al*., 2006).

(ii) *Netherlands*

Netherlands Cohort Study

This cohort was based on 204 municipal population registries throughout the Netherlands, and comprised 58 279 men and 62 573 women, aged 55–69 years in 1986, who completed a self-administered questionnaire at baseline. Follow-up was by record linkage to cancer registries and the Dutch database of pathology reports, initially to 1989, and subsequently to 1992. The cohort was analysed as a case–cohort; a subcohort of 3500 subjects randomly sampled from the cohort after baseline exposure measurement was followed to 1992 to obtain information on vital status and was used as control (Goldbohm *et al*., 1994; Schuurman *et al*., 1999; Zeegers *et al*., 2001; Schouten *et al*., 2004; Balder *et al*., 2005; Loerbroks *et al*., 2007).

(iii) *United Kingdom*

British Doctors' Study

In 1951, a questionnaire was sent to all British doctors included in the Medical Registry; 34 440 men and 6194 women responded, representing 69% and 60%, respectively, of those doctors not known to have died at the time of the inquiry. Further questionnaires were sent in 1957, 1966, 1972, 1978 and 1990 to men and in 1961 and 1973 to women; on each occasion, at least 94% of those alive responded. Reports were published on cause-specific deaths after 10, 20 and 40 years for men and after 10 and 22 years for women; more than 99% of the subjects had been traced. Information on causes of death was obtained principally from the Registrars General of the United Kingdom or from the records of the general Medical Council, the British Medical Association, relatives or friends. Because the subjects in the study were themselves physicians, they were a reasonably uniform socioeconomic group and the causes of death were certified more accurately than might have been the case among a sample of the general population. Data on alcoholic beverage consumption were available for the last 23 years of the study (1978–2001) and, for this period, data by drinking habit, adjusted for smoking (adjusted for 5-year calendar periods), were available, and were considered for 12 321 male doctors who were alive in 1978 (Doll *et al*., 1994, 2005).

Oxford Vegetarian Study

This cohort included 11 140 vegetarians and non-vegetarians recruited in the United Kingdom between 1980 and 1984, who were contacted through the Vegetarian Society of the United Kingdom, media publicity and through other participants. Non-vegetarian participants were nominated by vegetarian participants from among their friends and relatives. Upon entry into the study, participants completed a food-frequency questionnaire and answered questions on other lifestyle factors including information on alcoholic beverage consumption. Participants were followed for information on cancer and

death through the National Health Service central registry to 31 December 1999. The analysis cohort comprised 10 998 participants aged 16–89 years at entry (Sanjoaquin *et al*., 2004). This cohort is included in the European Prospective Investigation of Nutrition and Cancer (EPIC).

General Practitioner Research Database Study

The general practitioner research database contains longitudinal patient records, and totals >35 million patient–years of data on British primary care. The information was recorded by general practitioners during standard medical care, including patients' demographics, medical disorders, diagnoses from hospital referrals and drug prescriptions. Information on alcoholic beverage consumption was included when present in the records, but appears not to have been collected specifically; only information recorded at least 2 years before the index date was considered. The study period was from 1 January 1994 to 31 December 2001. The study was analysed as a nested case–control strudy; the index date was the date of diagnosis for cases, and was randomly selected for the 10 000 controls who were frequency-matched to the cases (Lindblad *et al*., 2005).

(iv) *Multiple countries in Europe*

Multicentric European Study of Second Primary Tumours

A cohort of 928 (876 male, 52 female) cases of laryngeal and hypopharyngeal cancer was identified between 1979 and 1982 from a multicentric population-based case–control study in Italy, Spain and Switzerland that was conducted to study the effects of tobacco, alcoholic beverage consumption, diet and occupation on the development of cancers. The cohort was followed until 2000 for the occurrence of second primary tumours using population, mortality and cancer-registry files. Exposure information was obtained through interviews. Approximately 7% of the cohort was lost to follow-up. Of the 876 men and 52 women, 145 men and six women developed second primary tumours during the follow-up period. The Cox proportional hazard model, adjusted for age, centre, occupation, smoking and site of first cancer, was used to estimate hazard ratios (Dikshit *et al*., 2005).

European Prospective Investigation into Cancer and Nutrition (EPIC)

A cohort of healthy adults was recruited from Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, the Netherlands and the United Kingdom to study multiple exposures, including cigarette smoking, vegetable/fruit intake and alcoholic beverage consumption, on risks for various cancers. Recruitment was initiated in 1992, and active and passive follow-up is ongoing. Exposure information was obtained from mailed questionnaires. Relative risks were obtained using the proportional hazard model adjusting for follow-up time, sex, education, body mass index, vegetable and fruit consumption, tobacco smoking and energy intake (Boeing, 2002; Rohrmann *et al*., 2006; Tjønneland *et al*., 2007).

Table 2.1b Cohort studies of cancer and alcoholic beverage consumption in special populations

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
North America								
Canada								
Canadian Alcoholics Study	1951	Schmidt & Popham (1981)	1951–70	9 889 alcoholic men, aged ≥15 years, admitted to the clinical service of the Addiction Research Foundation of Ontario between	Death records	Deaths	Buccal cavity, pharynx, oesophagus, stomach, large intestine, rectum, liver, pancreas, larynx, bronchus, lung, prostate, lymphoma, leukaemia	Local reference population, US veterans used as a reference population, no individual exposure data, no information on potential confounders
United States								
Massachusetts Cohort of Chronic Alcoholics	1930, 1935, 1940	Monson & Lyon (1975)	1930–71	1139 men and 243 women admitted in 1930, 1935 or 1940 to a mental hospital with a diagnosis of chronic alcoholism	Death certificates	Deaths	Buccal cavity, oesophagus, stomach, colon, rectum, large intestine, liver, biliary tract, pancreas, larynx, lung, breast, urogenital organs, prostate, urinary bladder, kidney, brain, leukaemia, other cancer	Compared with US population; half of group lost to follow-up; no individual exposure data; no information on confounders.

Table 2.1b (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Seventh-day Adventists study	1976	Mills *et al*. (1994); Singh & Fraser (1998)	1976–82	60 000 Seventh-day Adventists in California identified by census questionnaire, aged >25 years	Lifestyle questionnaire	Cases	Buccal cavity, oesophagus, stomach, large intestine, colon, rectum, biliary passages and liver, pancreas, bronchus, lung, melanoma, breast, cervix, corpus uteri, ovary, urinary bladder,kidney, brain, Hodgkin disease, leukaemias	Study population had a low prevalence of alcohol consumption; joint effect of alcohol and tobacco examined.
Scandinavia								
Denmark								
Danish Brewery Workers Cohort	1939–63	Jensen (1979); Thygesen *et al*. (2005)	1943–99	14 313 Danish brewery workers employed at least 6 months in 1939–63; age not given	Cancer registry database	Case/ deaths	Buccal cavity, pharynx, oesophagus, stomach, colon, rectum, liver, pancreas, nasal cavities, larynx, lung, melanoma, other skin, prostate, testis, penis, urinary bladder, kidney, ureter, brain, nervous system, lymphatic and haematopoeitic leukaemia	Local male population; national mortality rates used for comparison; no individual exposure data; no information on potential confounders

Table 2.1b (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Danish Alcohol Abusers Study	1954–87	Tønnesen *et al.* (1994)	1954–87	18 307 (15 214 men, 3 093 women) alcoholics from a public outpatient clinic for free treatment	Interview	Cases/ deaths	Lip, tongue, salivary glands, mouth, pharynx, oesophagus, stomach, kidney, colon, rectum, liver, gall bladder, urinary bladder, pancreas, larynx, lung, pleura, melanoma, non-melanoma skin, breast, cervix uteri, corpus uteri, ovary, prostate, testis, brain, endocrine, non-Hodgkin lymphoma, multiple myeloma, haematopoietic and lymphatic leukaemia	Cohort cancer incidence compared with total Danish population; no information on potential confounders; estimates not adjusted for smoking.
Nationwide Study of Patients with Cirrhosis	1977–89	Sørensen *et al.* (1998)	1977–93	11 605 1-year survivors of cirrhosis from the Danish National Registry of Patients	Registry database	Cases	Oral cavity, pharynx, oesophagus, stomach, colon, rectum, liver, gall bladder, biliary tract, pancreas, larynx, lung, melanoma, other skin, breast, cervix uteri, endometrium, ovary, prostate, testis, kidney, urinary bladder, brain, nervous system, thyroid, non-Hodgkin lymphoma, leukaemia	Expected rates from national incidences; estimates not adjusted for smoking

Table 2.1b (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Finland								
Finnish Alcoholics	1967–70	Hakulinen *et al*. (1974)	1967–70	Approximately 205 000 male alcohol misusers and mean of 4 370 male chronic alcoholics, aged >30 years	Finnish Cancer Registry	Cases	Salivary glands, pharynx, oesophagus, stomach, colon, liver, pancreas, larynx, lung, bone, skin, prostate, urinary organs, eye, nervous system, thyroid, lymphoma, Hodgkin disease, leukaemia	Local reference; no individual exposure data; no data on potential confounders
Norway								
Norwegian Alcoholics Study	1925–39	Sundby (1967)	1925–62	Alcoholics from Oslo psychiatric department, 1722 males, aged 15–70 years	Death certificate	Deaths	Oral cavity, pharynx, oesophagus, stomach, colon, rectum, liver, pancreas, larynx, lung, prostate, testis, penis, urinary bladder, kidney, brain, Hodgkin disease, multiple myeloma, leukaemia	Local reference; Oslo urban mortality data

Table 2.1b (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
International Organization of Good Templars Cohort	1980	Kjaerheim *et al.* (1993)	1980–89	5332 members of the International Organization of Good Templars, aged ≥10 years	Hospital and laboratory reports	Cases	Oral cavity, pharynx, oesophagus, stomach, colon, rectum, gall bladder, liver, pancreas, larynx, lung, breast, female genital, prostate, male genital, urinary bladder, kidney, brain, haematopoietic cancers	Expected rates from national incidence

Table 2.1b (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Sweden								
Temperance Boards Study	1947	Sigvardsson *et al.* (1996)	1947–77	15 508 alcoholic women ascertained through the Temperance Boards and 15 508 non-alcoholic women from population, born 1870–1961	Temperance Boards records	Cases	Lip, tongue, salivary glands, mouth, hypopharynx, pharynx, tonsil, oesophagus, stomach, small intestine, duodenum, colon, rectum, liver, gallbladder, bile ducts, pancreas, nose, larynx, bronchus, lung, bone, connective tissue, muscle, breast, malignant melanoma, other skin, uterus, cervix uteri, corpus uteri, ovary, vulva, vagina, other female genital, urinary bladder, kidney, eye, nervous system, thyroid, endocrine glands, non-Hodgkin lymphoma, Hodgkin disease, multiple myeloma, leukaemia, unspecified sites	No adjustment for smoking

Table 2.1b (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Swedish Brewery Workers Study	1960	Carstensen *et al*. (1990)	1961–79	6230 men employed in the Swedish brewery, aged 20–69 years	Swedish Cancer Registry	Cases	Buccal cavity, pharynx, oesophagus, stomach, colon, rectum, liver, pancreas, larynx, bronchus, lung, melanoma, prostate, male genital organs, urinary bladder, kidney, urinary system, brain, nervous system, leukaemia, lymphatic and haematopoetic cancers	Swedish male population used as a reference group
Swedish Inpatient Register/ Study of Patients with Chronic Pancreatitis	1964–83	Karlson *et al*. (1997); Ye *et al*. (2002)	1964–95	Karlson *et al*. (1997) Analytical cohort of 4043 patients discharged with pancreatitis in association with alcoholism Ye *et al*. (2002) 178 688 male and female patients with hospital discharge of alcoholism, 1964–95	Medical and cancer registry records	Cases	Pancreas	Incidence rates compared with national rates; no individual exposure data; no information on potential confounders; risks not adjusted for smoking

Table 2.1b (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
National Board of Health and Welfare Hospital Discharge study of Alcoholism	1965	Kuper *et al.* (2000c)	1965–95	Analytical cohort of 36 856 women diagnosed with alcoholism from hospital discharge data	Hospital-discharge records	Cases	Breast	Compared with national incidence rates; no individual exposure information; no adjustment for potential confounders
National Board of Health and Welfare Study of Alcoholic Women	1965–94	Lagiou *et al.* (2001); Weiderpass *et al.* (2001a,b),	1964–95	36 856 women hospitalized for alcoholism	Registry –based linkages		Trachea, bronchus, lung, cervix uteri, endometrium, ovary, vagina, vulva	No adjustment for smoking

Table 2.1b (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Swedish In-patient Register and National Cancer Register Study	1965–94	Boffetta *et al*. (2001)	1965–95	173 665 patients (138 195 men, 35 470 women) with a hospital discharge diagnosis of alcoholism, aged >20 years	National Cancer Registry	Cases	Lip, tongue, salivary gland, mouth, oral cavity, pharynx, mesopharynx, nasopharynx, hypopharynx, oesophagus, stomach, colon, rectum, liver, biliary tract, pancreas, larynx, lung, melanoma, breast, cervix, corpus uteri, ovary, prostate, testis, urinary bladder, kidney, brain, thyroid, lymphatic, haematopoietic cancers	Compared with incidence in the national population

Table 2.1b (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Uppsala Alcoholics Study	1965–83	Adami *et al.* (1992a,b)	1964–84	10 350 individuals from Swedish Uppsala Inpatients Register, with discharge diagnosis for alcoholism	Cancer registry	Cases	Lip, tongue, salivary gland, mouth, oral cavity, pharynx, mesopharynx, nasopharynx, hypopharynx, oesophagus, stomach, colon, rectum, liver, biliary tract, pancreas, larynx, lung, melanoma, breast, cervix, corpus uteri, ovary, prostate, testis, urinary bladder, kidney, brain, thyroid, lymphatic, haematopoietic cancers	

Table 2.1b (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Western Europe								
Republic of Ireland								
Dublin Brewers Study	1954–73	Dean *et al.* (1979)	1954–73	Deaths between 1954 and 1973 among male blue-collar brewery workers	Death certificates	Deaths	Oesophagus, stomach, colon, rectum, liver, gall bladder, pancreas, lung	Compared with Dublin skilled and unskilled manual workers; no individual exposure data; no information on confounders
United Kingdom								
Study of Patients Hospitalized for Alcohol-related Diseases	1948–1971	Prior (1988)	1948–81	1 110 patients/ hospitalized in the Birmingham region for alcohol-related conditions	Hospital-discharge records	Cases	Mouth, buccal cavity, pharynx, throat, oesophagus, liver, gall bladder, pancreas, digestive system, larynx, lung, respiratory system, skin, breast, cervix uteri, reproductive system, urinary system, lymphatic and haematopoietic systems	Compared with the West Midlands region

Table 2.1b (continued)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
England and Wales, UK Alcoholics Study	1953–57, 1964	Adelstein & White (1976); Nicholls *et al*. (1974)	1953–74	1 595 male and 475 female alcoholics aged 15–90 years	Hospital-discharge records	Deaths	Pharynx, oesophagus, stomach, intestine, rectum, liver, pancreas, larynx, lung, breast, cervix uteri, prostate	Reference death rates were sex-specific rates of England and Wales for 1972.

2.1.2 *Studies in special populations (Table 2.1b)*

This group of studies is characterized by the assumption that the study subjects have a pattern of consumption of alcoholic beverages that is different from that of the general population, e.g. alcoholics, brewery workers, members of a temperance organization. Because of the availability of national registries of populations, inpatients and cancer, most of these studies were performed in Scandinavian countries. The estimation of risk in these individuals is not based upon a comparison of exposed and unexposed subjects within the cohort, but with the expected rates of cancer in the general population.

(a) North America

(i) *Canada*

Canadian Alcoholics Study

The cohort consisted of 9889 men (79% middle-class; <1% nonwhite) who had been admitted to the main clinical services for alcoholics in Ontario between 1951 and 1970. No information on individual drinking or smoking habits was available, but investigations of samples of the cohort indicated an average daily consumption of 254 mL [~ 200 g] ethanol and that >92% were still drinking ten years after admission. A total of 94% of cohort members were current smokers, who smoked an average of 28 cigarettes per day. Altogether, 1823 deaths occurred before 1972; 960.9 were expected. Vital status could not be determined for 3.5% of cohort members. Cause-specific mortality was compared with that of the Ontario male population. A further comparison was made with US veterans who smoked 21-39 cigarettes per day, in an indirect attempt to control for the effect of tobacco on the risk of alcohol-related cancers. Results were also reported for 1119 women followed up for 14 years, but only a few cancer deaths were observed (Schmidt & Popham, 1981).

(ii) *United States*

Massachusetts Cohort of Chronic Alcoholics

To test the hypothesis that there is a positive association between chronic alcoholism and carcinoma of the pancreas, the mortality experience of 1382 chronic alcoholics was studied. Analysis was limited to a comparison of observed and expected proportional mortality of different causes of death in the 894 whites who were known to have died. For carcinoma of the pancreas, 3 deaths were observed and 5.2 were expected. The observed/expected ratios for other causes of death, including other sites of cancer, were in accordance with prior studies (Monson & Lyon, 1975).

Seventh-day Adventist Study

The study population was identified in 1973 from 437 California Seventh-day Adventists churches. Adventists are a religious group who do not consume tobacco, alcoholic beverages or pork, and half adhere to a lacto-ovo-vegetarian lifestyle. The list of households was computerized in 1974: 63 530 were identified to which a census

questionnaire was sent; 36 850 households returned a questionnaire listing 95 196 persons. Persons under 25 years of age were excluded from all analyses, and the study population analysed comprised 59 090 subjects. In 1976, a lifestyle questionnaire was sent to all living members (57 841); 40 398 participants returned the questionnaire; non-Hispanic whites had a response rate of 75%. Participant data was linked with data from two cancer registries, which were in operation in California. SIRs were calculated. The group of non-Hispanic members of the cohort was compared with an external population of Connecticut (93% whites) (Mills *et al*., 1994; Singh & Fraser, 1998).

(b) Scandinavia

(i) *Denmark*

Danish Brewery Workers Cohort

A total of 14 313 male members of the Danish Brewery Workers' Union who had been employed for six or more months in a brewery during the period 1939-63 were enrolled in this retrospective cohort study. The brewery workers had the right to consume six bottles (2.1 L) of light pilsener (lager) beer (alcohol content, 3.7 g [~ 78 g ethanol] per 100 mL) on the premises of the brewery per working day; 1063 members of the cohort worked in a mineral-water factory, with no free ration of beer. No information was available on alcohol consumption or smoking habits of individual members of the cohort; but, on the basis of comparisons with alcohol statistics and population surveys, it was estimated that cohort members with employment in a brewery had a four times higher average beer consumption than the general population. Vital status was ascertained for 99.4% of the cohort members. There were 3550 deaths (SMR, 1.1) in the cohort, and 1303 incident cases of cancer were identified during the period 1943-72 by record linkage with the Danish Cancer Registry. Expected numbers of cancer cases and deaths were computed on the basis of age-, sex-, residence- and time-specific rates (Jensen 1979, 1980).

Danish Alcohol Abusers Study

The study was based on 18 307 alcoholics from Copenhagen who entered a public outpatient clinic for free treatment for alcoholism from 1954 to 1987. From 1968, cohort members had population identification numbers. Prior to that date, the 5969 cohort members without a number were sought by computer linkages with municipal and Danish population registries. The resultant cohort consisted of 15 214 men who were observed for 12.9 years on average and 3093 women who were observed for an average of 9.4 years. The records of these cohort members were linked to the Danish Cancer Register to obtain information on cancer morbidity through to December 1987. The observed cancer incidence was compared with that expected in the Danish population (Tønnesen *et al*., 1994).

Nationwide Study of Patients with Cirrhosis

In a study based upon the Danish National Register of Patients, persons who were registered between 1977 and 1989 were enrolled if they had been discharged with

alcoholic cirrhosis (ICD-8 571.09), primary biliary cirrhosis (571.90), non-specified cirrhosis (571.92), chronic hepatitis (571.93) or 'other types of cirrhosis, alcoholism not indicated' (571.99). Cirrhosis was considered as a whole, but also as four separate types, largely following the ICD-8 codes given above, except that 'non-specified cirrhosis' and 'cirrhosis, alcoholism not indicated', were merged into one group termed 'nonspecified cirrhosis' (571.92 and 571.99). All members of the study cohort were linked through their personal identification number to the nationwide Danish Cancer Register and followed-up through to 1993. The cohort for this analysis consisted of 11 605 subjects (5079 men and 2086 women with alcoholic cirrhosis) who had survived for 1 year after registration. Expected numbers were computed from the rates in the Danish Cancer Register and compared with those observed (Sørensen *et al*., 1998).

(ii) *Finland*

Finnish Alcoholics

Between 1944 and 1959, male 'alcohol misusers' were registered by the Finnish State Alcohol Monopoly on the basis of conviction for drunkenness, sanctions imposed by the municipal social welfare boards, and various breaches against the regulations governing alcohol usage. No information was available on the amount of alcohol consumed by the cohort members, nor on types of beverage or smoking habits. The numbers of incident cases of cancer of the oesophagus, of the liver and of the colon among an estimated 205 000 men born 1881-1932 and alive in 1965-68 were obtained by a manual match between the files of the Finnish Cancer Register for these years and the files of the Alcohol Misusers Registry. Person-years at risk during the period 1965-68 were estimated from samples, and these formed the basis for computing expected numbers of cases. Lung cancer risk was determined in a similar fashion, but for only one-third of the group in 1968.

A second group of men more than 30 years of age, who in 1967-70 had been listed as chronic alcoholics by the Social Welfare Office of Helsinki, were also studied. The mean annual number of such men was estimated to be 4370. No information was available on type or amount of alcoholic beverages drunk or on tobacco smoking, but the persons in the group of chronic alcoholics were heavy alcohol drinkers, most of whom drank cheap, strong beverages, wines and denatured alcohols. Incident cases of cancer occurring during 1967-70 were identified by record linkage with the Finnish Cancer Register, and expected numbers were derived on the basis of national incidence rates and computed person-years (Hakulinen *et al.,* 1974).

(iii) *Norway*

Norwegian Alcoholics Study

A total of 1 722 men discharged during 1925-39 from the Psychiatric Department of an Oslo hospital with a diagnosis of alcoholism were enrolled in the study and observed until the end of 1962. No information was available on drinking and smoking habits of individual cohort members or of the cohort as a whole, 408 were considered

to be vagrant alcoholics. Evidence of persistent alcoholism was available for about 75% of the vagrants and for 50% of the remaining group. Follow-up was virtually complete, with 1 061 deaths. Death certificates were located for 1 028 of these, and information on cause of death was available for another 28 persons. The observed numbers of deaths were compared with expected numbers based on causes of deaths for all of Norway (496.9) and for Oslo (629.0). (Sundby, 1967).

International Organization of Good Templars Cohort

A cohort of 5332 members, aged 10 years and over, from the 200 larger and active lodges of the International Organization of Good Templars was followed for 10 years from 1980. Members of the Organization sign a statement that they will not drink alcoholic beverages. Cancer incidence and cause-specific mortality of the cohort was determined by linkage to the Cancer Register of Norway and was compared with that of the total Norwegian population (Kjaerheim *et al*., 1993).

(iv) *Sweden*

Temperance Boards Study

This cohort study comprised 15 508 Swedish women with a history of heavy alcoholic beverage consumption and 15 508 matched comparison subjects. The excessive alcoholic beverage users were ascertained through a review of the records of all Temperance Boards of Sweden, which operated between 1917 and 1977. During this time, 21 757 women were registered. Before 1947, personal identification numbers did not exist, so the cohort was limited to records after 1947. Linkages were made with the Swedish Cancer Register, which started in 1958 (Sigvardsson *et al*., 1996).

The Swedish Brewery Workers Study

This study was based upon the Cancer–Environment Register that links cancer incidence data from the Swedish Cancer Register for the period 1961–1979 with information on occupation, occupational status, industry and residence obtained in the 1960 population census. A group of 6230 men who were, according to the census, employed in the Swedish brewery industry in 1960, aged 20–69 years, was followed-up in 1961–79 by linkage to the Swedish Cancer Register. Person–years were computed by linkage with the Swedish Population Register. Relative risks were computed using all Swedish men as the reference group (Carstensen *et al*., 1990).

Swedish In-patient Register Study of Patients with Chronic Pancreatitis

This cohort was also based on the Swedish In-patient Register, and a very similar methodology to that of Boffetta *et al*. (2001) was used. Records of all patients with a diagnosis of acute, chronic or unspecified pancreatitis were identified, and linked to the Registries of Population, Death and Emigration held by Statistics Sweden. After exclusions of those who could not be identified in these registers and those with pancreatic or other cancers diagnosed at the index hospitalization, 29 530 subjects were included in the cohort. Incident cancers were identified by linkage with the [Swedish] National Cancer Register up to 31 December 1989 (Karlson *et al*., 1997). In a more recent report using the same database as above (Karlson *et al*., 1997; Boffetta *et al*., 2001),

five cohorts were considered: 178 688 subjects admitted to hospital for alcoholism, 3500 admitted for chronic alcoholic pancreatitis, 4952 admitted for chronic non-alcoholic pancreatitis, 13 553 admitted for alcoholic liver cirrhosis and 7057 admitted for non-alcoholic liver cirrhosis. Follow-up was through to 1995 by linkage with national registers. Standardized incidence ratios (SIRs) were computed taking the Swedish population as a reference (Ye *et al*., 2002).

National Board of Health and Welfare Hospital Discharge Study of Alcoholism

From 1965 onwards, the National Board of Health and Welfare started collecting data on individual hospital discharges in the Inpatient Register. From 1987, the register attained complete nationwide coverage. All patients recorded in the Inpatient Register with a discharge diagnosis of alcoholism were initially selected for inclusion in the study. A total of 196 803 individually unique national registration numbers, assigned to all Swedish residents, were registered at least once with a diagnosis of alcoholism between 1965 and 1994. December 31, 1995 was the end of the observation period. Record linkage of the study cohort to the nationwide Registers of Causes of Death, Emigration and Cancer allowed the calculation of follow-up time, in person-years, of eligible persons at risk as described previously in detail (Adami et al, 1992a, b). From the total cohort 7790 records were excluded because of erroneous or incomplete national registration numbers, a further 3405 patients were excluded because they had prevalent cancers at the time observation began and another 2941 patients because of inconsistencies uncovered during record linkage. Thus a total of 182 667 patients with alcoholism remained eligible, and of these 36 856 were women (Kuper *et al.,* 2000c).

National Board of Health and Welfare Study of Alcoholic Women

This study was essentially on the same female cohort as that considered by Boffetta *et al*. (2001). A total of 36 856 Swedish women (mean age, 42.7 years), who were hospitalized at least once in 1965–94 with a diagnosis of alcoholism and were residents in Sweden, were included in the study. SIRs were calculated by multiplying the number of person–years within 5-year age groups and calendar-year strata by the cancer incidence rates in Swedish women. Exclusions from observed and expected groups were secondary cancers and cancers found incidentally at autopsy. The person–time and events during the first year of follow-up were excluded to avoid increased likelihood of diagnosis of one disease following hospitalization for alcoholism in the presence of a yet undetected malignancy. The authors took co-morbidities into account (i.e. factors in the hospitalization record other than alcohol dependence) and assessed person–time within each co-morbidity stratum (Lagiou *et al*., 2001; Weiderpass *et al*., 2001a,b).

Swedish In-patient Register and the National Cancer Register Study

This cohort was based on the Swedish In-patient Register, a database provided by the National Board of Health and Welfare since 1964 that contains complete nationwide records since 1987, and is an expansion of the study of Adami *et al*. (1992a,b). Using the national identification number, which is a unique identifier for each citizen, the cohort was linked to the Registers of Population, Death and Emigration, and the National Cancer Register. The 196 803 persons aged ≥20 years who were identified had

a hospital discharge-diagnosis of alcoholism during 1965–94 and a unique national registration number. After exclusions for various reasons, 173 665 persons were included in the analytical cohort (138 195 men, 35 470 women). Incident cancers after discharge were identified by linkage with the National Cancer Register up to 31 December 1995 (Boffetta *et al*., 2001).

Uppsala Alcoholics Study

A cohort of 10 350 individuals was selected from the Uppsala Inpatient Register (Sweden), with a discharge diagnosis that contained a diagnostic code for alcoholism (International Classification of Diseases [ICD] 7: 307, 322; ICD 8: 291, 303) during 1965–83. After exclusion of those who had an inconsistent registry number, 9353 (8340 men, 1013 women) patients were entered into the study. Follow-up was by record linkage to the nationwide Register of Causes of Death and the National Swedish Cancer Register through to 1984. Expected numbers of cancers were computed from cancer incidence in the Uppsala health-care region to compare with the observed cases (Adami *et al*., 1992a).

The Uppsala Alcoholics cohort, identified at the same time and followed for the same period, was also analysed as three population-based cohorts with mutually exclusive hospital discharge-diagnoses of alcoholism, cirrhosis or both. It comprised 8517 patients with a diagnosis of alcoholism, 3589 subjects with cirrhosis and 836 subjects with both diagnoses (Adami *et al*., 1992b).

(c) Western Europe

(i) *Republic of Ireland*

Dublin Brewers Study

A list of 1628 deaths during the period 1954-73 was provided by a large brewery in Dublin, Ireland. On the basis of death certificates for all but two of these men and of statistics for the population of employees and pensioners in 1957, 1960, 1967 and 1970, relative risks for specific causes of death were estimated employing both national and regional rates. The expected number of deaths was 1675.8 (regional rates). It was estimated from previous research that ethanol intake among the brewery workers was 58 g per day, compared with 16-33 g per day for other groups of the Irish population. Beer (stout) was consumed on the premises. No information was available on individual consumption of alcohol or tobacco; smoking was forbidden at the brewery for many years. [The Working Group noted that the cohort at risk was estimated indirectly as 2000-3000 men at any one time during follow-up, and no individual follow-up of cohort members was performed.] (Dean *et al.,* 1979)

(ii) *United Kingdom*

Study of Patients Hospitalized for Alcohol-related Diseases

A series of 1110 patients seen at hospitals in the Birmingham Region between 1948 and 1971 for alcohol-related conditions were followed to 1981. By means of cohort analysis, the incidence of cancer in the series was compared with that in the West

Midlands Region. In men the cancer risk was increased 1.7-fold: individual sites at risk were liver (8-fold), buccal cavity and throat (27-fold), respiratory system (2.4-fold), and oesophagus (4-fold). No excess of colorectal cancers was observed. Although in women there was no overall excess of cancers, the risk was high in the biliary system (15-fold) and was moderately increased for *cervix uteri* (4-fold) (Prior, 1988).

A total of 935 patients who had been discharged from four mental hospitals in or near London, UK, during the years 1953-57, or who had died during the key hospitalization and who had been given a primary or secondary diagnosis implicating abnormal drinking, were followed for 10-15 years. Of the total sample, 70 (7.5%) remained untraced and 233 men (34.4%) and 76 women (29.6%) had died; a total of 112.7 deaths was expected. The study was extended to all of England and Wales 1953-64 by Adelstein and White (1976), who covered a total of 1595 men and 475 women (Nicholls et al., 1974)

2.2 Cancer of the oral cavity and pharyn*x*

The evidence for carcinogenic effects of alcoholic beverage consumption on the risk for cancers of the oral cavity and pharynx in humans was considered to be *sufficient* by a previous IARC Working Group (IARC, 1988). This section evaluates the evidence related to the risk for oral and pharyngeal cancer in humans based on relevant cohort and case–control studies published after 1988.

Exposure to alcoholic beverages is given in many different measurements. For comparability between studies, one drink is equivalent to 14 g, 18 mL or 0.49 oz of alcohol, which generally corresponds to 330 mL of beer, 150 mL of wine and 36 mL of hard liquor. Cancers of the oral cavity and pharynx are predominantly squamous-cell carcinomas. The histology of the tumours is given when available. Generally, studies on pharyngeal cancers are predominantly oropharyngeal and hypopharyngeal cancers, rather than nasopharyngeal cancer. Two case–control studies are, however, specifically focused on nasopharyngeal cancer, as noted in the Tables.

The risks for cancer of the oral cavity and pharynx in relation to total alcoholic beverage consumption are summarized in Tables 2.2–2.5. The effect of alcohol types are presented in Table 2.6, the combined or joint effects of alcohol drinking and tobacco smoking are shown in Table 2.7, and the effect of alcohol cessation and the association between alcoholic beverage consumption and risk for oral and pharyngeal cancers among nonsmokers are presented in Tables 2.8 and 2.9, respectively.

2.2.1 *Cohort studies (Table 2.2)*

Five cohort studies of the general population have been published since 1988 on the relationship between alcoholic beverage consumption and oral or pharyngeal cancer (Boffetta & Garfinkel, 1990; Chyou *et al*., 1995; Murata *et al*., 1996; Kjaerheim

Table 2.2 Cohort studies of cancers of the oral cavity and pharynx combined

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Boffetta & Garfinkel (1990), USA, American Cancer Society Prospective Study	Cohort of 276 802 white men from over 25 states; aged 40–59 years; enrolment in 1959; mortality follow-up until 1971; 3% of cohort lost to follow-up	Questionnaire	Oral cavity (ICD 140–145)	*Total alcohol* Non-drinker Occasional drinker 1 drink/day 2 drinks/day 3 drinks/day 4 drinks/day 5 drinks/day ≥6 drinks/day Irregular drinker	 55 10 6 12 13 13 5 26 15	 1.0 (reference) 1.2 (0.6–2.4) 0.4 (0.2–1.0) 1.0 (0.5–1.9) 2.2 (1.2–4.0) 3.2 (1.7–6.1) 2.7 (1.0–6.8) 6.2 (3.7–10.1) 2.0 (1.1–3.5)	Age, smoking	
Adami *et al.* (1992a,b) Uppsala, Sweden,	Cohort of 9353 patients (8340 men, 1013 women) diagnosed with alcoholism in the Inpatient Register; incidence follow-up 1965–83	Inpatient Register records	Oral cavity, pharynx (ICD7 140–148)	Overall *Age at follow-up* <50 years 50–64 years ≥65 years	36 NG NG NG	**SIR** 4.1 (2.9–5.6) 9.4 (1.9–27.3) 10.1 (6.6–14.7) 1.0 (0.4–2.2)	No information on potential confounders	Age-standardized expected rates from local population; confounding by smoking likely

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Kjaerheim *et al.* (1993), Norway	Cohort of 5332 members of the International Organization of Good Templars (signed statement that they will not drink alcoholic beverages), aged ≥10 years; enrolment in 1980; incidence follow-up until 1989		Oral cavity, pharynx (ICD7 141–148)	Non-drinkers	*Men* 2 *Women* 1 *Both sexes* 3	**SIR** [0.11] [0.01–0.40] [0.38] [0.01–2.12] 0.44 (0.09–1.27)	None	Age- and sex-specific expected rates from national incidence

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Day *et al.* (1994a), USA	Nested case–control study of second primary cancers; cohort of 1090 first primary cancers of oral cavity and pharynx; enrolment of first primary cancers in 1984–85; follow-up until 1989; 80 (56 men, 24 women) developed second primary cancers during follow-up; 189 (132 men, 57 women) randomly selected from cohort, matched on sex, study area and survival, free of second primary cancer at the end of follow-up	Interviewer-administered questionnaire	Oral cavity, pharynx, oesophagus (ICD9 141, 143–146, 148–149)	*Total alcohol* <5 drinks/week 5–14 drinks/ week 15–29 drinks/ week ≥30 drinks/ week	 9 10 14 24	**Odds ratio** 1.0 (reference) 1.6 (0.5–5.1) 2.1 (0.7–6.6) 1.5 (0.5–4.5)	Age, stage of disease, lifetime smoking	Nested case–control study of second primary cancers among cases of Blot *et al.* (1988) study; looked at type of alcoholic beverage and cessation of alcoholic beverage consumption

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Tønnesen *et al.* (1994), Copenhagen, Denmark	Cohort of 18 307 (15 214 men, 3093 women) alcoholics from a public outpatient clinic for free treatment; incidence follow-up 1954–87	Interview with a social worker and psychiatrist	Oral cavity, pharynx	Alcoholic	*Men* 112 W*omen* 22	 3.6 (3.0–4.3) 17.2 (10.8–26.0)	None	Age-, sex- and calendar period-specific cohort cancer incidence compared with total Danish population
Chyou *et al.* (1995), Hawaii, USA, American men of Japanese Ancestry	Cohort of 7995 men of Japanese ancestry identified by the Honolulu Heart Program, aged 45–68 years; recruitment in 1965–68, incidence follow-up until 1993; 1–2% lost to follow-up	Interviewer-administered questionnaire	Oral cavity, pharynx, oesophagus, larynx (ICD8 140–150, 161)	*Total alcohol* Non-drinker <4 oz/month 4–24.9 oz/ month ≥25 oz/month *p* for trend	 16 5 18 52	**Hazard ratio** 1.0 (reference) 0.6 (0.2–1.6) 1.7 (0.9–3.4) 4.7 (2.6–8.3) <0.0001	Age, number of cigarettes/ day, years smoked	Study population from Kato *et al.* (1992c); looked at type of alcoholic beverage and joint effects with smoking

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Murata *et al.* (1996), Japan	Nested case–control study among cohort of 17 200 men part of a gastric mass screening survey in 1984; incidence follow-up until 1993; 887 cases and 1774 controls matched on sex, birth year, city/ county	Self-administered questionnaire	Oral cavity, pharynx, oesophagus, larynx (ICD9 140-150, 161)	*Total alcohol*[*]			None	[*]Unit is cup of 180 mL of sake: corresponds to 27 mL ethanol
				0 cups/day	17	1.0 (reference)		
				0.1–1.0 cups/ day	13	1.0 (p>0.05)		
				1.1–2.0 cups/ day	11	1.9 (p>0.05)		
				≥2.1 cups/day	10	9.0 (p<0.01)		
				χ^2 for trend		9.6 (p<0.01)		
				Nonsmoker[*]				
				0 cups/day	7	1.0 (reference)		
				0.1–1.0 cups/ day	6	1.2 (p>0.05)		
				≥1.1 cups/day	5	2.1 (p>0.05)		
				Smoker[*]				
				0 cups/day	10	1.9 (p>0.05)		
				0.1–1.0 cups/ day	7	1.4 (p>0.05)		
				≥1.1 cups/day	16	5.9 (p<0.01)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Sigvardsson *et al.* (1996), Sweden	Cohort of 15 508 alcoholic women ascertained through the Temperance Boards and 15 508 non-alcoholic women from population matched individually on region and date of birth; enrolled in 1947–77; follow-up for incidence	Temperance Boards records	Tongue (ICD7 141), mouth (143, 144), tonsil (145), hypo-pharynx (147), Pharynx (148)	*Tongue* Comparisons Alcoholics *Mouth* Comparisons Alcoholics *Tonsil* Comparisons Alcoholics *Hypopharynx* Comparisons Alcoholics *Pharynx* Comparisons Alcoholics	 2 17 1 12 1 11 1 9 0 1	 1.0 (reference) 8.5 (2.0–37) 1.0 (reference) 12.0 (1.6–92) 1.0 (reference) 11.0 (1.4–85) 1.0 (reference) 9.0 (1.1–71) 1.0 (reference) NG	None	

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Kjaerheim *et al.* (1998), Norway	Cohort of 10 960 men born in 1893–1929 who completed two questionnaires sent to a probability sample of the Norwegian population; incidence follow-up 1968–92; mean age at start of follow-up, 59 years	Mailed survey	Oral cavity, pharynx, larynx, oesophagus (ICD7 141, 143–145, 147, 148, 150, 161)	*Total alcohol* Never or <1 time/week Previously 1–3 times/week 4–7 times/week *p* for trend *Beer* Never or <1 time/week Previously 1–3 times/week 4–7 times/week *p* for trend *Spirits* Never or <1 time/week Previously 1–3 times/week 4–7 times/week *p* for trend	 26 4 18 19 37 11 8 14 42 15 5 5 	 1.0 (reference) 0.9 (0.3–2.7) 1.1 (0.6–1.9) 3.9 (2.1–7.1) 0.003 1.0 (reference) 1.0 (0.5–1.9) 1.4 (0.7–3.1) 4.4 (2.4–8.3) <0.001 1.0 (reference) 1.3 (0.7–2.3) 1.4 (0.6–3.6) 2.7 (1.1–7.0) 0.06	Age, smoking	
Sørensen *et al.* (1998), Denmark	Cohort of 11 605 1-year survivors of cirrhosis from the Danish National Registry of Patients; recruitment in 1977–89; incidence follow-up until 1993	Admission records of Danish National Registry of Patients	Oral cavity, pharynx	Overall All cirrhosis Alcoholic cirrhosis Chronic hepatitis cirrhosis	 143 115 8	**SIR** 9.2 (7.8–10.8) 11.6 (9.6–14.0) 4.2 (1.8–8.2)	None	Expected rates from age-, sex- and site-specific national incidence rates

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Boeing (2002), Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, Netherlands, UK, European Prospective Investigation into Cancer and Nutrition	Cohort of 417 752 healthy adults; recruitment initiated in 1992; follow-up ongoing	Mailed questionnaire	Oral cavity, pharynx, oesophagus (ICDO C00.0–C10.9, C13.0–13.9, C15.0–15.9)	*Lifelong alcohol* No alcohol >0–30 g/day >30–60 g/day >60 g/day	 4 83 20 17	**Hazard ratio** 1.0 (reference) 1.2 (0.4–3.4) 3.2 (1.0–10.1) 9.2 (2.8–30.9)	Follow-up time, sex, education, body mass index, vegetable and fruit consumption, tobacco smoking, energy intake	Looked at joint effects with smoking and observed a synergistic effect
Dikshit *et al.* (2005), Italy, Spain, Switzerland	Occurrence of second primary tumours among a cohort of 876 male cases of laryngeal/ hypo-pharyngeal cancer from a multicentric population-based case–control study (1979–82); follow-up until 2000	Interviewer-administered questionnaire	Oral cavity, pharynx, oesophagus (ICD9 140–150)	*Total alcohol* 0–40 g/day 41–80 g/day 81–120 g/day ≥21 g/day	 4 4 12 17	**Hazard ratio** 1.0 (reference) 0.8 (0.2–3.3) 3.0 (0.9–9.5) 3.5 (1.1–11.2) p=0.003	Age, centre, occupation, smoking, site of first cancer	

CI, confidence interval; ICD, International Classification of Diseases; NG, not given; SIR, standardized incidence ratio; [a] p-value indicated when CI not presented

et al., 1998; Boeing, 2002), four of which reported smoking-adjusted relative risks but one did not (Murata *et al*., 1996). Increases in risk with consumption of alcoholic beverages were observed in all five cohort studies of populations from the USA, Europe and Asia, and heavy consumption was associated with a significantly increased risk. The adjusted relative risks were 9.22 (95% CI, 2.75–30.93) for more than 60 g (or more than four drinks) per day (Boeing, 2002), 6.2 (95% CI, 3.7–10.1) for more than 60 g (or more than four drinks per day) in the American Cancer Society Prospective Study (Boffetta & Garfinkel, 1990) and 3.9 (95% CI, 2.1–7.1) for consumption of alcoholic beverages four to seven times per week in a study in Norway (Kjaerheim *et al*., 1998). A strong dose–response relationship was reported in three studies (Murata *et al*., 1996; Kjaerheim *et al*., 1998; Boeing, 2002); however, two studies found a J-shaped relationship with an inverse association with low levels of alcoholic beverage consumption (Boffetta & Garfinkel, 1990; Chyou *et al*., 1995). In both studies, an increase in risk was observed with increasing levels of alcoholic beverage consumption thereafter.

Separating the effects of alcoholic beverages and tobacco smoking is generally very difficult. In most of these studies, however, smoking was controlled for in the analyses (Boffetta & Garfinkel, 1990; Chyou *et al*., 1995; Kjaerheim *et al*., 1998; Boeing, 2002). The increases in risk with consumption of alcoholic beverages were consistently seen in situations where smoking was controlled for as well as where smoking was not taken into account.

Five cohort studies were based on special populations (Adami *et al*., 1992a; Kjaerheim *et al*., 1993; Tønnesen *et al*., 1994; Sigvardsson *et al*., 1996; Sørensen *et al*., 1998). This type of study usually does not consider individual exposure levels. The point estimates were either the SIRs or standardized mortality ratios (SMRs) without adjusting for tobacco smoking. Among special cohorts of alcoholics, an increase in risk for cancers of the oral cavity and pharynx compared either with the local population rates (Adami *et al*., 1992a; Tønnesen *et al*., 1994; Sørensen *et al*., 1998) or with a population control group (Sigvardsson *et al*., 1996) has also been shown. Among Swedish alcoholics, Adami *et al*. (1992a) found a fourfold increase in risk (95% CI, 2.9–5.6) for oral cavity and pharyngeal cancers. Tønnesen *et al*. (1994) also found more than a 3.5-fold increase in risk (95% CI, 3.0–4.3) among men and a 17-fold increase (95% CI, 10.8–26.0) among women. In Danish 1-year survivors of cirrhosis, Sørensen *et al*. (1998) found a ninefold increase in risk (95% CI, 7.8–10.8) compared with national incidence rates. Furthermore, among alcoholic cirrhosis patients, the risk was increased more than 11.5-fold (95% CI, 9.6–14.0) compared with fourfold (95% CI, 1.8–8.2) among chronic hepatitis cirrhosis patients. By cancer site, Sigvardsson *et al*. (1996) found 8.5-fold (95% CI, 2.0–37), 12-fold (95% CI, 1.6–92), 11-fold (95% CI, 1.4–85) and ninefold (95% CI, 1.1–71) increases in risk for cancers of the tongue, mouth, tonsil and hypoharynx, respectively, in a Swedish population. Conversely, a cohort study among members of the International Organization of Good Templars in Norway, an organization for which members sign a statement that they will abstain from the consumption of alcoholic beverages, showed a 56% decrease in risk (SIR 0.44; 95% CI,

0.09–1.27) compared with the national incidence rates (Kjaerheim *et al*., 1993). Data on individual alcoholic beverage and tobacco consumption, however, were not obtained, which makes the separation of the protective effects of abstaining from either factor very difficult, especially since the two habits are usually correlated.

Alcoholic beverages have also been shown to be a risk factor for second primary cancers of the oral cavity and pharynx in two prospective studies of patients with a first primary cancer (Day *et al*., 1994a; Dikshit *et al*., 2005). Day *et al*. (1994a) and Dikshit *et al*. (2005) studied the risks for second primary cancers of the upper aerodigestive tract in relation to alcoholic beverage consumption among North Americans and Europeans (from Italy, Spain and Switzerland), respectively. In both studies, an increase in risk was found, although a more dramatic increase was found among Europeans (3–3.5-fold increase in risk among those who drank ≥81 g per day) than among North Americans (1.5–2-fold increase in risk among those who drank ≥15 drinks [≥210 g] per week or ≥30 g per day), which may be attributed to differences in categorization.

Results from prospective cohort studies of the general population provide *sufficient* evidence for the important role of alcoholic beverage consumption in the development of oral and pharyngeal cancer. The strength of the association is demonstrated by significantly increased relative risks that range from 3.5 to 9.2. A strong dose–response relationship was observed in almost all of the studies. Alcoholic beverage consumption was associated with an increase in risk for oral and pharyngeal cancer across different geographic regions and populations, which further supports the evidence.

2.2.2 *Case–control studies*

(a) Cancer of the oral cavity (Table 2.3)

All of the studies listed in Table 2.3 were hospital-based case–control studies (Franceschi *et al*., 1990; Zheng *et al*., 1990; Choi & Kahyo, 1991a; Zheng *et al*., 1997; Rao & Desai, 1998; Balaram *et al*., 2002; Znaor *et al*., 2003; De Stefani *et al*., 2007) and all but one (Rao & Desai, 1998) adjusted for tobacco smoking when evaluating the effect of alcoholic beverage consumption. All six studies of cancer of the oral cavity reported a positive association, with a dose–response relationship with alcoholic beverage consumption in different geographical areas of the world. A study of cancer of the tongue with a relatively large sample size reported increased risks for 20–30 years of alcoholic beverage consumption (odds ratio, 3.3; 95% CI, 1.4–8.9 for men; 2.0; 95% CI, 1.0–4.6 for women) (Rao & Desai, 1998). No obvious association was found in a study of cancer of the tongue with a limited sample size (Zheng *et al*., 1997).

Overall, the increase in risk for oral cancer associated with alcoholic beverage consumption is consistent, even after controlling for smoking. The strength of the association was shown by elevated adjusted odds ratios for heavy consumption that ranged from 3.0 to 14.8. Furthermore, a dose–response relationship was observed with elevated alcoholic beverage consumption and increased risk in most studies with multiple exposure levels when adjusted for tobacco smoking. The association has been observed

Table 2.3 Case-control studies of cancer of the oral cavity and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Franceschi *et al.* (1990), Milan, Pordenone, Italy, 1986–89	157 men identified from hospitals in Milan and Pordenone; under 75 years of age; histologically confirmed; response rate, 98% overall for cases	1272 hospital-based, male non-cancer patients from same hospitals as cases matched on age, area of residence; excluded patients with alcohol- and tobacco-related conditions; response rate, 97%	Interviewer-administered questionnaire	Oral cavity (ICD9 140, 141, 143–145)	*Total drinks/ week* ≤19 20–34 35–59 ≥60 *p* for trend	 15 14 63 65	 1.0 (reference) 1.1 (0.5–2.5) 3.2 (1.6–6.2) 3.4 (1.7–7.1) <0.01	Age, area of residence, education, occupation, smoking habits	Also looked at pharyngeal cancers; looked at type of alcoholic beverage and joint effects with smoking
Zheng *et al.* (1990), Beijing, China, 1988–89	404 cases (248 men, 156 women) diagnosed at seven participating hospitals in the Beijing area; histologically confirmed; response rate, 100%	404 randomly selected non-cancer, hospital-based controls individually matched on age, sex, hospital; response rate, 100%	Interviewer-administered standardized questionnaire	Oral cavity (ICD9 141, 143–145)	**Men only** *Total alcohol in spirit equivalent* Never drinker <26 g/day 26–49 g/day 50–99 g/day >99 g/day	 42 52 42 39	 1.0 (reference) 1.3 (0.7–2.3) 1.1 (0.6–2.1) 1.4 (0.7–2.6) 2.8 (1.2–6.3)	Age, education, smoking	Assessed type of alcoholic beverage and joint effects with smoking

Table 2.3 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Choi & Kahyo (1991a), Seoul, Republic of Korea, 1986–89	157 cases (113 men, 44 women) from the Korea Cancer Center Hospital; cytological and/or histopathological confirmation	471 (339 men, 132 women) hospital-based, non-cancer controls matched (3:1 controls:cases) on age, sex, admission date; excluded patients with alcohol- and tobacco-related conditions	Interviewer-administered standardized questionnaire in hospital	Oral cavity (ICDO 140, 141, 143–145)	**Men only** *Total alcohol*[a] Non-drinker <1 hop/day 1–2 hops/day 2–4 hops/day >4 hops/day	 16 9 45 32 11	 1.0 (reference) 0.6 (0.3–1.4) 3.6 (1.8–7.2) 4.2 (2.1–8.4) 14.8 (5.0–43.7)	Smoking	Also looked at pharynx and larynx; [a]1 hop = 90 mL of soju [generally 20% alcohol, 14 g ethanol]; soju is most frequent alcoholic beverage type
Zheng *et al.* (1997), Beijing, China, 1988–89	111 cases (65 men, 46 women) diagnosed at seven participating hospitals in the Beijing area; aged 20–80 years; histologically confirmed	111 randomly selected non-cancer, hospital-based controls individually matched on age, sex, hospital; excluded patients with alcohol- and tobacco-related conditions	Interviewer-administered standardized questionnaire	Tongue	*Total alcohol in spirit equivalent* Never drinker <50 g/day 50 g/day >50 g/day *Spirits frequency* <5 days/week ≥5 days/week	 64 20 8 19 18 27	 1.0 (reference) 1.2 (0.5–3.2) 0.7 (0.2–2.3) 1.6 (0.6–4.4) 0.70 (0.28–1.70) 2.34 (0.90–6.06)	Education, smoking (matched on age, sex)	Same population as Zheng *et al.* (1990); looked at type of alcoholic beverage and joint effects with smoking

Table 2.3 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Rao & Desai (1998), Bombay, India, 1980–84	637 men from the hospital	635 hospital-based, unmatched controls; free from cancer, infectious disease, benign lesion	Interviewer-administered questionnaire before clinical examination	Tongue (ICD 140–144)	*Total duration of alcoholic beverage consumption*			Age, residence	
				Anterior tongue	Non-user	102	1.0 (reference)		
					1–10 years	11	1.2 (0.6–2.6)		
					11–20 years	12	2.0 (0.9–4.4)		
					21–30 years	12	3.3 (1.4–8.9)		
					≥31 years	4	1.3 (0.3–4.8)		
				Base tongue	Non-user	382	1.0 (reference)		
					1–10 years	38	1.5 (0.9–2.5)		
					11–20 years	35	1.6 (0.9–2.9)		
					21–30 years	32	2.0 (1.0–4.6)		
					≥31 years	8	0.5 (0.2–1.4)		
Balaram *et al.* (2002), southern India, 1996–99	591 cases (309 men, median age 56 years; 282 women, median age 58 years) from three centres in Bangalore, Madras, Trivandrum; response rate, 97%	582 (292 men, 290 women) hospital-based controls from the same hospitals as cases frequency matched by centre, age, sex; response rate, 90%	Interviewer (social worker)-administered questionnaire	Oral cavity	*Men only*			Centre, age, education, paan chewing, smoking	Looked at cessation of alcoholic beverage consumption and joint effects with paan chewing; former drinkers abstained ≥12 months
					Abstainers	102	1.0 (reference)		
					Former drinkers	65	1.78 (0.97–3.28)		
					Current drinkers				
					<3 drinks/week	29	2.17 (1.00–4.69)		
					3–13 drinks/week	22	2.14 (0.89–5.19)		
					≥14 drinks/week	29	1.97 (0.85–4.57)		
					p for trend		0.01		

Table 2.3 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Znaor *et al.* (2003), Chennai, Trivandrum, India, 1993–99	1563 men from the Cancer Institute (Chennai) and the Regional Cancer Center (Trivandrum); histologically confirmed	1711 male patients with non-tobacco-related cancers from same centres as cases and 1927 healthy male hospital visitors from Chennai only	Interviewer-administered questionnaire	Oral cavity (ICD9 140, 141, 143–5)	*Total alcohol; average amount of ethanol*[a] Never drinker <20 mL/day 20–50 mL/day >50 mL/day	 780 213 256 308	 1.0 (reference) 1.2 (1.0–1.5) 2.4 (1.9–3.1) 3.0 (2.3–3.8)	Age, centre, education, smoking	Looked at pharynx also [a] Reference was new drinkers
De Stefani *et al.* (2007), Montevideo, Uruguay, 1988–2000	335 men identified in the four major hospitals in Montevideo; microscopically confirmed; response rate, 97%	1501 male hospital-based non-cancer controls; excluded patients with alcohol- and tobacco-related conditions with no recent changes in diet; response rate, 97%	Interviewer-administered questionnaire in hospital	Oral cavity (excluding lip)	*Total alcohol* Never drinkers 1–60 mL 61–120 mL 121–240 mL ≥241 mL *p* for trend	 34 47 91 86 77	 1.0 (reference) 1.2 (0.8–2.0) 4.3 (2.7–6.8) 4.9 (3.1–7.9) 7.0 (4.2–11.5) <0.0001	Age, residence, urban/rural status, hospital, year of diagnosis, education, family history of cancer, occupation, vegetable and fruit consumption, maté intake, smoking	Looked at pharynx also; looked at type of alcoholic beverage and joint effects with smoking

CI, confidence interval; ICD, International Classification of Diseases

across different geographical regions and populations, which further supports the key role of alcoholic beverage consumption in oral and pharyngeal carcinogenesis.

(b) Cancer of the pharynx (Table 2.4)

Among nine case–control studies of cancer of the pharynx, three were population-based (Tuyns *et al*., 1988; Nam *et al*., 1992; Cheng *et al*., 1999) and six were hospital-based (Franceschi *et al*., 1990; Choi & Kahyo, 1991a; Maier *et al*., 1994; Znaor *et al*., 2003; De Stefani *et al*., 2004, 2007). All studies adjusted for or were stratified by tobacco smoking. Results from all of the studies showed a strong association with alcoholic beverage consumption, except for one study of nasopharyngeal cancer in Taiwan, China (Cheng *et al*., 1999).

Alcoholic beverage consumption was associated with an increase in risk for cancers of the oropharynx and hypopharynx across different geographical regions and populations and the point estimates of adjusted odds ratios ranged from 3.6 to 125.2. Furthermore, all studies but one (Cheng *et al*., 1999) observed a strong dose–response trend between alcoholic beverage consumption and risk for oro- and hypopharyngeal cancer. A possible explanation for the lack of association in the study from Taiwan may be the categorization of exposure: the highest exposure group contained people who consumed ≥15 g (equivalent to just over one drink) per day, which may be too low a level to detect an association.

(c) Cancer of the oral cavity and pharynx combined (Table 2.5)

A total of 19 studies of cancer of the oral cavity and pharyngeal cancer combined were identified (Blot *et al*., 1988; Merletti *et al*., 1989; Barra *et al*., 1990, 1991; Maier *et al*., 1992a; Marshall *et al*., 1992; Mashberg *et al*., 1993; Kabat *et al*., 1994; Sanderson *et al*., 1997; Hayes *et al*., 1999; Franceschi *et al*., 2000; Garrote *et al*., 2001; Schwartz *et al*., 2001; Altieri *et al*., 2004; Castellsagué *et al*., 2004; Llewellyn *et al*., 2004a,b; Rodriguez *et al*., 2004; Shiu & Chen, 2004). Six were population-based (Blot *et al*., 1988; Merletti *et al*., 1989; Marshall *et al*., 1992; Sanderson *et al*., 1997; Hayes *et al*., 1999; Schwartz *et al*., 2001) and the rest were hospital-based. Tobacco smoking was considered as a potential confounding factor in almost all of the studies. Seventeen studies reported a strong association, with a dose–response trend, between alcoholic beverage consumption and cancers of the oral cavity and pharynx and two reported an increased risk, but the 95% CIs included a null value (Merletti *et al*., 1989; Llewellyn *et al*., 2004b).

An increase in risk for cancers of the oral cavity and pharynx has been observed in most studies across different geographical regions and populations and the point estimates of adjusted odds ratios ranged from 4.1 to 8.8 for heavy consumption of alcoholic beverages when adjusted for tobacco smoking and other confounding factors. The lack of significant associations in two studies (Merletti *et al*., 1989; Llewellyn *et al*., 2004b) may be explained by small sample size (86 male and 36 female cases in the former and

Table 2.4 Case–control studies of pharyngeal cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment factors	Comments
Tuyns *et al.* (1988), France, Italy, Spain, Switzerland, 1980–83	281 men from Calvados (France), Turin and Varese (Italy), Navarra and Zaragoza (Spain), Geneva (Switzerland); histologically confirmed; response rate, 75% (Spain, Italy), 92% (Geneva)	3057 men stratified by age from census lists, electoral lists, or population registries; response rate, 75% (64% in Geneva, 56% in Turin)	Interviewer-administered questionnaire	Hypopharynx (ICD9 148.0, 148.1, 148.3, 149.8)	*Total alcohol* 0–20 g/day 21–40 g/day 41–80 g/day 81–120 g/day ≥121 g/day	 NG NG NG NG NG	 1.0 (reference) 1.6 (0.7–3.4) 3.2 (1.6–6.2) 5.6 (2.8–11.2) 12.5 (6.3–25.0)	Age, place, age/place interaction, cigarettes/day	Looked at joint effects with smoking
Franceschi *et al.* (1990), Milan, Pordenone, Italy, 1986-89	134 men, under age 75 years; histologically confirmed; response rate, 98% overall	1272 male hospital-based non-cancer patients from same hospitals as cases matched on age, area of residence; excluded patients with alcohol- and tobacco-related conditions; response rate, 97%	Interviewer-administered questionnaire	Pharynx, hypopharynx/larynx junction included (ICD9 146, 148, 161.1)	*Total alcohol* ≤19 drinks/week 20–34 drinks/week 35–59 drinks/week ≥60 drinks/week *p* for trend	 13 14 34 73	 1.0 (reference) 0.9 (0.4–2.0) 1.5 (0.8–3.1) 3.6 (1.8–7.2) 0.01	Age, area of residence, education, occupation, smoking habits	Also looked at oral cancers; looked at type of alcoholic beverage and joint effects with smoking

Table 2.4 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment factors	Comments
Choi & Kahyo (1991a), Seoul, Republic of Korea, 1986–89	152 cases (133 men, 19 women) from the Korea Cancer Centre Hospital; cytological and/or histopathological confirmation	456 (399 men, 57 women) hospital-based non-cancer patients from same hospital matched (3 controls per case) on age, sex, admission date; excluded patients with alcohol- and tobacco-related conditions	Interviewer-administered questionnaire	Pharynx (ICDO 146–149)	**Men only** *Total alcohol*[a] Non-drinker <1 hop/day 1–2 hops/day 2–4 hops/day >4 hops/day	 16 20 44 40 13	 1.0 (reference) 1.2 (0.6–2.5) 2.2 (1.1–4.2 4.1 (2.1–7.9) 11.2 (4.2–29.8)	Smoking	Looked at oral cavity also; [a]1 hop = 90 mL of soju [generally 20% alcohol, 14 g ethanol]; soju is most frequent alcoholic beverage type

Table 2.4 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment factors	Comments
Nam *et al.* (1992), USA, 1986	204 (141 men, 63 women) whites from the National Mortality Followback Survey who died of NPC, age <65 years; overall response rate, 89% for whole study population	408 (282 men, 126 women) randomly selected (2:1 controls:cases) whites from the same survey matched on age, sex; died from causes unrelated to smoking or alcoholic beverage use	Questionnaire from next of kin	Nasopharynx	*Total alcohol*			Smoking, sex	Looked at joint effects with smoking
					0–3 drinks/week	107	1.0 (reference)	None	
					4–23 drinks/week	40	0.9 (0.5–1.4)	None	
					≥24 drinks/week	57	1.8 (1.1–3.1)		
					Men only				
					Total alcohol				
					0–3 drinks/week	64	1.0 (reference)		
					4–23 drinks/week	32	1.1 (0.6–1.8)		
					≥24 drinks/week	45	1.9 (1.1–3.2)		
					p for trend		0.007		
					Women only				
					Total alcohol				
					0–3 drinks/week	43	1.0 (reference)		
					4–23 drinks/week	8	1.2 (0.4–3.1)		
					≥24 drinks/week	12	7.3 (2.1–32.5)		
					p for trend		<0.001		

Table 2.4 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment factors	Comments
Maier *et al.* (1994), Heidelberg, Germany, 1990–91	105 men from the Otorhinolaryngology-Head and Neck Surgery Department of the University of Heidelberg; histologically confirmed	420 male outpatients without known cancer from the same centre as cases matched (4:1 controls:cases) on age, residential area	Interviewer-administered standardized questionnaire	Oropharynx, hypopharynx	*Total alcohol* <25 g/day 25–50 g/day 50–75 g/day 75–100 g/day >100 g/day *p* for trend	 11 17 22 20 35	 1.0 (reference) 3.5 (1.4–8.6) 12.9 (4.7–35.6) 54.7 (13.5–221.0) 125.2 (28.4–551.6) 0.0001	Tobacco smoking	Beer preferred alcoholic beverage in this area
Cheng *et al.* (1999), Taipei, Taiwan, China, 1991–94	375 cases (260 men, 115 women) from two teaching hospitals in Taipei; histologically confirmed; response rate, 99%	327 (223 men, 104 women) population controls with no history of NPC using the National Household Registration System individually matched on age, sex, residence; response rate, 88%	Interviewer-administered structured questionnaire	Nasopharynx	*Total alcohol (in g ethanol/day)* 0 <15 ≥15 *p* for trend	 270 47 57	 1.0 (reference) 0.7 (0.5–1.2) 1.1 (0.7–1.7) 0.9	Age, sex, race, education, family history of NPC, smoking	
Znaor *et al.* (2003), Chennai, Trivandrum, India, 1993–99	636 men from the Cancer Institute (Chennai) and the Regional Cancer Center (Trivandrum); histologically confirmed	1711 male patients with non-tobacco-related cancers from same centres as cases and 1927 healthy male hospital visitors from Chennai only	Interviewer-administered questionnaire	Pharynx (ICD9 146, 148, 149)	*Total alcohol, average amount of ethanol*[a] Never drinker <20 mL/day 20–50 mL/day >50 mL/day	 297 70 106 162	 1.0 (reference) 1.1 (0.8–1.5) 2.3 (1.7–3.2) 3.6 (2.7–4.8)	Age, centre, education, smoking	Looked at oral cavity also [a] Reference category was new drinkers

Table 2.4 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment factors	Comments
De Stefani *et al.* (2004), Montevideo, Uruguay, 1997–2003	85 men identified in the four major hospitals in Montevideo; microscopically confirmed; response rate, 97.5%	640 hospital-based men from the same hospitals as cases; excluded patients with alcohol- and tobacco-related conditions with no recent changes in diet; frequency matched (2:1 controls:cases) on age, residence; response rate, 97%	Interviewer-administered questionnaire	Hypopharynx	*Total alcohol (in mL ethanol/day)* Never drinkers 1–60 61–120 121–240 ≥241 *p* for trend	 191 175 116 88 70	 1.0 (reference) 2.3 (0.7–8.1) 7.6 (2.3–24.4) 5.6 (1.7–18.6) 12.8 (4.0–41.2) <0.0001	Age, residence, urban/rural status, education, smoking, body mass index	Looked at cessation of alcoholic beverages, type of alcoholic beverages and joint effects with smoking
De Stefani *et al.* (2007), Montevideo, Uruguay, 1988–2000	441 men identified in the four major hospitals in Montevideo; microscopically confirmed; response rate, 97%	1501 male hospital-based non-cancer controls; excluded patients with alcohol- and tobacco-related conditions with no recent changes in diet; response rate, 97%	Interviewer-administered questionnaire in hospital	Pharynx (excluding nasopharynx)	*Total alcohol (in mL ethanol/day)* Never drinkers 1–60 61–120 121–240 ≥241 *p* for trend	 33 53 97 136 122	 1.0 (reference) 1.4 (0.9–2.2) 4.4 (2.8–7.0) 7.9 (5.0–12.3) 11.7 (7.2–18.9) <0.0001	Age, residence, urban/rural status, hospital, year of diagnosis, education, family history of cancer, occupation, vegetable and fruit consumption, maté intake, smoking	Looked at oral cavity also; looked at type of alcoholic beverages and joint effects with smoking

CI, confidence interval; ICD, International Classification of Diseases; NPC, nasopharyngeal carcinoma

Table 2.5 Case–control studies of cancers of the oral cavity and pharynx combined and alcoholic beverage consumption

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Blot *et al.* (1988), USA, 1984–85	1114 (762 men, 352 women) cases; identified from the population-based registries covering metropolitan Atlanta (GA), Los Angeles, Santa Clara, San Mateo counties (CA), New Jersey; aged 18–79 years; pathologically confirmed; response rate, 75%; 1268 population controls	Interviewer-administered standardized questionnaire	Oral cavity, pharynx (ICD9 141, 143–146, 148, 149), excluding salivary gland, nasopharynx	**Men** *Hard liquor* <1 drink/week 1–4 drinks/week 5–14 drinks/week 15–29 drinks/week ≥30 drinks/week *Beer* <1 drink/week 1–4 drinks/week 5–14 drinks/week 15–29 drinks/week ≥30 drinks/week *Wine* <1 drink/week 1–4 drinks/week 5–14 drinks/week 15–29 drinks/week ≥30 drinks/week	 40 71 99 154 389 146 130 141 134 195 497 114 70 31 35	 1 (reference) 1.0 (0.7–1.3) 1.3 (0.9–1.8) 2.6 (1.7–3.9) 5.5 (3.4–9.1) 1 (reference) 1.2 (0.8–1.7) 1.7 (1.2–2.4) 3.4 (2.7–5.1) 4.7 (3.0–7.3) 1 (reference) 0.7 (0.5–1.0) 0.7 (0.4–1.0) 0.9 (0.5–1.8) 2.5 (0.9–6.5)	Age, race, study location, respondent status (self versus proxy), tobacco smoking, other two types of alcoholic beverages	

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Blot *et al.* (1988) (contd)	1268 population controls from random-digit dialling; aged 18–64 years, frequency-matched on age, sex, race (black, white); response rate, 79% (under 65 years) and 76% (≥ 65 years)			**Women**				
				Hard liquor		1 (reference)		
				<1 drink/week	135	1.3 (0.9–2.1)		
				1–4 drinks/week	78	1.5 (0.9–2.5)		
				5–14 drinks/ week	65	4.9 (1.6–14.3) 7.8 (2.1–29.2)		
				15–29 drinks/ week	32	1 (reference) 2.2 (1.4–3.6)		
				≥30 drinks/week	41	2.9 (1.5–5.6)		
				Beer		2.3(0.9–6.5)		
				<1 drink/week	180	18.0 (2.1–159)		
				1–4 drinks/week	73	1 (reference)		
				5–14 drinks/ week	48	0.6 (0.4–1.0) 0.8 (0.4–-1.4)		
				15–29 drinks/ week	24	0.5 (0.1–2.3) 1.6 (0.2–13.6)		
				≥30 drinks/week	27			
				Wine				
				<1 drink/week	230			
				1–4 drinks/week	60			
				5–14 drinks/ week	41			
				15–29 drinks/ week	1			
				≥30 drinks/week	7			

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Merletti *et al.* (1989) Torino, Italy, 1982–84	122 cases (86 men, 36 women); histologically confirmed; response rate, 85% 606 (385 men, 221 women) population-based controls, randomly selected from files of residents, stratified by age, sex; response rate, 55%	Interviewer-administered standardized questionnaire	Oral cavity, oropharynx (ICD9 140.3–140.5, 141, 143–146)	**Total alcohol** *Men* 1–20 g/day 21–40 g/day 41–80 g/day 81–120 g/day >120 g/day *Women* 1–20 g/day 21–40 g/day >40 g/day	 8 9 29 14 22 6 13 12	 1.0 (reference) 0.7 (0.2–2.6) 1.3 (0.4–3.8) 0.6 (0.2–2.1) 2.1 (0.6–6.8) 1.0 (reference) 3.0 (0.9–10.5) 3.4 (0.9–12.9)	Age, education, area of birth, tobacco habits	Looked at type of alcoholic beverage and joint effect of smoking
Barra *et al.* (1990), Milan, Pordenone, Italy, 1986–90	305 men from hospitals in Pordenone and Milan; median age, 58 years; histologically confirmed; refusal rate, 2% 1621 men, hospital-based non-cancer patients; median age, 57 years; matched by area of residence, age; excluded patients with alcohol- and tobacco-related conditions; refusal rate, 3%	Interviewer-administered questionnaire in hospital	Oral cavity, pharynx	*Total alcohol* ≤20 drinks/week 21–55 drinks/week 56–83 drinks/week ≥84 drinks/week	 17 5 12 41	 1 (reference) 0.8 (0.3–2.3) 1.8 (0.8–4.4) 4.1 (2.0–8.2)	Age, area of residence, occupation, tobacco smoking	Includes study population from Franceschi *et al.* (1990); looked at types of alcoholic beverage

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Barra *et al.* (1991), Pordenone, Italy, 1985–90	272 (236 men, 36 women) cases from hospitals in Pordenone; median age, 60 years; histologically confirmed; refusal rate, 3% 1884 (1122 men, 762 women) non-cancer, hospital-based patients; median age, 58 years; matched by area of residence, age; excluded patients with alcohol- and tobacco-related conditions; refusal rate, 3%	Interviewer-administered questionnaire in hospital	Oral cavity, pharynx	*Total alcohol* ≤20 drinks/week 21–34 drinks/week 35–55 drinks/week 56–83 drinks/week ≥84 drinks/week *p* for trend	 24 28 21 31 83 106	Non-cancer controls 1.0 (reference) 2.2 (1.2–4.0) 2.4 (1.2–4.7) 6.6 (3.5–12.5) 11.4 (6.0–21.4) ≤ 0.01	Age, sex, education, occupation, tobacco	Includes study population from Barra *et al.*(1990) study; also compared results with cancer control group with similar results; looked at types of alcoholic beverage

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Maier *et al.* (1992a), Giessen & Heidelberg, Germany	200 male patients selected from ENT departments from University of Heidelberg and Giessen with squamous cells cancer of the head and neck; 800 male subjects without known cancer served as controls selected from out patients clinics	Interviewer-administered questionnaire	Head and neck	Total alcohol <25 g/day 25–50 g/day 50–75g/day 75–100 g/day >100 g/day		 1.0 (reference) 1.7 (1.0–2.7) 6.7 (3.9–11.3) 16.2 (7.1–36.8) 21.4 (11.2–40.6)	Tobacco	Females excluded due to low number of cases

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Marshall *et al.* (1992), New York, USA, 1975–83	290 (201 men, 89 women) identified from pathology records of 20 major hospitals in Erie, Niagara, Monroe (New York); aged 45 years or younger; pathologically confirmed; response rate of those contacted, 60% 290 (201 men, 89 women) population-based individually matched on age, sex, neighborhood; response rate, 41%	Interviewer-administered standardized questionnaire	Oral cavity, pharynx	Quantity–frequency–duration derived quintiles 1 2 3 4 5 *p* for trend		 1 (reference) 2.4 (1.1–5.2) 2.7 (1.2–6.1) 3.4 (1.6–7.4) 14.8 (6.8–32.3) <0.0001		Black cases excluded from analysis

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Mashberg *et al.* (1993) New Jersey, USA, 1972–83	359 white and black male veterans with invasive cancer and in-situ carcinoma identified in the Department of Veterans Affairs Medical Center; median age, 57 years; histologically confirmed 2280 white or black male patients from the same centre as cases of the same age range as cases (37–80 years); median age, 58 years; excluding patients with cancer or dysplasia of the pharynx, larynx, lung, oesophagus	Interviewer-administered standardized questionnaire	Oral cavity, oropharynx	*Total alcohol (in whiskey equiv./ day)*[a] Minimal drinking 2–5 per day 6–10 per day 11–21 per day ≥22 per day Former drinker (abstained ≥2 years)	 17 37 91 112 98 4	 1 (reference) 2.6 (1.4–4.7) 6.4 (3.7–11.0) 7.9 (4.6–13.4) 7.1 (4.1–12.2) 1.9 (0.6–5.7)	Age, race, tobacco smoking	Looked at type of alcoholic beverage and joint effects with smoking; 1 whiskey equivalent = 10.2 g alcohol

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Kabat *et al.* (1994), USA, 1977–90	1560 (1097 men, 463 women) enrolled in 28 hospitals in eight US cities 2948 (2075 men, 873 women) hospital-based; matched on age, sex, race, hospital, date of interview	Interviewer-administered questionnaire	Oral cavity, pharynx (excluding nasopharynx)	*Total alcohol (whiskey equiv.)*		*Men*	Age, education, smoking, race, time period, type of hospital	Looked at type of alcoholic beverage and joint effects of smoking; 1 oz whiskey equivalent = 10.2 g alcohol
				Non-drinker	50	1		
				Occasional	142	1.4 (0.9–2.0)		
				1–2.9 oz/day	246	2.9 (2.0–4.2)		
				4–6.9 oz/day	169	4.7 (3.2–7.1)		
				≥7 oz/day	466	7.3 (5.1–10.7)		
Kabat *et al*. (1994) (contd)						*Women*		
				Non-drinker	123	1 (reference)		
				Occasional	130	1.2 (0.9–1.6)		
				1–3.9 oz/day	108	1.8 (1.3–2.6)		
				4–6.9 oz/day	98	4.8 (2.9–7.8)		
				≥7 oz/day	–	–		
Maier *et al.* (1994), Heidelberg, Giessen, Germany, 1987–88	200 men from the ENT departments of the Universities of Heidelberg and Giessen; histologically confirmed 800 male outpatients without known cancer; matched on age, residential area (4:1 controls:cases)	Interviewer-administered questionnaire	Oral cavity, pharynx, larynx	*Total alcohol*			Tobacco smoking	Beer preferred alcoholic beverage in the area; looked at joint effect of smoking
				<25 g/day		1 (reference)		
				25–50 g/day		1.7 (1.0–2.7)		
				50–75 g/day		6.7 (3.9–11.3)		
				75–100 g/day		16.2 (7.1–36.8)		
				>100 g/day		21.4 (11.2–40.6)		

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Sanderson *et al.* (1997) Netherlands, 1980–90	303 women aged ≥40 years from the University Hospital's Head Cancer Centre 1779 women from a national survey by National Central Bureau of Statistics; matched on age	Hospital records (cases) and national survey (controls)	Oral cavity, oropharynx (excluding salivary glands and lip)	*Total alcohol* Non-drinker 1–5 units/day >5 units/day	 153 104 46	 1 (reference) 3.5 (2.5–4.8) 20.8 (11.4–37.8)	Age	Looked at joint effect of smoking
Hayes *et al.* (1999), Puerto Rico, 1992–95	342 (286 men, 56 women) identified through pathology laboratories and Central Cancer Registry; aged 21–79 years; histologically confirmed; response rate, 70% 521 (417 men, 104 women) population-based; frequency-matched by age, gender; response rate, 83%	Interviewer-administered questionnaire	Oral cavity, pharynx (ICD9 141–143–146, 148, 149)	*Total alcohol*[a] Non-drinker 1–7 drinks/week 8–21 drinks/week 22–42 drinks/week >42 drinks/week *p* for trend Non-drinker 1–7 drinks/week 8–21 drinks/week 22–42 drinks/week >42 drinks/week *p* for trend	 9 19 28 49 164 26 13 1 12 – 	*Men* 1 (reference) 0.8 (0.3–2.1) 1.4 (0.6–3.4) 3.3 (1.4–8.0) 7.7 (3.3–17.9) <0.0001 *Women* 1 (reference) 0.8 (0.3–2.1) 0.9 (0.0–17.0) 9.1 (0.9–94.2) – (–) 0.02	Age, tobacco use	Looked at cessation of alcoholic beverage consumption and joint effect of smoking

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Franceschi *et al.* (2000), Italy, Switzerland, 1992–97	754 (638 men, 116 women) from major teaching and general hospitals in Pordenone, Rome, Latina (Italy) and Vaud (Switzerland); aged 22–77 years; histologically confirmed; response rate, 95% 1775 (1254 men, 521 women) hospital-based non-cancer from the same network of hospitals as cases; excluded tobacco- and alcohol-related conditions; frequency-matched (5:1 for women, 2:1 for men controls:cases) on age, sex, area of residence; response rate, 95%	Interviewer-administered questionnaire	Oral cavity, pharynx (excluding lip, salivary glands, nasopharynx)	*Total alcohol* Current drinkers Never 1–20 drinks/week 21–62 drinks/week 63–90 drinks/week ≥91 drinks/week χ^2 for trend	 32 82 271 145 98	 1 (reference) 0.7 (0.4–1.2) 2.6 (1.6–4.2) 8.9 (5.0–15.9) 16.7 (8.6–32.7) 160.5 $p < 0.001$	Age, sex, study centre, education, interviewer, tobacco smoking, drinking status	Study population from Franceschi *et al.* (1999); looked at alcoholic beverage consumption cessation

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Garrote *et al.* (2001), Havana, Cuba, 1996–99	200 (143 men, 57 women) from the Instituto Nacional de Oncologia y Radiobiologia of Havana; age, 64 years; response rate, 88%. 200 (136 men, 64 women) hospital-based controls admitted to same hospital and three other major hospitals in Havana; excluded patients with alcohol- and tobacco-related conditions; frequency-matched on age, sex; median age, 62 years; response rate, 79%	Interviewer (dentist)-administered questionnaire	Oral cavity, oropharynx	*Total alcohol* Abstainers Former drinkers (abstained ≥12 months) *Current drinkers* <7 drinks/week 7–20 drinks/week 21–69 drinks/week ≥70 drinks/week χ^2 for trend	 83 36 15 25 21 20	 1 (reference) 1.04 (0.5-2.1) 1.1 (0.5–2.6) 1.6 (0.7–3.7) 2.2 (0.9–5.5) 5.7 (1.8–18.5) 8.75 p <0.01	Age, sex, area of residence, education, tobacco smoking	Looked at cessation, type of alcoholic beverage and joint effect of smoking

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Schwartz *et al.* (2001), Washington, USA, 1985–95	333 (237 men, 96 women) in-situ and invasive cancers ascertained through the population-based Cancer Surveillance System (participant of SEER); aged 18–65 years from two original studies; response rates, 54% and 63%. 541 (387 men, 154 women) population-based; frequency-matched on age, sex; response rates, 63% and 61%	Interviewer-administered structured questionnaire	Oral cavity, oropharynx (excluding lip)	*Total alcohol* <1 drink/week 1–7 drinks/week 8–14 drinks/week 15–42 drinks/week ≥43 drinks/week		1 (reference) 1.0 (0.6–1.5) 1.7 (1.0–2.9) 2.8 (1.7–4.8) 4.7 (2.4–9.4)	Age, sex, race, tobacco smoking	Looked at joint effect of smoking and *ADH3*

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Altieri *et al.* (2004), Italy, Switzerland, 1992–97	749 (634 men, 115 women) from Pordenone, Rome, Latina (Italy) and Vaud (Switzerland) admitted to major teaching and general hospitals in area under surveillance; aged 22–77 years; histologically confirmed 1772 (1252 men, 520 women) hospital-based from the same network of hospitals as cases; aged 20–78 years; excluded patients with alcohol- and tobacco-related conditions	Interview-administered structured questionnaire	Oral cavity, pharynx	*Total alcohol* Non-drinkers 1–2 drinks/day 3–4 drinks/day 5–7 drinks/day 8–11 drinks/day ≥12 drinks/day χ^2 for trend	 33 93 95 132 199 196	 – 1 (reference) 2.1 (1.5–2.9) 5.0 (3.5–7.1) 12.2 (8.4–17.6) 21.1 (14.0–31.8) 272.07 p<0.0001	Age, sex, study centre, education, tobacco smoking	

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Castellsagué *et al.* (2004), Spain, 1996–99	375 (304 men, 71 women) identified from hospitals in Granada, Sevilla, Barcelona; mean age, 60 years; histologically confirmed; response rate, 76.5% 375 (304 men, 71 women) non-cancer hospital-based from same hospitals as cases; frequency-matched on age, sex; mean age, 60 years; excluded patients with alcohol- and tobacco-related diagnoses; response rate, 91%	Interviewer-administered standardized questionnaire in hospital	Oral cavity, oropharynx (ICDO C1-C10)	*Average no. of drinks/day* Never drinker 1 2 3–4 5–6 7–10 ≥11 *p* for trend	 35 59 27 49 55 68 82	 1 (reference) 2.0 (1.1–3.8) 3.7 (1.6–8.6) 6.2 (2.8–13.7) 10.6 (4.6–24.5) 10.3 (4.6–23.2) 13.7 (6.0–31.0) <0.0001	Age group, sex, education, tobacco smoking, centre	Looked at type of alcoholic beverage and joint effect of smoking

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Llewellyn *et al.* (2004a), United Kingdom, 1999–2001	53 (28 men, 25 women) from 14 participating hospitals in the Southeast of England; aged ≤ 45 years; response rate, 80% 91 (45 men, 46 women) non-cancer patients; matched (2:1 controls:cases when feasible) on age, sex, area of residence	Interviewer-administered standardized questionnaire and self-completed questionnaire	Oral cavity, oropharynx (ICD-10 C00-C06, C0, C10)	**Total alcohol** *Men* Within recommended levels[a] Over recommended levels *Women* Within recommended levels[a] Over recommended levels		 1 (reference) 8.1 (1.6–40.1) 1 (reference) 3.8 (0.7–20.7)	Social class, race, ever smoking (matching variables: age, sex, area of residence)	[a]Recommended levels: for men, ≤21 units/ week; for women, ≤14 units/ week
Llewellyn *et al.* (2004b), United Kingdom, 1990–97	116 (65 men, 51 women) identified by the Thames Cancer Registry; aged ≤ 45 years; response rate, 59% 207 (112 men, 95 women) non-cancer patients; matched (2:1 controls:cases when feasible) on age, sex, area of residence	Self-completed questionnaire	Oral cavity, oropharynx (ICD-10 C00-C06, C0, C10)	**Total alcohol** *Men* Within recommended levels[a] Over recommended levels *Women* Within recommended levels[a] Over recommended levels		 1 (reference) 1.6 (0.8–3.1) 1 (reference) 1.6 (0.6–4.2)	Social class, race, ever smoking (matching variables: age, sex, area of residence)	[a]Recommended levels : for men, ≤21 units/ week; for women, ≤14 units/ week

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Rodriguez *et al.* (2004), Italy, Switzerland, 1984–93, 1992–97	137 (113 men, 24 women) from Milan and Pordenone, Italy (1984–93) and Vaud, Switzerland (1992–97), under age 46 years; histologically confirmed; response rate, 95%. 298 (226 men, 72 women) non-cancer hospital-based; matched 2:1 (control:case) for men and 3:1 for women on age, sex, study centre; below age 46 years; excluded patients with alcohol- and tobacco-related conditions; response rate, 95%	Interviewer-administered questionnaire	Oral cavity, pharynx	*Total alcohol* Non-drinkers <3 drinks/day 3–<6 drinks/day 6–<10 drinks/day ≥10 drinks/day χ^2 for trend	 13 20 19 37 46	 1 (reference) 0.7 (0.3–1.8) 1.0 (0.4–2.8) 3.7 (1.2–11.1) 4.9 (1.6–15.1) 17.5 p<0.0001	Age, sex, study centre, education, marital status, body mass index, tobacco smoking, coffee consumption	Study populations from Franceschi *et al.* (1990, 2000)

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Shiu & Chen (2004), Taipei, Taiwan, 1988–98	74 (71 men, 3 women) randomly selected from 1688 cancers identified at a medical centre; response rate, 74% 187 patients with periodontal disease free of leukoplakia and oral cancer, randomly selected from 25 882 patients; response rate, 94%	Interviewer-administered questionnaire	Oral cavity, pharynx (140–149, except 142 and 147)	**Total alcohol** *Leukoplakia versus normal* No Yes *Oral cancer versus leukoplakia* No Yes		 1 (reference) 0.76 (0.4–1.4) 1 (reference) 2.37 (1.5–3.8)	Tobacco smoking, betel-quid chewing	

ADH3, alcohol dehydrogenase 3 gene; CI, confidence interval; ICD, International Classification of Diseases; SEER, Surveillance, Epidemiology and End Result

65 male and 51 female cases in the latter), which limits the power to detect an association, as well as the inclusion of light drinkers in the baseline comparison group (1–20 g per day in the former and within the recommended level in the latter).

2.2.3 *Types of alcoholic beverage (Table 2.6)*

In a study not described previously, Schildt *et al*. (1998) investigated the effects of snuff, smoking and alcoholic beverage consumption on the risk for cancer of the oral cavity. Among 354 histologically confirmed cases reported to the Cancer Registry from Norrbotten, Vasterbotten, Jamtland and Vasternorrland, Sweden, between 1980 and 1989 and 354 individually matched population controls, beer and liquor were found to be the types of alcoholic beverage associated with a higher risk (odds ratio for beer, 1.5; 95% CI, 0.7–3.2; odds ratio for liquor, 1.5; 95% CI, 0.9–2.3) in a model that contained snuff, smoking and the other types of alcohol. Self-completed questionnaires were completed by proxies for 60% of the participants.

Assessment of risk associated with different types of alcoholic beverage is a difficult task; drinkers rarely consume only one type of alcoholic beverage, and isolating the effects of a single type in the presence of the other types is not easy to accomplish. Furthermore, heterogeneity of effects across different populations further complicates the interpretation of results. Overall, among studies in the USA, the ranking from highest to lowest risk by alcoholic beverage type is beer, hard liquor and wine (Blot *et al*., 1988; Mashberg *et al*., 1993; Day *et al*., 1994b; Kabat *et al*., 1994). Among the Italian studies, the highest risk was associated with wine consumption (Franceschi *et al*., 1990). In Latin America, hard liquor was associated with the highest risk among Cuban (Garrote *et al*., 2001) and Brazilian populations (Schlecht *et al*., 2001), and wine was associated with the highest risk among Uruguayans (De Stefani *et al*., 2004). In several studies, the other types of alcoholic beverage were not controlled for in the analyses which may distort the association under study. Generally, the types of alcoholic beverage that are the largest contributors to alcoholic beverage consumption are usually associated with the greatest increases in risk.

2.2.4 *Joint effects (Table 2.7)*

The joint effects of alcoholic beverage consumption and tobacco smoking on cancers of the oral cavity and pharynx have been assessed extensively. The studies varied in their methods and in the approaches used to assess effect modification, which ranged from descriptive to formal estimation of interaction in multivariate models.

For cancers of the oral cavity and pharynx, the evidence comes almost entirely from case–control studies carried out in Asia, Australia, Europe and the USA. Two prospective cohort studies have reported joint effects of alcoholic beverage consumption and tobacco smoking including the European Prospective Investigation into Cancer and Nutrition (EPIC) study (Boeing, 2002) and a cohort study of Japanese men (Chyou

Table 2.6 Consumption of different types of alcoholic beverage and incidence of cancers of the oral cavity and pharynx

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Blot *et al.* (1988), USA, 1984–85	1114 (762 men, 352 women) cases; identified from the population-based registries covering metropolitan Atlanta (GA), Los Angeles, Santa Clara, San Mateo counties (CA), New Jersey; aged 18–79 years; pathologically confirmed; response rate, 75%; 1268 population controls	Interviewer-administered standardized questionnaire	Oral cavity, pharynx (ICD9 141, 143–146, 148, 149), excluding salivary gland and nasopharynx	**Men** *Hard liquor* <1 drink/week 1–4 drinks/week 5–14 drinks/week 15–29 drinks/week ≥30 drinks/week *Beer* <1 drink/week 1–4 drinks/week 5–14 drinks/week 15–29 drinks/week ≥30 drinks/week *Wine* <1 drink/week 1–4 drinks/week 5–14 drinks/week 15–29 drinks/week ≥30 drinks/week	 40 71 99 154 389 146 130 141 134 195 497 114 70 31 35	 1 (reference) 1.0 (0.7–1.3) 1.3 (0.9–1.8) 2.6 (1.7–3.9) 5.5 (3.4–9.1) 1 (reference) 1.2 (0.8–1.7) 1.7 (1.2–2.4) 3.4 (2.7–5.1) 4.7 (3.0–7.3) 1 (reference) 0.7 (0.5–1.0) 0.7 (0.4–1.0) 0.9 (0.5–1.8) 2.5 (0.9–6.5)	Age, race, study location, respondent status (self versus proxy), tobacco smoking, other two types of alcoholic beverage	

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Blot *et al*. (1988) (contd)	Population controls from random-digit dialling; aged 18–64 years; frequency-matched on age, sex, race (black, white); response rate, 79% (under 65 years) and 76% (≥65 years)			**Women**				
				Hard liquor				
				<1 drink/week	135	1 (reference)		
				1–4 drinks/week	78	1.3 (0.9–2.1)		
				5–14 drinks/week	65	1.5 (0.9–2.5)		
				15–29 drinks/week	32	4.9 (1.6–14.3)		
				≥30 drinks/week	41	7.8 (2.1–29.2)		
				Beer				
				<1 drink/week	180	1 (reference)		
				1–4 drinks/week	73	2.2 (1.4–3.6)		
				5–14 drinks/week	48	2.9 (1.5–5.6)		
				15–29 drinks/week	24	2.3 (0.9–6.5)		
				≥30 drinks/week	27	18.0 (2.1–159)		
				Wine				
				<1 drink/week	230	1 (reference)		
				1–4 drinks/week	60	0.6 (0.4–1.0)		
				5–14 drinks/week	41	0.8 (0.4–-1.4)		
				15–29 drinks/week	1	0.5 (0.1–2.3)		
				≥30 drinks/week	7	1.6 (0.2–13.6)		

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Merletti *et al.* (1989), Torino, Italy, 1982–84	122 (86 men, 36 women) cases; histologically confirmed; response rate, 85%. 606 (385 men, 221 women) population-based controls randomly selected from files of residents; stratified by age, sex; response rate, 55%	Interviewer-administered questionnaire	Oral cavity, oropharynx (ICD9 140.3–140.5, 141, 143–146)	Wine only Beer Aperitifs Liquor Wine only Beer Aperitifs Liquor		**Men** 1 (reference) 2.1 (1.1–4.0) 1.4 (0.7–2.6) 0.7 (0.4–1.4) **Women** 1 (reference) 6.1 (1.4–26.5) 0.4 (0.1–1.7) 0.8 (0.3–2.3)	Age, education, area of birth, smoking habits, alcoholic beverage consumption	

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Barra *et al.* (1990), Milan, Pordenone, Italy, 1986–90	305 cases (all men); median age, 58 years; histologically confirmed; refusal rate, 2% 1621 (all men) hospital-based controls; median age, 57 years; matched by area of residence, age; excluded patients with alcohol- and tobacco-related conditions; refusal rate, 3%	Interviewer-administered standardized questionnaire	Oral cavity, pharynx	*Wine only* ≤20 glasses wine/week 21–55 drinks/week 56–83 drinks/week ≥84 drinks/week *Wine and beer* ≤20 glasses wine/wk 21–55 drinks/week 56–83 drinks/week ≥84 drinks/week *Wine and spirits* ≤20 glasses wine/wk 21–55 drinks/week 56–83 drinks/week ≥84 drinks/week	 17 44 48 14 17 3 13 21 17 13 34 32	 1 1.9 (1.0–3.4) 7.3 (3.8–14.1) 11.2 (3.8–33.1) 1 0.7 (0.2–2.5) 3.9 (1.6–9.6) 7.4 (3.2–17.3) 1 1.1 (0.5–2.4) 3.5 (1.7–6.9) 9.9 (4.3–22.7)	Age, area of residence, occupation, smoking and drinking habits	Includes study population from Franceschi *et al.* (1990); area of very high wine intake

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Franceschi *et al.* (1990), Milan, Pordenone, Italy, 1986–89	157 male cases; below age 75 years; histologically confirmed; response rate, 98% 1272 hospital-based non-cancer male controls from same hospitals as cases, matched on age, area of residence; excluded patients with alcohol- and tobacco-related conditions; response rate, 97%	Interviewer-administered questionnaire	Oral cavity (ICD9 140, 141, 143–145)	*Wine (glasses/week)*			Age, area of residence, education, occupation, smoking habits	Study population from Barra *et al.* (1990); area of very high wine intake
				0–6	12			
				7–20	6	1		
				21–34	20	1.1 (0.5–2.3)		
				35–55	27	1.9 (0.9–3.7)		
				56–83	68	4.9 (2.6–9.5)		
				≥84	24	8.5 (3.6–20.2)		
				χ^2 for trend		47.68 (p<0.01)		
				Beer (glasses/week)				
				0	111	1		
				1–13	20	1.0 (0.6–1.8)		
				≥14	26	0.8 (0.5–1.4)		
				χ^2 for trend		0.30 (NS)		
				Hard liquor (glasses/week)				
				0	91	1		
				1–6	19	0.7 (0.4–1.3)		
				≥7	47	0.9 (0.6–1.3)		
				χ^2 for trend		0.66 (NS)		

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Franceschi *et al.* (1990) (contd)	134 male cases, below age 75 years; histologically confirmed; response rate, 98%		Pharynx (ICD9 146, 148, 161.1)	*Wine (glasses/week)*				
				0–6	9			
				7–20	6	1		
				21–34	16	0.7 (0.3–1.6)		
				35–55	28	1.9 (0.9–3.7)		
				56–83	45	3.1 (1.6–6.1)		
				≥84	30	10.9 (4.7–25.3)		
				χ^2 for trend		46.44 (p<0.01)		
				Beer (glasses/week)				
				0	94	1		
				1–13	11	0.5 (0.3–1.0)		
				≥14	28	0.9 (0.5–1.5)		
				χ^2 for trend		0.47 (NS)		
				Hard liquor (glasses/ week)				
				0	73	1		
				1–6	10	0.4 (0.2–0.9)		
				≥7	51	1.2 (0.8–1.8)		
				χ^2 for trend		0.24 (NS)		

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Zheng *et al.* (1990), Beijing, China, 1988–89	404 (248 men, 156 women) cases diagnosed at seven participating hospitals in the Beijing area; histologically confirmed; response rate, 100%; 404 randomly selected non-cancer hospital-based controls; individually matched on age, sex, hospital; response rate, 100%.	Interviewer-administered questionnaire	Oral cavity (ICD9 141, 143-145)	*Type of alcohol* None Spirits only Beer/wine only Mixed	 83 144 7 14	 1 1.5 (0.9–2.3) 1.0 (0.3–3.1) 1.1 (0.5–2.8)	Age, sex, education, smoking	Most alcoholic beverages in study population were consumed in form of spirits.

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Barra *et al.* (1991), Pordenone, Italy, 1985–90	272 (236 men, 36 women) cases; median age, 60 years; histologically confirmed; refusal rate, 3% 1884 (1122 men, 762 women) non-cancer, hospital-based controls; median age, 58 years; matched by area of residence, age; excluded patients with alcohol- and tobacco-related conditions; refusal rate, 3%	Interviewer-administered standardized questionnaire	Oral cavity, pharynx	*Wine* ≤20 drinks/week 21–34 drinks/week 35–55 drinks/week 56–83 drinks/week ≥84 drinks/week χ^2 for trend *Beer* 0 drink/week 1–13 drinks/week ≥14 drinks/week χ^2 for trend *Spirits* 0 drink/week 1–13 drinks/week ≥14 drinks/week χ^2 for trend	 31 35 46 99 61 168 32 72 137 69 28 	 1 1.7 (1.0–3.1) 3.3 (1.8–5.9) 6.8 (3.9–12.1) 15.6 (8.2–29.7) 107.9 (p<0.01) 1 0.7 (0.4–1.0) 1.4 (1.0–1.9) 1.5 (NS) 1 0.8 (0.6–1.1) 1.6 (1.1–2.3) 1.1 (NS)	Age, sex, education, occupation, tobacco	Area of very high wine intake; no mention of controlling for other types of alcoholic beverage; includes participants from Barra *et al.* (1990)
Mashberg, *et al.* (1993), New Jersey, USA, 1972–83	359 white and black men with invasive cancer and in-situ carcinoma 2280 white or black male controls from the same centre as cases	Interviewer-administered questionnaire	Oral cavity, oropharynx	*Type of alcohol* Minimal drinking Mixed consumption Whiskey only Whiskey predominantly Beer only Beer predominantly	 17 125 32 77 40 61	 1 (reference) 8.3 (4.7–14.8) 3.8 (1.8–8.1) 5.3 (1.1–26.3) 2.6 (1.3–5.2) 8.3 (3.4–20.2)	Age, race, tobacco smoking, average total alcoholic beverage consumption	

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Ng *et al.* (1993), USA	173 (100 men, 73 women) non smoking cases 613 (254 men, 359 women) nonsmoking hospital-based controls; matched on age, sex, date of interview		Oral cavity	*Men only*				
				Beer				
				Non-drinker	24	1 (reference)		
				<1 oz/day	24	1.9 (0.9–3.8)		
				1–2.9 oz/day	16	2.6 (1.1–5.9)		
				≥3 oz/day	9	5.1 (1.8–14.2)		
				χ^2 for trend		13.6 ($p < 0.001$)		
				Wine				
				Non-drinker	38	1 (reference)		
				<1 oz/day	28	0.9 (0.5–1.8)		
				1–2.9 oz/day	6	1.5 (0.5–4.9)		
				≥3 oz/day	0	1.6 (0.0–29.7)		
				χ^2 for trend		0.01 (NS)		
				Liquor				
				Non-drinker	13	1 (reference)		
				<1 oz/day	20	1.1 (0.6–2.2)		
				1–2.9 oz/day	19	2.0 (0.7–5.3)		
				≥3 oz/day	13	0.4 (0.0–7.1)		
				χ^2 for trend		0.25 (NS)		

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Day *et al.* (1994a), USA, 1984–85	80 (56 men, 24 women) cases with second primary cancers from cohort of 1090 first primary cancers) 189 (132 men, 57 women) controls randomly selected from the cohort that were free of second primary cancer at the end of follow-up (1989)	Interviewer-administered standardized questionnaire	Oral cavity, pharynx, oesophagus, larynx	*Beer*			Age, stage of disease, lifetime smoking, other two types of alcoholic beverage	Nested case–control study of second primary cancers among cases of Blot *et al.* (1988) study
				<1 drink/week	14	1 (reference)		
				1–14 drinks/week	18	2.4 (0.8–7.1)		
				≥15 drinks/week	25	3.8 (1.2–12.0)		
				Liquor				
				<1 drink/week	16	1 (reference)		
				1–14 drinks/week	26	1.2 (0.5–2.9)		
				≥15 drinks/week	15	0.4 (0.1–1.1)		
				Wine				
				<1 drink/week	46	1 (reference)		
				≥1 drink/week	11	0.6 (0.2–1.3)		
	921 cases and 900 controls who drank hard liquor			*Dark liquor*			Age, sex, race, study location, education, smoking, intake of beer and wine	
				<1 drink/week	138	1 (reference)		
				1–4 drinks/week	120	1.1 (0.7–1.5)		
				5–14 drinks/week	142	1.2 (0.9–1.8)		
				15–29 drinks/week	111	2.7 (1.7–4.3)		
				≥30 drinks/week	139	4.6 (2.7–7.9)		
				Light liquor				
				<1 drink/week	50	1 (reference)		
				1–4 drinks/week	37	1.4 (0.8–2.5)		
				5–14 drinks/week	53	1.7 (0.9–3.0)		
				15–29 drinks/week	42	5.6 (2.5–12.5)		
				≥30 drinks/week	74	13.2 (5.2–33.5)		

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Kabat *et al.* (1994), USA, 1977–90	1560 (1097 men, 463 women) cases enrolled in 28 hospitals in eight US cities 2948 (2075 men, 873 women) hospital-based controls; matched on age, sex, race, hospital, date of interview	Interviewer-administered standardized questionnaire	Oral cavity, pharynx (excluding nasopharynx)	*Whiskey equivalents/day* **Men** *Beer* Non-drinker Occasional 1–3.9 oz/day 4–6.9 oz/day ≥7 oz/day *Wine* Non-drinker Occasional 1–3.9 oz/day 4–6.9 oz/day ≥7 oz/day	 178 254 240 136 279 646 300 83 13 50	 1 (reference) 1.5 (1.2–1.9) 2.5 (2.0–3.3) 4.1 (2.9–5.7) 5.3 (4.0–7.0) 1 (reference) 0.8 (0.7–1.0) 1.3 (0.9–1.8) 1.0 (0.5–2.3) 2.7 (1.6–4.6)	Age, education, smoking, race, time period, type of hospital	1 oz whiskey equivalent = 10.2 g of alcohol

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Kabat *et al.* (1994) (contd)				*Hard liquor*				
				Non-drinker	303	1		
				Occasional	228	1.0 (0.8–1.3)		
				1–3.9 oz/day	214	1.7 (1.4–2.3)		
				4–6.9 oz/day	103	2.6 (1.8–3.7)		
				≥7 oz/day	235	3.1 (2.4–4.1)		
				Women				
				Beer				
				Non-drinker	290	1 (reference)		
				Occasional	90	1.3 (1.0–1.9)		
				1–3.9 oz/day	46	1.9 (1.1–3.1)		
				4–6.9 oz/day	37	3.6 (1.7–7.5)		
				Wine				
				Non-drinker	284	1 (reference)		
				Occasional	130	0.8 (0.6–1.1)		
				1–3.9 oz/day	31	0.8 (0.5–1.4)		
				4–6.9 oz/day	16	2.7 (1.0–7.7)		
				Hard liquor				
				Non-drinker	217	1 (reference)		
				Occasional	112	1.1 (0.8–1.5)		
				1–3.9 oz/day	64	1.9 (1.2–2.9)		
				4–6.9 oz/day	70	7.6 (3.9–14.8)		

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Chyou *et al.* (1995), Hawaii, USA, 1965-93	Cohort of 7995 men of Japanese ancestry, aged 45–68 years; recruitment from 1965–68, incidence follow-up until 1993; 1–2% lost to follow-up.	Interviewer-administered questionnaire	Oral cavity, pharynx, oesophagus, larynx (ICD8 140–150, 161)	*Beer*			Age, number of cigarettes/ day, years smoked	
				Non-drinker	161	1 (reference)		
				<49 oz/month	5	0.7 (0.3–1.8)		
				49–360 oz/month	17	1.9 (1.0–3.8)		
				≥361 oz/month	39	3.7 (2.0–6.7)		
				p for trend	<0.0001			
				Wine				
				Non-drinker	16	1 (reference)		
				≤4 oz/month	10	2.5 (1.2–5.6)		
				>4 oz/month	12	3.8 (1.8–8.2)		
				p for trend	0.0001			
				Spirits				
				Non-drinker	16	1 (reference)		
				≤4 oz/month	18	1.6 (0.8–3.2)		
				>4 oz/month	34	3.6 (2.0–6.6)		
				p for trend	<0.0001			

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Zheng *et al.* (1997), Beijing, China, 1988–89	111 (65 men, 46 women) cases diagnosed at seven participating hospitals in the Beijing area; aged 20–80 years; histologically confirmed; 111 randomly selected non-cancer hospital-based controls; individually matched on age, sex, hospital	Interviewer-administered questionnaire	Tongue	*Type of alcohol* None Spirits only Beer/wine	 64 41 6	 1 (reference) 1.2 (0.3–4.0) 1.2 (0.6–2.4)	Education, smoking (age and sex matched on)	Part of Zheng *et al.* (1990)

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Grønbaek *et al.* (1998), Denmark, 1975–94	Cohort of 15 117 men and 13 063 women from prospective population studies of the Copenhagen city heart study the Copenhagen male study, and the Copenhagen county centre of preventive medicine; aged 20–98 years; cases identified by linkage with the Danish Cancer registry; follow-up through to 1993 (mean follow-up, 13.5 years).	Self-administered questionnaire	Oral cavity, pharynx, oesophagus (ICD7 140.0–149.0, 150.0)	*Beer* 0 drink/week 1–6 drinks/week ≥7 drinks/week *Wine* 0 drinks/week 1–6 drinks/week ≥7 drinks/week *Spirits* 0 drinks/week 1–6 drinks/week ≥7 drinks/week		 1 (reference) 1.5 (0.9–2.5) 2.9 (1.8–4.8) 1 (reference) 0.8 (0.5–1.1) 0.4 (0.2–0.8) 1 (reference) 0.7 (0.5–1.1) 1.5 (1.2–1.9)	Age, sex, smoking, education, other types of alcoholic beverage	One drink = 12 g ethanol

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Schildt *et al.* (1998), Sweden, 1980–89	410 (276 men, 134 women) cases from Norrbotten, Vasterbotten, Jamtland, Vasternorrland reported to the Cancer Registry (175 living, 235 deceased); histologically confirmed; response rate, 96% (11 living, seven proxies refused). 410 (276 men, 134 women) population controls; individually matched on age, sex, county; response rate, 91% (21 living, 17 proxies refused); after refusals, 354 (237 men, 117 women) matched pairs	Self-completed questionnaire	Oral cavity (ICD7 140, 141, 143–145)	*Overall* Light beer Beer Wine Liquor *Amount*frequency score* *Wine* Low Medium High *Liquor* Low Medium High	 150 25 8 125 60 42	 1.2 (0.7–1.7) 1.5 (0.7–3.2) 1.0 (0.6–1.5) 1.5 (0.9–2.3) 1.3 (0.9–1.8) 0.9 (0.5–1.8) 8.6 (1.0–70.0) 1.3 (0.9–2.0) 1.6 (1.0–2.7) 3.6 (1.8–7.2)	Snuff and smoking in addition to types of alcoholic beverage listed	Proxies used for 60% of participants; looked at joint effects of smoking and liquor

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Garrote *et al.* (2001), Havana, Cuba, 1996–99	200 (143 men, 57 women) cases identified in the Instituto Nacional de Oncologia y Radiobiologia of Havana; median age, 64 years; response rate, 88% 200 (136 men, 64 women) hospital-based controls admitted to same institute and three other major hospitals in Havana; excluded patients with alcohol- and tobacco-related conditions; frequency-matched on age, sex; median age, 62 years; response rate, 79%	Interviewer (dentist)-administered questionnaire	Oral cavity, oropharynx	*Hard liquor* 0 drink/week 1–7 drinks/week 8–20 drinks/week 21–69 drinks/week ≥70 drinks/week χ^2 for trend *Beer* 0 drink/week <7 drinks/week ≥7 drinks/week χ^2 for trend *Wine* 0 drink/week <2 drinks/week ≥2 drinks/week χ^2 for trend	 86 19 25 15 15 98 36 29 129 26 9 	 1 (reference) 1.3 (0.5–3.3) 1.0 (0.4–2.4) 4.2 (1.1–16.5) 5.1 (1.1–23.3) 4.58 ($p < 0.05$) 1 (reference) 1.5 (0.6–3.9) 1.5 (0.5–4.6) 0.85 ($p = 0.36$) 1 (reference) 1.0 (0.4–2.4) 0.8 (0.2–3.2) 0.15 ($p = 0.70$)	Age, sex, area of residence, education, smoking, other two types of alcoholic beverage	Looked at cessation, type of alcoholic beverage and joint effect of smoking

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Schlecht *et al.* (2001), Brazil, 1986–89	784 cases selected from hospitals in Sao Paulo, Curitiba, Goiania; histopathologically confirmed 1578 hospital-based non-cancer controls; matched (2:1 controls:case) on age, sex, hospital area, admission period	Interviewer-administered questionnaire	Oral cavity, pharynx, larynx (ICD9 140–149, 161; excluding 142 and 147)	Lifetime consumption **Oral cavity** *Beer* Non-drinker 1–10 g 11–100 g >100 g Other than beer *Wine* Non-drinker 1–10 g 11–100 g >100 g Other than wine *Hard liquor* Non-drinker 1–10 g 11–100 g >100 g Other than hard liquor *Cachaca* Non-drinker 1–10 g 11–100 g 101–500 g 501–1000 g 1001–2000 g >2000 g Other than cachaca		 1 (reference) 3.6 (1.9–7.0) 2.8 (1.4–5.6) 3.7 (1.4–10.3) 3.1 (1.6–5.8) 1 (reference) 3.4 (1.8–6.5) 4.3 (1.9–10.1) 3.0 (1.2–7.3) 2.9 (1.6–5.5) 1 (reference) 3.3 (1.3–8.2) 3.1 (1.5–6.6) 6.9 (2.8–17.1) 3.2 (1.7–5.8) 1 (reference) 1.4 (0.4–5.4) 2.0 (1.0–4.2) 4.5 (2.2–9.2) 7.2 (3.5–14.7) 8.7 (4.3–17.6) 9.9 (3.8–25.5) 3.7 (1.8–7.8)	Remaining alcohol consumption, tobacco smoking, income, education, race, beverage temperature, religion, wood stove use, spicy food (matched variables: age, sex, study location, admission period)	Same study population as Schlecht *et al.* (1999)

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Schlecht *et al.*(2001) (contd)				**Pharynx**				
				Beer				
				Non-drinker		1 (reference)		
				1–10 g		3.2 (1.1–9.2)		
				11–100 g		3.4 (1.1–10.4)		
				>100 g		1.1 (0.3–4.1)		
				Other than beer		3.1 (1.0–9.2)		
				Wine				
				Non-drinker		1 (reference)		
				1–10 g		3.1 (1.0–9.2)		
				11–100 g		2.8 (0.8–9.4)		
				>100 g		3.0 (0.8–11.1)		
				Other than wine		3.6 (1.3–10.5)		
				Hard liquor				
				Non-drinker		1 (reference)		
				1–10 g		4.1 (1.0–17.7)		
				11–100 g		4.6 (1.5–14.1)		
				>100 g		2.5 (0.7–9.8)		
				Other than hard liquor		3.1 (1.1–8.8)		
				Cachaca				
				Non-drinker		1 (reference)		
				1–10 g		2.8 (0.4–19.6)		
				11–100 g		2.9 (0.9–9.1)		
				101–500 g		5.4 (1.7–17.5)		
				501–1000 g		9.2 (2.9–29.3)		
				1001–2000 g		14.3 (4.4–45.8)		
				>2000 g		12.5 (2.9–53.7)		
				Other than cachaca		2.1 (0.6–7.8)		

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Huang *et al.* (2003), Puerto Rico, 1992–95	286 male cases identified through the Central Cancer Registry and by abstracting patients' medical records; aged 21–79 years; histologically confirmed; response rate, 70% 417 male population controls selected from among all Puerto Ricans; frequency-matched on age; response rate, 83%.	Interviewer-administered questionnaire	Oral cavity, pharynx (ICD9 141, 143–146, 148, 149)	*Beer* Non-drinker >0–<8 drinks/week 8–<43 drinks/week ≥43 drinks/week *p* for trend *Wine* Non-drinker >0–<8 drinks/week ≥8 drinks/week *p* for trend *Liquor* Non-drinker >0–<8 drinks/week 8–<43 drinks/week ≥43 drinks/week *p* for trend	 47 70 119 42 0.004 194 62 27 0.2 22 40 90 128 <0.0001	 1 (reference) 0.5 (0.3–1.0) 1.1 (0.6–2.0) 1.8 (0.8–4.1) 1 (reference) 1.0 (0.6–1.7) 1.8 (0.8–4.3) 1 (reference) 1.7 (0.9–3.2) 3.5 (1.8–6.7) 13.2 (6.5–26.6)	Age, tobacco use, raw fruit and vegetable intake, education, other types of alcoholic beverage	Same population as Hayes *et al.* (1999)

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Altieri *et al.* (2004), Italy, Switzerland, 1992–97	749 (634 men, 115 women) cases from Pordenone, Rome, Latina (Italy) and Vaud (Switzerland) admitted to major teaching and general hospitals in area under surveillance; aged 22–77 years; histologically confirmed 1772 (1252 men, 520 women) hospital controls from the same network of hospitals as cases; aged 20–78 years; excluded patients with alcohol- and tobacco-related conditions	Interview-administered structured questionnaire	Oral cavity, pharynx	*Beer* Non-drinkers 1–2 drinks/day ≥3 drinks/day χ^2 for trend *Wine* Non-drinkers 1–2 drinks/day 3–4 drinks/day 5–7 drinks/day 8–11 drinks/day ≥12 drinks/day χ^2 for trend *Spirits* Non-drinkers 1–2 drinks/day ≥3 drinks/day χ^2 for trend	 284 380 84 43 110 127 157 177 134 297 386 66 	 1 (reference) 1.2 (1.0–1.5) 2.3 (1.4–3.7) 9.86 (p = 0.02) – – 1 (reference) 2.2 (1.6–3.0) 7.1 (5.0–10.1) 11.8 (8.1–17.2) 16.1 (10.2–25.3) 221.83 (p <0.0001) 1 (reference) 1.0 (0.8–1.2) 1.9 (1.1–3.3) 1.14 (p = 0.29)	Age, sex, study centre, education, smoking habit, other types of alcoholic beverage	

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Castellsagué et al. (2004), Spain, 1996–99	375 (304 men, 71 women) cases identified from hospitals; histologically confirmed; response rate, 76.5% 375 (304 men, 71 women) non-cancer hospital controls from same hospitals as cases; frequency-matched on age, sex; mean age, 60 years; excluded patients with alcohol- and tobacco-related diagnoses; response rate, 91%	Interviewer-administered questionnaire	Oral cavity, oropharynx (ICDO C1-C10)	*Type of alcohol* Only beer Only wine and beer Only wine Spirits with or without wine/beer *p* for trend	 12 47 32 248 <0.0001	 1.2 (0.5–2.8) 2.0 (1.0–4.0) 2.7 (1.3–5.6) 7.3 (3.7–14.5)	Age group, sex, education, tobacco smoking, centre	

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
De Stefani *et al.* (2004), Montevideo, Uruguay, 1997–2003	85 male cases identified in the four major hospitals in Montevideo; microscopically confirmed; response rate, 97.5% 640 hospital-based male controls from the same hospitals as cases; excluded patients with alcohol- and tobacco-related conditions with no recent changes in diet; frequency matched (2:1 controls:cases) on age, residence; response rate, 97%	Interviewer-administered questionnaire	Hypopharynx	**Ethanol/day (mL)** *Beer* Beer abstainers 1–60 ≥61 *p* for trend *Red wine* Wine abstainers 1–60 61–120 ≥121 *p* for trend *Hard liquor* Liquor abstainers 1–60 61–120 ≥121 *p* for trend	 75 8 2 0.08 9 20 29 27 0.0001 45 12 10 18 0.0008	 1 (reference) 0.8 (0.3–1.9) 0.2 (0.1–1.1) 1 (reference) 2.3 (0.9–5.5) 5.2 (2.2–12.4) 4.5 (1.9–10.8) 1 (reference) 0.9 (0.4–1.9) 2.2 (0.9–5.2) 3.3 (1.6–6.8)	Age, residence, urban/rural status, education, body mass index, smoking, other types of alcoholic beverage	

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
De Stefani *et al.* (2007), Montevideo, Uruguay, 1988–2000	335 male cases identified in the four major hospitals in Montevideo; microscopically confirmed; response rate, 97% 1501 hospital-based non-cancer male controls; excluded patients with alcohol- and tobacco-related conditions with no recent changes in diet; response rate, 97%	Interviewer-administered questionnaire	Oral cavity (excluding lip)	**Ethanol/day (mL)** *Beer* Beer abstainers 1–22 ≥23 *p* for trend *Wine* Wine abstainers 1–60 61–120 ≥121 *p* for trend *Hard liquor* Liquor abstainers 1–60 61–120 ≥121 *p* for trend		 1 (reference) 0.5 (0.3–0.9) 0.4 (0.2–0.9) 0.004 1 (reference) 0.8 (0.6–1.2) 1.5 (1.0–2.1) 1.4 (0.9–2.4) 0.03 1 (reference) 0.8 (0.6–1.2) 1.8 (1.2–2.7) 1.4 (0.8–2.2) 0.03	Age, residence, urban/ rural status, hospital, year of diagnosis, education, family history of cancer, occupation, vegetable and fruit consumption, mate, smoking, total alcoholic beverage	

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
De Stefani *et al.* (2007) (contd)	441 male cases identified in the four major hospitals in Montevideo; microscopically confirmed; response rate, 97%		Pharynx (excluding nasopharynx	*Beer*				
				Beer abstainers		1 (reference)		
				1–22		0.8 (0.4–1.3)		
				≥23		0.3 (0.2–0.7)		
				p for trend		0.001		
				Wine				
				Wine abstainers		1 (reference)		
				1–60		1.1 (0.8–1.5)		
				61–120		2.7 (1.9–3.8)		
				≥121		2.5 (1.6–3.9)		
				p for trend		<0.0001		
				Hard liquor				
				Liquor abstainers		1 (reference)		
				1–60		0.9 (0.7–1.3)		
				61–120		1.6 (1.1–2.3)		
				≥121		0.9 (0.5–1.4)		
				p for trend		0.5		

CI, confidence interval; ICD, International Classification of Diseases; NS, not significant

Table 2.7 Joint effects of alcoholic beverage consumption and tobacco smoking on cancers of the oral cavity and pharynx

Reference, study location, period	Tobacco	Alcoholic beverages					Comments/ adjustment factors
Blot *et al.* (1988), USA, 1984–85		No. of cases (odds ratio)					[a]Quit for ≥10 years or smoked for <20 years; adjusted for age, race, study location, respondent status (self vs next-of-kin)
		<1 drink/week	1–4 drinks/week	5–14 drinks/week	15–29 drinks/week	≥30 drinks/week	
	Men						
	Nonsmoker	12 (1)	12 (1.3)	15 (1.6)	5 (1.4)	6 (5.8)	
	Short duration/ former[a]	8 (0.7)	24 (2.2)	21 (1.4)	25 (3.2)	43 (6.4)	
	1–19/day for ≥20 years	2 (1.7)	7 (1.5)	8 (2.7)	16 (5.4)	22 (7.9)	
	20–39/day for ≥20 years	8 (1.9)	17 (2.4)	28 (4.4)	52 (7.2)	145 (23.8)	
	≥40/day for ≥20 years	9 (7.4)	6 (0.7)	19 (4.4)	43 (20.2)	148 (37.7)	
	Pipe/cigar only	1 (0.6)	5 (1.0)	8 (3.7)	13 (4.7)	25 (23.0)	
	Women						
	Nonsmoker	36 (1)	11 (0.7)	7 (1.3)	0 (0.0)	0 (0.0)	
	Short duration/ former[a]	7 (1.0)	8 (1.6)	4 (0.4)	3 (1.1)	3 (~)	
	1–19/day for ≥20 years	4 (0.9)	22 (5.1)	11 (2.8)	3 (4.6)	9 (11.0)	
	20–39/day for ≥20 years	12 (2.2)	20 (2.7)	35 (6.9)	31 (12.4)	38 (46.0)	
	≥40/day for ≥20 years	4 (~)	14 (9.3)	15 (7.8)	18 (18.0)	37 (107.9)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
Tuyns *et al.* (1988), France, Italy, Spain, Switzerland, 1980–83		No. of cases/odds ratio (95% CI)				Adjusted for age, place, age/place interaction
		0–40 g/day	41–80 g/day	81–120 g/day	≥121 g/day	
	0–7 cigarettes/ day	4 (1)	10 (3.0)	7 (5.5)	11 (15.0	
	8–15 cigarettes/ day	9 (4.7)	32 (14.6)	28 (27.5)	39 (71.6)	
	16–25 cigarettes/ day	27 (13.9)	42 (19.5)	52 (48.3)	56 (67.8)	
	≥26 cigarettes/ day	5 (4.9)	15 (18.4)	22 (37.6)	50 (135.5)	
Merletti *et al.* (1989), Torino, Italy, 1982–84		No. of cases/odds ratio (95% CI)				Adjusted for age, education, area of birth
		0–40g/day	41–120g/day	>120g/day		
	Men					
	0–7 g/day	4/1.0 (reference)	4/0.6 (0.2–2.0) (categories combined)			
	8–15 g/day	7/3.3 (0.9–12.4)	15/3.6 (1.1–12.0)	5/8.6 (1.9–39.0)		
	>16 g/day	10/2.5 (0.7–8.5)	25/3.6 (1.2–11.3)	16/21.4 (5.9–77.7)		
	Women					
	0 g/day	6/1.0 (reference)	5/1.1 (0.3–4.1)	2/0.8 (0.1–4.2)		
	≥1 g/day	5/2.8 (0.7–11.1)	8/6.5 (1.7–24.5)	10/21.3 (5.1–88.6)		

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
Franceschi *et al.* (1990), Milan, Pordenone, Italy, 1986–89		No. of cases (odds ratio)				Adjusted for age, area of residence, education, occupation; oral cavity and pharynx cases combined
		<35 drinks/week	35–59 drinks/week	≥60 drinks/week		
	Nonsmoker	3 (1)	2 (1.6)	1 (2.3)		
	Light smoker	7 (3.1)	7 (5.4)	12 (10.9)		
	Intermediate smoker	39 (10.9)	79 (26.6)	102 (36.4)		
	Heavy smoker	7 (17.6)	8 (40.2)	19 (79.6)		
Zheng *et al.* (1990), Beijing, China, 1988–89		No. of cases (odds ratio)				Adjusted for age, education
		Lifetime consumption of spirit equivalents				
		0 kg	<217 kg	217–801 kg	>801 kg	
	0 pack–years	20 (1)	9 (1.2)	4 (0.8)	4 (2.4)	
	1–18 pack–years	15 (1.4)	15 (2.8)	13 (5.6)	4 (15.2)	
	19–32 pack–years	12 (2.1)	14 (4.9)	9 (1.7)	19 (10.1)	
	>32 pack–years	13 (2.5)	2 (5.9)	14 (5.9)	31 (17.4)	
Nam *et al.* (1992), USA, 1986		Odds ratio (*p*-value)				Adjusted for sex
		0–3 drinks/week	4–23 drinks/week	≥24 drinks/week		
	≤30 pack–years	1	0.6	1.4		
	31–59 pack–years	1.5	2.3 (<0.05)	2.6 (<0.01)		
	≥60 pack–years	2.2 (<0.05)	2.3 (<0.05)	5.2 (<0.01)		

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages					Comments/ adjustment factors
Maier *et al.* (1994), Heidelberg, Giessen, Germany, 1987–88		No. of cases/odds ratio (95% CI)					
		<25 g/day	25–75 g/day	>75 g/day			
	<5 tobacco–years	5/1	5/2.3 (0.6–8.8)	3/10.3 (1.9–55.8)			
	5–50 tobacco–years	27/5.7 (1.9–17.3)	50/14.6 (4.8–43.9)	44/153.2 (44.1–532)			
	>50 tobacco–years	14/23.3 (6.6–82.5)	27/52.8 (15.8–176.6)	25/146.2 (37.7–566)			
Mashberg *et al.* (1993), New Jersey, USA, 1972–83		No. of cases (odds ratio)					Adjusted for age, race
		Minimal drinkers	2–5 WE/day	6–10 WE/day	11–21 WE/day	≥22 WE/day	
	Minimal smokers	1 (1)	1 (2.7)	2 (11.9)	3 (12.5)	2 (8.3)	
	Cigar/pipe	6 (20.5)	6 (17.0)	13 (53.4)	6 (27.3)	5 (23.1)	
	6–15 cigarettes/day	3 (10.8)	7 (24.2)	17 (50.9)	8 (30.9)	6 (27.5)	
	16–25 cigarettes/day	4 (7.6)	16 (29.7)	23 (28.9)	34 (44.8)	31 (61.7)	
	26–35 cigarettes/day	0 (–)	2 (5.3)	18 (61.9)	18 (79.5)	22 (70.3)	
	≥36 cigarettes/day	1 (3.2)	4 (10.2)	17 (26.8)	40 (98.4)	30 (32.0)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
Kabat *et al.* (1994), USA, 1977–90		Odds ratio (95% CI)				
		Non-drinker/ occasional	1–3.9 oz/day	4–6.9 oz/day	≥7 oz/day	
	Men					
	Never	1	1.6 (0.9–2.7)	1.2 (0.4–3.7)	2.9 (1.1–8.1)	
	Former smoker (abstained for ≥12 months)	1 (0.7–1.6)	1.7 (1.1–2.6)	3.1 (1.9–5.2)	5.1 (3.3–7.8)	
	1–20 cigarettes/ day	1.5 (0.9–2.51)	5.8 (3.7–9.1)		11.9 (7.7–18.4)	
	21–30 cigarettes/ day	2.2 (1.1–4.3)	6.8 (3.6–12.7)		13.5 (7.9–23.2)	
	≥31 cigarettes/ day	2.0 (1.1–3.7)	6.9 (3.9–12.4)		20.1 (12.9–31.5)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages			Comments/ adjustment factors
		Non-drinker/ occasional	≥4 oz/day	1–3.9 oz/day	
Kabat *et al.* (1994) (cont)	**Women**				Adjusted for age, education, race, time period, type of hospital
	Never	1	3.5 (0.9–13.4)	0.7 (0.3.–1.4)	
	Former smoker (abstained for ≥12 months)	1.3 (0.9–2.0)	2.7 (1.0–7.9)	2.1 (1.2–3.8)	
	1–20 cigarettes/ day	2.9 (1.9–4.3)	17.6 (8.1–37.5)	5.8 (3.5–9.8)	
	≥21 cigarettes/ day	3.8 (2.3–6.2)	26.7 (12.3–58.6)	22.3 (9.6–51.8)	
Chyou *et al.* (1995), Hawaii, USA		No. of cases/odds ratio (95% CI)			Study population from Kato *et al.* (1992c); adjusted for age
		0 oz/month	>0–<14 oz/month	≥14 oz/month	
	0 cigarette/ day	3/1 (reference)	3/1.3 (0.3–6.3)	6/6.5 (1.6–26.0)	
	>0–≤20 cigarettes/ day	8/3.0 (0.8–11.3)	6/1.9 (0.5–7.7)	24/10.7 (3.2–35.4)	
	>20 cigarettes/ day	5/3.2 (0.8–13.4)	7/4.6 (1.2–17.7)	28/14.4 (4.4–47.4)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
Murata *et al.* (1996), Japan 1984–93		No. of cases (odds ratio; *p*-value)				In sake-equivalents (180 mL sake contains ~27 mL ethanol)
		0 cup/day	0.1–1.0 cup/day	≥1 cup/day		
	Nonsmoker	7 (1)	6 (1.2)	5 (2.1)		
	Smoker	10 (1.9)	7 (1.4)	16 (p <0.01)		
Sanderson, *et al.* (1997), Netherlands, 1980–90		No. of cases/odds ratio (95% CI)				
		Non-drinker	1–5 units/day	>5 units/day		
	Nonsmoker	125 Ref	39/2.4 (1.6–3.6)			
	Smoker	28/1 (0.6–1.5)	65/6.5 (4.4–9.7)			
	Nonsmoker and smoker			46/32.9 (18.3–59.2)		
Zheng *et al.* (1997), Beijing, China, 1988–89		No. of cases (odds ratio; *p*-value) (Lifetime intake, spirit equivalents in kg)				Adjusted for education (matching variables: age, sex)
		Never	≤255 kg	>255 kg		
	Never	39 (1)	6 (1.9)	3 (2.4)		
	≤ 20 pack–years	10 (1.2)	9 (1.6)	4 (3.0)		
	>20 pack–years	15 (7.6; p<0.05)	8 (23.3; p<0.05)	17 (4.1)		
Schildt *et al.* (1998), Sweden, 1980–89		No. of cases/odds ratio (95% CI)				
		Never liquor	Low liquor intake	Medium liquor intake	High liquor intake	
	Never	80/1.0	50/1.2 (0.8–1.9)	7/1.4 (0.8–2.6)	4/4.2 (1.8–9.4)	
	Low consumption	15/1.0 (0.6–1.6)	26/1.2 (0.6–2.1)	19/1.4 (0.7–2.7)	4/4.0 (1.6–9.8)	
	High consumption	8/1.4 (0.8–2.3)	30/1.6 (0.9–2.9)	27/2.0 (1.0–3.6)	30/5.7 (2.4–14)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages					Comments/ adjustment factors
Schlecht *et al.* (1999), Brazil, 1986–89		Odds ratio (95% CI) for lifetime consumption					Same study population as Schlecht *et al.* (2001); adjusted for race, beverage temperature, religion, wood stove use, spicy food intake (matching variables: age, sex, study location, admission period)
		0–10 kg	11–530 kg	>530 kg			
	Oral cavity						
	0–5 pack–years	1	1.2 (0.4–3.4)	2.3 (0.6–9.1)			
	6–42 pack–years	2.9 (1.2–6.8)	6.2 (2.7–14.1)	19.5 (2.6–147)			
	>42 pack–years	7.8 (2.9–21.0)	11.2 (4.8–26.3)	20.3 (9.0–45.3)			
	Pharynx						
	0–5 pack–years	1	6.2 (0.7–56.6)	22.3 (2.1–238)			
	6–42 pack–years	2.4 (0.2–24.0)	21.7 (2.6–180)	66.3 (1.7–2,556)			
	>42 pack–years	69.4 (6.9–694)	43.0 (4.9–340)	77.3 (9.2–625)			
Hayes *et al.* (1999), Puerto Rico, 1992–95		No. of cases/odds ratio (95% CI)					Adjusted for age
		None	1–7 drinks/week	8–21 drinks/week	22–42 drinks/week	≥42 drinks/week	
	None	6/1.00 (reference)	1/0.2 (0.0–1.5)	2/0.6 (0.1–3.5)	2/1.6 (0.3–9.6)	4/6.4 (1.3–31.9)	
	Low	0	10/1.6 (0.5–4.8)	3/1.3 (0.3–5.7)	11/3.7 (0.8–16.4)	9/5.5 (1.6–19.0)	
	10–19 cigarettes/ day	1/11.3 (0.6–213.0)	2/1.3 (0.2–7.2)	3/1.8 (0.4–8.3)	8/18.6 (4.1–84.0)	10/12.2 (3.3–45.6)	
	20–39 cigarettes/ day	1/1.8 (0.2–19.0)	10/3.8 (1.2–12.0)	13/6.2 (2.0–19.3)	19/11.3 (3.7–34.0)	60/50.2 (16.6–152.0)	
	≥40 cigarettes/ day	1/2.4 (0.2–27.6)	6/4.3 (1.1–16.7)	4/7 (0.9–18.7)	10/10.5 (2.9–37.9)	67/38.7 (13.6–110.0)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
Franceschi *et al.* (1999), Italy, Switzerland, 1992–97		No. of cases/odds ratio (95% CI)				Study population from Franceschi *et al.* (2000); adjusted for age, area of residence, interviewer, education, vegetable and fruit intake, total energy intake *categories combined
		0–20 drinks/week	21–48 drinks/week	49–76 drinks/week	≥77 drinks/week	
	Oral cavity					
	Never smoker	3/1 (reference)	5/2.7 (0.6–11.6)	3/4.5 (0.8–24.2)*	3/4.5 (0.8–24.2)*	
	1–14 cigarettes/ day	2/2.2 (0.4–13.5)	6/5.9 (1.4–25.1)	11/30.6 (7.3–128.2)	8/52.4 (10.4–264.2)	
	15–24 cigarettes/ day	4/3.0 (0.6–13.8)	28/22.9 (66.6–79.4)	35/62.5 (17.4–224.2)	31/110.3 (29.1–418.1)	
	≥25 cigarettes/ day	4/5.6 (1.2–26.3)	12/22.7 (5.9–86.9)	25/103.1 (26.4–402.7)	31/227.8 (54.6–950.7)	
	Former smoker (abstained ≥12 months)	12/3.9 (1.1–14.1)	20/6.0 (1.7–21.0)	17/10.5 (2.9–38.6)	17/25.4 (6.7–96.0)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
Franceschi *et al.* (1999) (contd)	*Pharynx*					*Categories combined
	Never smoker	6/1 (reference)	2/0.4 (0.1–2.3)	1/0.5 (0.1–4.3)*	1/0.5 (0.1–4.3)*	
	1–14 cigarettes/ day	4/2.3 (0.6–8.4)	11/4.5 (1.5–13.4)	17/16.3 (5.3–50.5)	13/27.5(7.2–105.1)	
	15–24 cigarettes/ day	12/4.4 (1.6–12.5)	32/11.7 (4.6–30.2)	40/26.9 (10.0–72.3)	48/58.3 (20.3–167.3)	
	≥25 cigarettes/ day	7/5.5 (1.7–17.8)	22/18.6 (6.8–51.3)	18/32.2 (10.3–100.4)	36/100.4 (30.8–327.7)	
	Former smoker (abstained ≥12 months)	11/1.7 (0.6–4.9)	22/2.7 (1.0–7.1)	31/6.8 (2.6–17.8)	31/14.8 (5.4–40.9)	
Schwartz *et al.* (2001), Washington, USA, 1985–95		No. of cases/odds ratio (95% CI)				Adjusted for age, sex, race
		<1 drink/week	1–14 drinks/week	≥15 drinks/week		
	Never	26/1 (reference)	19/0.8 (0.4–1.5)	5/1.2 (0.4–3.6)		
	1–20 pack–years	9/0.8 (0.3–1.8)	27/0.9 (0.5–1.6)	13/3.8 (1.5–9.4)		
	≥ 20 pack–years	10/1.8 (0.7–4.5)	94/3.3 (1.9–5.7)	130/9.9 (5.5–17.9)		

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages			Comments/ adjustment factors
Garrote *et al.* (2001), Havana, Cuba, 1996–99		No. of cases/odds ratio (95% CI)			Adjusted for age, sex, area of residence, education, smoking (former smokers only)
		0 drink/week	<21 drinks/week	≥21 drinks/week	
	Never smokers	14/1 (reference)	1	0	
	1–29 cigarettes/ day	35/6.6 (2.8–15.7)	17/11.0 (3.7–32.8)	15/26.7 (7.2–99.9)	
	≥ 30 cigarettes/ day	15/10.5 (2.9–38.2)	15/42.3 (8.4–212.3)	21/111.2 (22.7–543.7)	
Balaram *et al.* (2002); southern India, 1996–99		No. of cases/odds ratio (95% CI)			Adjusted for age, centre, education, oral hygiene, smoking, chewing, drinking habits
		Never drinker	Current drinker		
	Never paan chewer	64/1 (reference)	48/2.8 (1.6–5.1)		
	Current paan chewer	48/7.3 (3.8–14.1)	46/8.6 (4.1–18.1)		
Boeing (2002), Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, Netherlands, United Kingdom		No. of cases/hazard rate ratio (95% CI)			Adjusted for sex, follow-up time, education, body mass index, vegetable and fruit intake, energy intake
		0–30 g/day	>30–60 g/day	>60 g/day	
	Nonsmoker	58/1 (reference)	7/2.6 (1.1–6.0)	4/6.9 (2.3–2.7)	
	1–20 cigarettes/ day	22/2.0 (1.2–3.5)	6/5.1 (2.1–12.7)	6/22.0 (8.3–58.1)	
	>20 cigarettes/ day	7/6.8 (3.0–15.5)	7/20.7 (8.7–49.0)	7/48.7 (20.0–118.9)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
Rodriguez *et al.* (2004), Italy, Switzerland, 1984–93, 1992–97		No. of cases/odds ratio (95% CI)				Study populations from Franceschi *et al*. (1990, 1999); adjusted for education, marital status, body mass index, coffee consumption (matched variables: age, sex, study centre)
		<6 drinks/day	6–<10 drinks/day	≥10 drinks/day		
	Never/ former smokers (abstained ≥ 12 months)	22/1 (reference)	4/1.9 (0.5–7.1)	5/15.7 (3.6–67.9)		
	1–15 cigarettes/ day	9/2.4 (0.9–6.4)	9/21.2 (5.2–87.7)	2/8.1 (1.0–64.8)		
	>15 cigarettes/ day	20/8.3 (3.3–20.6)	24/44.2 (14.9–131.2)	39/48.1 (17.6–131.0)		
Castellsagué *et al.* (2004), Spain, 1996–99		No. of cases/ odds ratio (95% CI)				Adjusted for age, sex, centre, education
		Never drinker	1–2 drinks/day	3–5 drinks/day	≥6 drinks/day	
	Never smoker	28/1 (reference)	23/2.0 (0.9–4.4)	2/1.1 (0.9–6.4)	2/6.2 (1.0–39.2)	
	1–10 cigarette/ day	3/2.9 (0.6–14.8)	14/4.7 (1.7–12.9)	10/32.2 (8.1–127.1)	1/2.7 (0.3–26.5)	
	11–20 cigarette/ day	2/1.0 (0.2–6.0)	27/11.1 (4.0–30.6)	22/26.6 (8.6–82.0)	46/43.1 (15.0–123.8)	
	≥21 cigarettes/ day	2/1.9 (0.3–11.1)	22/8.2 (2.9–22.9)	40/22.0 (8.0–61.0)	131/50.7 (19.1–134.2)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages			Comments/ adjustment factors
De Stefani, *et al.* (2004), Montevideo, Uruguay, 1997–2003		Odds ratio (95% CI)			Adjusted for age, residence, urban/ rural status, education, body mass index
		0–60 mL/day	61–120 mL/day	≥121 mL/day	
	0–14 cigarettes/ day	1 (reference)	5.1 (1.1–23.3)	4.6 (0.8–25.6)	
	15–24 cigarettes/ day	1.9 (0.3–12.8)	16.3 (4.2–62.9)	22.3 (5.8–86.3)	
	≥25 cigarettes/ day	4.3 (0.8–23.5)	5.6 (2.4–13.1)	43.9 (11.5–116.8)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
De Stefani *et al.* (2007), Montevideo, Uruguay, 1988–2000		Odds ratio (95% CI)				Adjusted for age, residence, urban/ rural status, hospital, year at diagnosis, education, family history of cancer, occupation, vegetable and fruit intake, mate intake
		0–60 mL/day	61–120 mL/day	121–240 mL/day	≥ 241 mL/day	
	Oral cavity					
	0–9 cigarettes/ day	1	3.5 (1.2–10.5)	2.9 (90.8–11.2)	1.9 (0.2–15.9)	
	10–19 cigarettes/ day	4.4 (2.1–9.4)	8.9 (3.9–20.4)	14.5 (6.1–34.2)	24.5 (8.3–72.1)	
	20–29 cigarettes/ day	4.8 (2.3–10.2)	24.1 (11.5–50)	21.2 (9.6–46.8)	50.5 (21–119)	
	≥30 cigarettes/ day	6.5 (3.1–13.8)	29.6 (13.7–64)	42.5 (19.9–90)	33.4 (15.8–70)	
	Pharynx					
	0–9 cigarettes/ day	1	0.9 (0.2–4.4)	2.5 (0.8–8.2)	9.8 (3.7–26.3)	
	10–19 cigarettes/ day	2.8 (1.4–5.6)	8.8 (4.3–17.9)	18.6 (9.1–38.0)	12.4 (4.0–38.7)	
	20–29 cigarettes/ day	3.7 (1.9–7.1)	16.8 (8.6–33	31.4 (16.0–62)	53.2 (25–114)	
	≥30 cigarettes/ day	4.7 (2.4–9.2)	24.0 (12.8–48)	36.4 (18.7–71)	43.8 (23.0–84)	

CI, confidence interval; WE whiskey equivalent

et al., 1995). The evaluation of effect modification was descriptive, without formal assessment of multiplicative interaction in most of studies.

Overall, a large majority of studies on joint exposure to alcoholic beverage and tobacco consumption demonstrated a synergistic effect. Many studies demonstrated a greater than multiplicative interaction (Tuyns *et al*., 1988; Merletti *et al*., 1989; Franceschi *et al*., 1990; Zheng *et al*., 1990; Mashberg *et al*., 1993; Kabat *et al*., 1994; Franceschi *et al*., 1999; Hayes *et al*., 1999; Schlecht *et al*., 1999; Garrote *et al*., 2001; Schwartz *et al*., 2001; Boeing, 2002; Castellsagué *et al*., 2004; De Stefani *et al*., 2007). In contrast, some other studies demonstrated a greater than additive but less than multiplicative interaction (Maier *et al*., 1992a; Chyou *et al*., 1995; Schildt *et al*., 1998). Among tobacco chewers in India, there appears to be no interaction between chewing and alcoholic beverage consumption (Balaram *et al*., 2002).

2.2.5 *Effect of cessation of alcoholic beverage consumption (Table 2.8)*

Studies of cessation of alcoholic beverage consumption may be confounded by the fact that precursors and early malignancies of the oral cavity and pharynx may lead to such cessation. Nevertheless, this type of confounding may result in underestimation of the effect of cessation. For recent quitters, the risk for oral and pharyngeal cancers increases above that of current drinkers; as the number of years since quitting increases, however, that elevated risk gradually drops to below that of current drinkers and near to the levels of non-drinkers in some studies. Hayes *et al*. (1999) observed that risk could drop to near the levels of non-drinkers after 20 years of quitting among men. Castellsagué *et al*. (2004) showed that risk can be reduced to near levels of never drinkers after 14 years and De Stefani *et al*. (2004) showed that this occurs after 10 years of quitting. In contrast, Franceschi *et al*. (2000) showed that a reduction in risk with quitting compared with current drinkers is not attained even 11 years after quitting.

2.2.6 *Effect of alcoholic beverage consumption in nonsmokers (Table 2.9)*

Because tobacco smoking is a major risk factor for oral and pharyngeal cancer, the study of nonsmoking subjects can avoid the strong confounding effect of tobacco smoking. Of the studies that focused on the effects of alcoholic beverage consumption in nonsmokers, an increase in risk in relation to alcoholic beverages was consistent. Talamini *et al*. (1990a) compared 27 nonsmoking cases identified between 1986 and 1989 in Milan and Pordenone and 572 nonsmoking hospital-based controls matched on age and area of residence. A significant dose–response relationship between alcoholic beverage consumption and cancer of the oral cavity and pharynx was observed (P=0.04). Ng *et al*. (1993) identified 173 white nonsmoking cases of oral and hypopharyngeal cancer between 1977 and 1991 in eight US cities and compared them with 613 hospital-based controls matched on age, sex and date of interview. A significant dose–response relationship was also observed in this study (P<0.001). Sixty nonsmoking

Table 2.8 Effect of cessation of alcoholic bevarage consumption on the incidence of cancers of the the oral cavity and pharynx

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Day *et al.* (1994a), USA, 1984–85	80 (56 men, 24 women) with second primary cancers from cohort of 1090 (first primary cancers) 189 (132 men, 57 women) randomly selected from cohort that were free of second primary cancer at the end of follow-up (1989)	Interviewer-administered questionnaire	Oral cavity, pharynx, oesophagus, larynx	*Years since last drank alcohol* Current drinker <5 years ≥5 years	 29 17 7	 1 (reference) 5.4 (1.6–18.0) 1.9 (0.6–6.7)	Age, stage of disease, amount smoked and drunk	

Table 2.8 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Hayes *et al*. (1999), Puerto Rico, 1992–95	342 (286 men, 56 women) identified through pathology laboratories and Central Cancer Registry; aged 21–79 years; histologically confirmed; response rate, 70% 521 (417 men, 104 women) population-based controls; frequency-matched by age, gender; response rate, 83%	Interviewer-administered questionnaire	Oral cavity, pharynx (ICD9 141–143–146, 148, 149)	*Years since last drink* **Men** Non-drinker Recent use Quit 2–9 years Quit 10–19 years Quit ≥20 years **Women** Non-drinker Recent use Quit 2–9 years Quit 10–19 years Quit ≥20 years	 9 163 60 34 20 26 15 6 5 4	 1 (reference) 2.4 (.0–5.4) 3.6 (1.5–9.0) 2.7 (1.0–7.0) 1.3 (0.5–3.6) 1 (reference) 1.2 (0.4–3.4) 1.0 (0.2–5.4) 1.1 (0.2–6.4) 0.9 (0.2–4.8)	Age, tobacco use	

Table 2.8 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Franceschi *et al.* (2000), Italy, Switzerland, 1992–97	754 (638 men, 116 women) cases from major teaching and general hospitals in Pordenone, Rome, Latina (Italy) and Vaud (Switzerland); aged 22–77 years; histologically confirmed; response rate, 95% 1775 (1254 men, 521 women) hospital-based non-cancer controls from the same network of hospitals as cases; excluded tobacco- and alcohol-related conditions; frequency-matched (5:1 for women, 2:1 for men controls:cases) on age, sex, area of residence; response rate, 95%	Interviewer-administered questionnaire	Oral cavity, pharynx (excluding lip, salivary glands, nasopharynx)	*Years since quit drinking* 1–3 years 4–6 years 7–10 years ≥11 years χ^2 for trend	 27 37 36 26	 1.2 (0.6–2.4) 1.8 (1.0–3.5) 3.3 (1.5–7.3) 1.9 (1.0–3.8) 1.6 (p = 0.21)	Age, sex, study centre, education, interviewer, tobacco smoking, total alcoholic beverage consumption	Study population from Franceschi *et al.* (1999)

Table 2.8 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Garrote *et al.* (2001), Havana, Cuba, 1996–99	200 (143 men, 57 women) cases identified in the Instituto Nacional de Oncologia y Radiobiologia of Havana; median age, 64 years; response rate, 88% 200 (136 men, 64 women) hospital-based controls admitted to same institute and three other major hospitals in Havana; excluded patients with alcohol- and tobacco-related conditions; frequency-matched on age, sex; median age, 62 years; response rate, 79%	Interviewer (dentist)-administered questionnaire	Oral cavity, oropharynx	*Years since quit drinking* Current drinker <10 years ≥10 years χ^2 for trend	 81 21 14	 1 0.7 (0.3–1.8) 0.3 (0.1–0.8) 5.00 (p=0.03)	Age, sex, area of residence, education, smoking	

Table 2.8 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Balaram, *et al.* (2002), southern, India, 1996–99	591 (309 men, median age, 56 years; 282 women, median age, 58 years) from three centres in Bangalore, Madras, Trivandrum; response rate, 97% 582 (292 men, 290 women) hospital-based from the same hospitals as cases; frequency-matched by centre, age, sex; response rate, 90%	Interviewer-administered questionnaire	Oral cavity	**Men only** *Years since quit drinking* Current drinkers <10 years ≥ 10 years *p* for trend	 84 49 16	 1 0.94 (0.43–2.09) 0.62 (0.19–2.05) 0.55	Centre, age, education, paan chewing, smoking, drinking	
Castellsagué, *et al.* (2004), Spain, 1996–99	375 (304 men, 71 women); mean age, 60 years; response rate, 76.5% 375 (304 men, 71 women); mean age, 60 years; response rate, 91%	Interviewer-administered questionnaire	Oral cavity, oropharynx	*Years since quit drinking* Never drinker Current drinker 1–2 years 3–7 years 8–13 years ≥14 years *p* for trend	 35 251 28 22 20 19	 1 (reference) 3.5 (1.9–6.5) 3.9 (1.7–9.1) 1.7 (0.8–3.9) 2.3 (1.0–5.3) 1.5 (0.7–3.3) 0.003	Age group, sex, education, centre, average number of cigarettes per day	

Table 2.8 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
De Stefani *et al.* (2004), Montevideo, Uruguay, 1997–2003	85 men identified in the four major hospitals in Montevideo; microscopically confirmed; response rate, 97.5% 640 hospital-based men from the same hospitals as cases; excluded patients with alcohol- and tobacco-related conditions with no recent changes in diet; frequency-matched (2:1 controls:cases) on age, residence; response rate, 97%	Interviewer-administered questionnaire	Hypopharynx	*Years since quit drinking* Current drinker 1–4 years 5–9 years ≥10 years Never drinker *p* for trend	 66 8 4 3 4	 1 (reference) 1.4 (0.6–3.2) 1.3 (0.4–4.3) 0.4 (0.1–1.5) 0.2 (0.1–0.5) 0.0007	Age, residence, urban/ rural status, education, body mass index, smoking	Looked at oral cavity, type of alcoholic beverage and joint effect of smoking

CI, confidence interval; ICD, International Classification of Diseases

Table 2.9 Risk of consumption of alcoholic beverages for cancers of the oral cavity and pharynx among nonsmokers

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Talamini *et al.* (1990a), Milan, Pordenone, Italy, 1986–89	27 (six men, 21 women) 572 (288 men, 284 women) hospital-based; matched on age, area of residence	Interviewer-administered questionnaire	Oral cavity, pharynx	*Total alcohol* <14 drinks/ week 14–55 drinks/ week >55 drinks/ week χ^2 for trend	 11 14 2	 1 (reference) 1.5 (0.6–3.7) 2.2 (0.2–27.9) 4.08 (p=0.04)	Age, sex	Includes study population from Franceschi *et al.* (1990); reference group included '0' drinks/ week and <14 drinks/ week

Table 2.9 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Ng *et al.* (1993), USA, 1977–91	173 (100 men, 73 women) whites in eight US cities; histologically confirmed 613 (254 men, 359 women) hospital-based; matched (up to 4:1 controls:cases) on age, sex, date of interview; excluded patients with tobacco-related conditions	Interviewer-administered questionnaire	Oral cavity, pharynx (ICD9 141, 143–146, 148, 149)	*Total alcohol (oz. of whiskey equiv./day)*				Nonsmokers of study from Kabat *et al.* (1994)
				Men				
				Non-drinker	13	1 (reference)		
				<1 oz/day	20	1.3 (0.6–3.1)		
				1–2.9 oz/day	19	2.4 (1.0–5.6)		
				3–6.9 oz/day	13	2.9 (1.1–7.6)		
				≥7 oz/day	8	4.4 (1.4–13.7)		
				χ^2 for trend		11.7 (p<0.001)		
				Women				
				Non-drinker	55	1 (reference)		
				<1 oz/day	34	0.9 (0.5–1.6)		
				1–2.9 oz/day	7	0.9 (0.3–2.6)		
				3–6.9 oz/day	1	0.4 (0.0–7.1)		
				≥7 oz/day	3	2.6 (0.5–13.3)		
				χ^2 for trend		0.00 (NS)		

Table 2.9 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Talamini *et al.* (1998), Italy, Switzerland, 1992–97	60 (20 men, 40 women) from Pordenone, Rome, Latina (Italy) and Vaud (Switzerland); aged 22–77 years; histologically confirmed; response rate, 95% 692 (346 men, 346 women) hospital-based; response rate, 95%	Interviewer-administered questionnaire	Oral cavity, pharynx	*Total alcohol* Never drinkers <21 drinks/ week 21–34 drinks/ week 35–55 drinks/ week ≥56 drinks/ week Former drinkers (abstain ≥1 year) χ^2 for trend	 16 23 4 7 3 7	 1 (reference) 0.8 (0.4–1.6) 0.8 (0.2–2.7) 5.0 (1.5–16.1) 5.3 (1.1–24.8) 2.0 (0.7–5.4) 6.2 (0.01)	Age, sex, education, study centre	Study population from Franceschi *et al.* (2000)

Table 2.9 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Fioretti *et al.* (1999), Milan, Pordenone, Italy, 1984–93	42 (10 men, 32 women) lifelong nonsmokers from a network of general and teaching hospitals in Milan and Pordenone; histologically confirmed 864 (442 men, 422 women) hospital-based non-cancer nonsmokers; matched on age, area of residence; excluded patients with tobacco-related conditions	Interviewer-administered questionnaire	Oral cavity, pharynx	*Total alcohol* Non-drinkers >0–<3 drinks/day ≥3 drinks/day Wine drinkers Beer drinkers Spirit drinkers	 4 25 13 37 7 5	 1 (reference) 3.4 (1.1–10.1) 2.6 (0.7–9.3) 3.3 (1.1–9.6) 3.3 (0.7–16.4) 1.0 (0.2–6.1)	Age, sex, education, study centre	Study population from Franceschi *et al.* (1990)

Table 2.9 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Hashibe *et al.* (2007a), International Consortium of Head and Neck Cancer; combined analysis of 15 studies from USA, South and Central American, European countries	383 who never used tobacco 5775 who never used tobacco	Interview or self-administered questionnaire	Oral cavity (ICD9 140, 141, 143–5)	*Total alcohol*			Adjusted for age, sex, race/ ethnicity, education, study centre	
				Never	243	1.00 (reference)		
				Ever	137	1.17 (0.92–1.48)		
				<1 drink/day	44	1.14 (0.8–1.63)		
				1–2 drinks/day	60	1.64 (1.19–2.25)		
				3–4 drinks/day	10	1.11 (0.57–2.15)		
				≥5 drinks/day	8	1.23 (0.59–2.57)		
				p for trend		0.032		
				Duration				
				1–10 years	21	2.36 (1.43–3.88)		
				11–20 years	17	1.09 (0.65–1.85)		
				21–30 years	19	0.81 (0.49–1.33)		
				31–40 years	35	1.29 (0.88–1.9)		
				>40 years	32	1.15 (0.77–1.73)		
				p for trend		<0.001		

Table 2.9 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Hashibe *et al.* (2007a) (contd)	369 who never used tobacco 5775 who never used tobacco		Oro-pharynx/ hypo-pharynx (ICD9 146, 148)	*Total alcohol*				
				Never	153	1.00 (reference)		
				Ever	216	1.38 (0.99–1.94)		
				<1 drink/day	73	1.39 (0.99–1.96)		
				1–2 drinks/day	83	1.66 (1.18–2.34)		
				3–4 drinks/day	24	2.33 (1.37–3.98)		
				≥5 drinks/day	29	5.50 (2.26–13.36)		
				p for trend		<0.001		
				Duration				
				1–10 years	18	1.76 (0.99–3.14)		
				11–20 years	28	1.34 (0.81–2.11)		
				21–30 years	63	1.95 (1.37–2.77)		
				31–40 years	61	1.44 (0.78–2.66)		
				>40 years	37	1.51 (0.68–3.37)		
				p for trend		<0.001 (0.003)		

Table 2.9 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Hashibe *et al*. (2007a) (contd)	155 who never used tobacco 4983 who never used tobacco		Oral cavity or pharynx NOS (ICD9)	*Total alcohol*				
				Never	80	1.00 (reference)		
				Ever	72	1.09 (0.77–1.54)		
				<1 drink/day	25	1.08 (0.67–1.75)		
				1–2 drinks/day	26	1.24 (0.77–1.99)		
				3–4 drinks/day	13	2.32 (1.24–4.34)		
				≥5 drinks/day	4	0.77 (0.27–2.18)		
				p for trend		<0.891		
				Duration				
				1–10 years	13	2.59 (1.38–4.86)		
				11–20 years	11	1.09 (0.56–2.11)		
				21–30 years	18	1.26 (0.73–2.17)		
				31–40 years	14	0.86 (0.47–1.57)		
				>40 years	13	0.92 (0.49–1.71)		
				p for trend		<0.014		

CI, confidence interval; ICD, International Classification of Diseases; NOS, not otherwise specified; NS, not significant

cases from Pordenone, Rome, Latina (Italy) and Vaud (Switzerland) were identified from 1992 to 1997 and compared with 692 hospital-based controls (Talamini *et al*., 1998). Again, a dose–response relationship was seen between alcoholic beverage consumption and cancer of the oral cavity and pharynx (P=0.01). The Pooling Project, the International Head and Neck Cancer Epidemiology Consortium, reported associations between alcoholic beverage consumption and oral and pharyngeal cancer among nonsmokers (Hashibe *et al*., 2007a). The study included 384 cases of oral cancer, 369 oropharyngeal or hypopharyngeal cancers, 155 cases of oral and pharyngeal (not otherwise specified) cancer and 5775 controls. A significant dose–response relationship was observed for oro- and hypopharyngeal cancer for both frequency and duration of alcoholic beverage consumption. The adjusted odds ratios were 1.66 (95% CI, 1.18–2.34) for 1–2 drinks per day, 2.33 (95% CI, 1.37–3.98) for 3–4 drinks per day and 5.5 (95% CI, 2.26–13.36) for five or more drinks per day. The association was weaker for cancer of the oral cavity.

In addition, among 25 studies of effect modification listed in Table 2.7, the effect of alcoholic beverage consumption was presented in 17 (Blot *et al*., 1988; Franceschi *et al*., 1990; Zheng *et al*., 1990; Kabat *et al*., 1994; Chyou *et al*., 1995; Murata *et al*., 1996; Sanderson *et al*., 1997; Zheng *et al*., 1997; Schildt *et al*., 1998; Franceschi *et al*., 1999; Hayes *et al*., 1999; Schlecht *et al*., 1999; Garrote *et al*., 2001; Schwartz *et al*., 2001; Balaram *et al*., 2002; Boeing, 2002; Castellsagué *et al*., 2004). The majority of these studies found a strong association with alcoholic beverage consumption among nonsmokers with a dose–response relationship. A strong association and a dose–response relationship between alcoholic beverage consumption and the risk for oral and pharyngeal cancers demonstrated strong evidence for the carcinogenic effect of alcoholic beverage consumption.

2.3 Cancer of the larynx

The consumption of alcoholic beverages and tobacco smoking are the two major risk factors for laryngeal cancer (Austin & Reynolds, 1996; Doll *et al*., 1999). A relationship between the consumption of alcoholic beverages and cancer of the larynx was first suggested in the early 1900s by mortality statistics and clinical reports, and was subsequently supported by ecological studies that compared per-capita alcoholic beverage consumption and trends in the incidence of and mortality from laryngeal cancer (Wynder, 1952; Tuyns, 1982). However, the definition of alcoholic beverages as an independent etiological factor for laryngeal cancer and its quantification was not obtained until the late 1950s and early 1960s following ad-hoc epidemiological investigations (Schwartz *et al*., 1962; Wynder *et al*., 1976; Jensen, 1979).

Several case–control studies found an independent dose–risk relationship between alcoholic beverage consumption and the risk for laryngeal cancer, as well as a synergistic effect with tobacco smoking. Studies published up to 1988 were reviewed in a previous monograph (IARC, 1988). These included six prospective studies (Sundby, 1967;

Hakulinen *et al*., 1974; Monson & Lyon, 1975; Robinette *et al*., 1979; Jensen, 1980; Schmidt & Popham, 1981) and 14 case–control studies conducted in North America and Europe (Wynder *et al*., 1956; Schwartz *et al*., 1962; Vincent & Marchetta, 1963; Wynder *et al*., 1976; Spalajkovic, 1976; Williams & Horm, 1977; Burch *et al*., 1981; Herity *et al*., 1982; Elwood *et al*., 1984; Olsen *et al*., 1985; Zagraniski *et al*., 1986; Brugère *et al*., 1986; Tuyns *et al*., 1988). Four of the six prospective studies showed significant increases in risk. Furthermore, all of the case–control studies showed an association with alcoholic beverage consumption, and a trend in risk for the amount consumed, but no indication of a difference in risk for various types of alcoholic beverage. The previous IARC Working Group concluded that the occurrence of malignant cancer of the larynx was causally related to the consumption of alcoholic beverages (IARC, 1988).

However, several important aspects of the relationship between alcoholic beverage consumption and the risk for laryngeal cancer remained unsolved. These included the role of time-related variables, such as duration of the habit, age at starting, time since cessation of consumption for former drinkers and the effect of different types of alcoholic beverage. Further, the risk may differ by anatomical subsite, such as the supraglottis and the glottis/subglottis.

The epidemiological evidence for an association between alcoholic beverage consumption and the risk for laryngeal cancer includes at least four cohort and 18 case–control studies that have been published since 1988.

2.3.1 *Cohort studies (Table 2.10)*

Since 1988, six prospective studies have examined the relationship between alcohol beverage consumption and laryngeal cancer.

A study from Sweden (Adami *et al*., 1992b) of 9353 individuals discharged from care facilities with a diagnosis of alcoholism, including 11 cases of laryngeal cancer, showed an SIR of 3.3 for this cancer type. No information on individual consumption of alcoholic beverages was available, although the level of consumption of these subjects was presumably much higher and of longer duration than that of the general population. Moreover, no adjustment was available for tobacco consumption or for other potentially confounding factors such as socioeconomic status or diet, although an unfavourable risk pattern in alcoholics is probable. In the largest study of subjects who had a hospital discharge diagnosis of alcoholism in Sweden (Boffetta *et al*., 2001), the relative risk for laryngeal cancer was 4.21 (95% CI, 3.78–4.68; based on 347 cases).

The Honolulu Heart Program study (Chyou *et al*., 1995) was based on 7995 American men of Japanese ancestry who lived in Hawaii, and included 93 cases of cancers of the oral cavity and pharynx, oesophagus and larynx. A strong dose–risk relationship with alcoholic beverage consumption was found with a relative risk of 4.7 for ≥25 oz/month of total alcoholic beverage intake, compared with non-drinkers. In a prospective study of 10 960 Norwegian men followed from 1962 through to 1992 (Kjaerheim

Table 2.10 Selected prospective studies of laryngeal cancer and alcoholic beverage consumption

Reference, location	Study subjects	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Adami *et al*. (1992b), Uppsala, Sweden	9353 patients, 8340 men, 1013 women diagnosed with alcoholism from the Uppsala In-patient Register	Not reported	*Men* 10 *Women* 1 *Total* 11	 3.1 (1.5–5.7) 23.2 (0.3–129.1) 3.3 (1.7–6.0)	Age, sex	SIR reported
Chyou *et al*. (1995), Japan	7995 men of Japanese-American descent; interviewed and examined from 1965–1968; aged 45–68 years; identified through continuous surveillance of Oahu hospitals and linkage with the Hawaiian Tumor Registry	Non-drinkers <4 oz/month 4–24.9 oz/month ≥25 oz/month	16 5 18 52	1.00 0.57 (0.21–1.57) 1.74 (0.88–3.41) 4.67 (2.62–8.32) $p<0.0001$	Age, number of cigarettes/day, number of years smoked	
Kjaerheim *et al*. (1998), Oslo, Norway	10 960 Norwegian men born between 1893 and 1929; no prior diagnosis of upper aerogastric tract disease	*Total alcohol* Never or <1 time/week Previously 1–3 times/week 4–7 times/week Unknown	 26 4 18 19 4	 1.00 0.9 (0.3–2.7) 1.1 (0.6–1.9) 3.9 (2.1–7.1) 0.6 (0.2–1.8) $p=0.003$	Age, smoking level	

Table 2.10 (continued)

Reference, location	Study subjects	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Boffetta *et al*. (2001), Sweden	182 667 patients with a diagnosis of alcoholism aged 20 years or over and hospitalized during 1965–1994; identified in the In-patient Register and the National Cancer Register	Not reported	347	4.21 (3.78–4.68)	Not reported	SIR reported

CI, confidence interval; SIR, standardized incidence ratio

et al., 1998) that included 71 incident cases of upper digestive tract and respiratory neoplasms, the relative risk for the highest level of alcoholic beverage consumption (4–7 times/week) was 3.9 compared with never or occasional drinkers. These results were not confounded by marital status, occupational group or body-mass index. In the two latter prospective studies, no separate risk estimates were given for laryngeal cancer.

2.3.2 *Case–control studies (Table 2.11)*

Twenty case–control studies published since 1988 have included information on alcoholic beverage consumption and laryngeal cancer. All of these included overall allowance for tobacco use. Two additional case–control studies from China of 99 and 116 patients also found an excess risk in heavy alcoholic beverage drinkers, but did not allow for tobacco smoking.

The dose–risk relationship between alcoholic beverage consumption and major digestive and respiratory tract neoplasms was estimated from the data of a series of Italian case–control studies using regression spline models, and showed substantial increases in risk for laryngeal cancer with regular consumption of more than 50 g ethanol per day (Polesel *et al*., 2005).

A meta-analysis of 20 case–control studies (Bagnardi *et al*., 2001) included over 3500 cases of laryngeal cancer and reported a strong direct trend in risk, with multivariate relative risks of 1.38 (95% CI, 1.32–1.45) for 25 g alcohol per day, 1.94 (95% CI, 1.78–2.11) for 50 g per day and 3.95 (95% CI, 3.43–4.57) for 100 g per day, based on a dose–risk regression model. Corrao *et al*. (2004) found significantly increased risks for laryngeal cancer when comparing point-based and model-based relative risks to that of meta-pooled relative risks from studies that provided information on low doses (i.e., $\leq$ 25g of alcohol per day), thus confirming the evidence of an association for modest doses as well.

2.3.3 *Subsites of the larynx (Table 2.12)*

The larynx can be divided into the supraglottis (also called extrinsic larynx) and epilarynx, which border on the hypopharynx, and the glottis (also called intrinsic larynx) and subglottis, which lie wholly within the respiratory system (Spleissl *et al*., 1990). These various subsites of the larynx are exposed to potential carcinogens at different levels: the glottis and subglottis are more highly exposed to inhaled agents and the supraglottis to ingested agents, while the junctional area between the larynx and the pharynx is exposed to both inhaled and ingested agents. Thus, each site could react differently to different etiological factors.

At least seven case–control studies (Brugère *et al*., 1986; Guénel *et al*., 1988; Falk *et al*., 1989; Maier *et al*., 1992b; Muscat & Wynder, 1992; Talamini *et al*., 2002; Menvielle *et al*., 2004) and one meta-analysis (Bagnardi *et al*., 2001) suggested that the risk from alcoholic beverage consumption was stronger for cancer of the supraglottis than for

Table 2.11 Case–control studies of laryngeal cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Burch *et al*. (1981), Canada, 1977–79	204 newly diagnosed cases of laryngeal cancer; 100% histologically confirmed	204 individually matched neighbourhood controls, matched on age (±5 years), sex		*Ounces of ethanol in lifetime* 0 <10 000 10 000–25 000 ≥26 000		 1.0 2.0 3.9 7.7	Smoking	Presented results were limited to men
Elwood *et al*. (1984), Canada 1977–1980	374 patients diagnosed primary epithelial cancers of the oral cavity, oro- and hypopharynx and larynx	374 patients diagnosed with another cancer within 3 months of the date of diagnosis of the study patient; diagnoses were not related to smoking, alcohol or occupational exposure; 1:1 matched for age (±2 years), sex; interview time of patient (within 3 years)	Larynx (ICD0 161)	See Table 2.12	See Table 2.12	See Table 2.12	Socioeconomic status, marital status, dental care, history of tuberculosis, smoking	Including age and sex in the multivariate model did not substantially change the estimates.
Olsen *et al*. (1985), Denmark 1980–82	326 newly diagnosed cases of laryngeal cancer	1134 matched for sex and closest date of birth	ICD161.1, 161.2, 161.0	See Table 2.12	See Table 2.12	See Table 2.12		

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Brugère *et al.* (1986), France 1975–82	2540 male patients with cancer of larynx, pharynx and mouth, selected from male and female patients treated in the Neck and Head Department of the Institut Curie in Paris	National Institute of Statistics and Economic Studies data; more than 4000 men; stratified by age and cancer location for analysis		See Table 2.12	See Table 2.12	See Table 2.12	Smoking	Data collected by different methods between patients and controls
Guénel *et al.* (1988), France, 1975–85	197 glottis, 214 supraglottis; males >25 years old; cases with squamous-cell carcinoma	4135 controls from the population	ICD-8 161.5, 161.4	See Table 2.12	See Table 2.12	See Table 2.12	Age, tobacco	Relative risk for combined heavy tobacco and alcoholic beverage consumption, 289.4 (83.0–705.8) for glottis and 1094 (185.8–2970.7) for supraglottis
Tuyns *et al.* (1988), France, Italy, Spain, Switzerland	727 endolarynx, 188 epilarynx	3057 men from the population		0–20 g/day 21–40 g/day 41–80 g/day 81–120 g/day ≥121 g/day		1 (reference) 0.9 (0.7–1.3) 1.1 (0.8–1.5) 1.7 (1.2–2.4) 2.6 (1.8–3.6)	Age, residence, smoking	Relative risk for >120 g/day: 2.6 for endolarynx, 10.6 for epilarynx

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Falk *et al*. (1989), Texas, USA, 1975–80	151 men from 56 hospitals in Texas and identified through hospital records	235 identified from Texas Department of Public Safety drivers license files or HCFA medicare recipients roster; frequency-matched by residence, age, ethnicity	ICD-9 161.X, 231.0	Non-drinkers	13	1 (reference)	Age, residence, employment, smoking, fruit and vegetable consumption	No consistent linear trend in risk, but relatively low consumption
				<2 drinks/week	8	0.8 (0.3–2.6)		
				2–3 drinks/week	6	0.5 (0.2–1.6)		
				4–6 drinks/week	17	2.1 (0.8–5.3)		
				7–10 drinks/week	19	2.3 (0.9–5.8)		
				11–15 drinks/week	17	1.5 (0.6–3.8)		
				16–21 drinks/week	22	1.8 (0.7–4.6)		
				22–29 drinks/week	14	1.3 (0.5–3.4)		
				≥30 drinks/week	35	2.1 (0.9–5.0)		
Franceschi *et al*. (1990), Italy, 1986–89	162 men with laryngeal cancer from hospitals in northern Italy	1272 men admitted with acute illnesses not related to alcohol or tobacco consumption	ICD-9 161	*Total number of drinks per week*			Age, smoking, residence, education, occupation	Combined effect with tobacco compatible with a multiplicative effect
				≤19	39	1 (reference)		
				20–34	27	0.8 (0.5–1.4)		
				35–59	51	1.3 (0.8–2.1)		
				≥60	45	2.1 (1.2–3.8)		
Sankaranarayanan *et al*. (1990), India, 1983–84	191 men with squamous cell cancer	549 hospital patients attending the Regional Cancer Centre	ICD-0 161	Never	98	1 (reference)		No data on dose
				≥20 years	13	2.7 (0.9–4.5)		
				>21 years	47	4.2 (1.5–4.3)		
						p-trend<0.001		

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Ahrens *et al.* (1991), Germany, 1986–87	100 prevalent male cases of laryngeal cancer; cases recruited from Ear, Nose and Throat Clinic; 100% histologically confirmed	100 hospital controls with diseases not related to alcohol, smoking or occupational exposures; same age distribution as cases; admission diagnosis with an expected length of stay in hospital comparable with that of laryngeal cancer		Non-drinkers Occasional drinkers Daily drinkers	 28 	1 (reference) 3.2 (1.4–7.5) 1.1 (0.5–2.3)	Age, smoking, occupation	Number of cases among non-drinkers or daily drinkers not given
Choi & Kahyo (1991a), Seoul, Republic of Korea, 1986–89	94 male cases of laryngeal cancer; 100% histologically confirmed	282 hospital controls from Korea Cancer Center Hospital; non-cancer, non-alcohol or tobacco-related diseases	161	Non-drinkers Light Moderate Medium–heavy Heavy	17 5 28 29 15	1 (reference) 0.3 (0.1–0.7) 1.2 (0.6–2.5) 2.4 (1.2–4.9) 11.1 (3.8–32.4)	Age (matched), smoking	Data related to alcohol consumption among women were limited.

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Zatonski *et al*. (1991), Warsaw, Poland, 1986–87	249 men with cancer of the larynx; 70% supraglottis, 30% glottis; response rate, 88%	965 men from the general population aged 25–65 years; response rate, 94%		Irregular 1–15 years 16–30 years >30 years	142 18 65 24	1 (reference) 3.4 (1.6–7.0) 9.5 (5.2–17.2) 10.4 (4.0–27.2)	Age, residence, education, smoking	Vodka main type of alcoholic beverage; higher risk for regular than for irregular drinkers
Freudenheim *et al*. (1992), New York, USA, 1975–85	250 pathologically confirmed cases of laryngeal cancer; white men	250 age- and neighbourhood-matched controls		0–339 drinks/year 340–1243 drinks/year 1244–2925 drinks/year ≥2926 drinks/year	32 33 48 137	1 (reference) 1.5 (0.7–3.2) 1.1 (0.6–2.1) 3.5 (1.8–6.9) *p*-trend<0.001	Education, smoking	Race and gender differences
Maier *et al*. (1992b), Germany, 1988–89	164 men with histologically proven squamous-cell carcinoma	656 matched male controls with no known tumorous disease selected from outpatient clinics		<25 g/day 25–75 g/day ≥75 g/day		1 (reference) 2.6 (1.6–4.0) 9.0 (5.2–15.53)	Age, residence, smoking	Number of cases not reported

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Muscat & Wynder (1992), USA, 1985–90	194 men with histologically confirmed laryngeal cancer; Memorial Sloan-Ketterling and 7 other hospitals	184 hospital controls admitted for unrelated tobacco-induced disease; age matched (±5 years)		Never/ <29.6 mL/ day	40	1 (reference)	Age (matched), education, smoking, quetelet index	Relative risk 14.8 for binge drinkers
				29.7–88.9 mL/day	19	1.1 (0.6–2.3)		
				89–206 mL/ day	41	2.8 (1.5–5.2)		
				≥207 mL/ day	55	4.8 (2.5–9.4)		
				Binge drinkers	31	14.8 (1.6–46.3)		
Zheng *et al.* (1992), China, 1988–90	201 male residents of urban Shanghai; aged 20–75 years diagnosed with laryngeal cancer	414 hospital controls; age and sex matched; Shanghai Resident Registry		Never drinkers	80	1 (reference)	Age, education, smoking	Absence of association attributed to alcoholic beverage consumption during meals; data for female alcohol consumption not presented
				<144 g/week	16	0.8 (0.4–1.7)		
				144–284 g/ week	22	1.0 (0.5–2.0)		
				285–479 g/ week	27	0.9 (0.5–1.9)		
				≥480 g/week	32	0.8 (0.4–1.6)		
Hedberg *et al.* (1994), western Washington, USA, 1983–87	235 patients with laryngeal cancer aged 20–74 years; from 3 counties in western Washington state; response rate, 81%	547 controls identified through random-digit dialing; response rate, 75%	ICD-9 161.0–161.9	<7 drinks/ week	89	1 (reference)	Age, sex, smoking, MAST score	
				7–13 drinks/ week	42	1.9 (1.1–3.2)		
				14–20 drinks/week	27	2.1 (1.0–4.4)		
				21–41 drinks/week	37	2.8 (1.4–5.7)		
				>42 drinks/ week	24	3.1 (1.2–7.9)		

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Dosemeci *et al*. (1997), Istanbul, Turkey, 1979–84	832 men with laryngeal cancer; selected from oncology treatment centre	829 hospital patients with selected cancers not related to alcohol or tobacco use	ICD-0 161.0–161.3; 161.9	Never drinkers	625	1 (reference)	Age, smoking	Possible underestimation of alcohol drinking due to low social acceptance; females excluded due to low prevalence of smoking and alcohol use among women in Turkey
				1–35 cL/ week	46	1.7 (1.0–3.2)		
				36–140 cL/ week	85	1.8 (1.1–2.9)		
				>141 cL/ week	41	1.5 (0.8–2.9)		
Rao *et al*. (1999), India, 1980–84	427 men diagnosed with cancer of vocal cords, supraglottis and larynx	635 male hospital patients free from cancer, infectious disease and benign lesions	ICD-9 161.0, 161.1, 161.9	Non-drinkers	308	1 (reference)		Multivariate relative risk for drinkers versus non-drinkers, adjusted for tobacco smoking and chewing and education, 1.64 (1.16–2.31; p=0.005)
				Once per day	85	1.5 (1.0–2.2)		
				Twice per day	17	2.8 (1.4–7.5)		

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Schlecht *et al.* (2001), Brazil, 1986–89	784 newly diagnosed cases of carcinoma of the oral cavity, pharynx and larynx; selected from hospitals in 3 metropolitan areas in Brazil	1578 controls 2:1 matched by age (±5 years), gender, trimester of admission	ICD-9 140–145, 146–149, 161	*>100 kg of lifetime condumption versus non-drinker*			Age, study location, admission period, tobacco smoking, remaining alcohol consumption, income, education, race, beverage temperature, religion, wood stove use, consumption of spicy food	
				Beer	39	1.8 (0.6–5.7)		
				Wine	60	1.5 (0.6–4.0)		
				Hard liquor	61	1.3 (0.6–5.4)		
Bosetti *et al.* (2002), Italy, Switzerland, 1986–92; 1992–2000	40 non smoking cases and 68 non-drinking cases of laryngeal cancer; aged 30–74 years	160 nonsmoking and 161 non-drinking controls matched on study, sex, age, study centre; aged 31–79 years; admitted for acute, non-neoplastic conditions		*Drinks per day*			Smoking	
				<8	31	1		
				≥8	9	2.46 (0.98–6.20)		

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Talamini *et al* (2002), Italy, Switzerland, 1992–2000	527 cases of squamous-cell carcinoma of the larynx; <79 years old; response rate, 97%	1297 hospital subjects admitted for non-alcohol-or tobacco-related illnesses	ICD-9 161.0–161.3, 161.8, 161.9	Abstainers >0–13 drinks/week 14–27 drinks/week 28–55 drinks/week ≥56 drinks/week	19 37 68 159 184	1 (reference) 0.9 (0.5–1.8) 1.2 (0.6–2.2) 2.6 (1.4–4.7) 5.9 (3.1–11.3) *p*-trend<0.0001	Age, sex, centre, education, smoking	No clear risk for duration; association in women too
Corrao *et al*., (2004) 1966–1998	Meta analyses of 99 case-control and 57 cohort studies published between 1966–88; for larynx, 20 case-control studies were the basis of the analysis			25 g/day 50 g/day 100 g/day		1.43 (1.38–1.48) 2.02 (1.89–2.16) 3.86 (3.42–4.35)		

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Menvielle *et al*. (2004), France, 1989–91	504 men (125 glottis, 80 supraglottis, 97 epilarynx, 201 hypopharynx)	242 men with non-respiratory cancers; frequency-matched by age		Occasional drinkers	22	1 (reference)	Age, tobacco	Relative risk higher for hypopharynx compared with the glottis, supraglottis and epipharynx
				1–2 drinks/day	56	1.4 (1.2–1.6)		
				3–4 drinks/day	80	2.0 (1.5–2.7)		
				5–8 drinks/day	156	2.9 (1.9–4.4)		
				9–12 drinks/day	109	4.1 (2.4–7.2)		
				≥13 drinks/day	81	5.9 (2.9–11.8)		
Lee *et al*. (2005), Taiwan, China, 2000–03	128 male laryngeal cancer patients	255 hospital controls non-frequency matched; 40 years of age and older	ICD-10 C32	Non-drinkers	56	1 (reference)	Age, tobacco, use of betel quid	
				≤750 mL	52	3.1 (1.7–5.8)		
				>750 mL	15	10.3 (3.0–42.5)		
						p-trend<0.0001		

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Polesel *et al*. (2005), Italy, Switzerland, 1982–99	588 histologically confirmed cases of laryngeal cancer	1663 patients <80 years of age, admitted to the same network of hospitals as cases, any acute non-neoplastic condition frequency matched by area of residence, age and year of interview						Spline models showed an increased risk with increasing alcohol consumption. See Polesel *et al*. (2005) for details regarding the estimation of spline model fit.
Garavello *et al*. (2006), Italy, 1986–2000	672 cases of laryngeal cancer (613 men and 59 women) aged 30–80 years; histologically confirmed; admitted to major teaching and general hospitals	3454 hospital-based controls (2646 men, 808 women); admitted to same network of hospitals as cases for non-neoplastic conditions not associated with smoking or alcohol		*Total alcohol* 0 1–2 drinks/day 3–4 drinks/day 5–7 drinks/day 8–11 drinks/day ≥12 drinks/day	 46 96 111 149 180 84	 1.00 * 1.12 (0.83–1.50) 2.43 (1.79–3.28) 3.65 (2.68–4.98) 4.83 (3.18–7.33) $p<0.0001$	Study centre, sex, age, education, body mass index, smoking	Pattern of increasing risk with increasing number of drinks was similar for drinkers of wine only and of wine plus beer and spirits; *for multivariate models, abstainers (0 drinks/day) or light drinkers (1–2 drinks/day) were compared with other levels of drinking.

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Hashibe *et al.* (2007a), central and eastern Europe, 2000–02	384 incident (254 glottis, 108 supraglottis)	918 hospital	ICD-10 C32.0, C32.1, C32.2, C32.8, C32.9	Non-drinker	6	0.6 (0.22–1.65)	Age, sex, education, body mass index, fruit intake, study centre, pack–years of tobacco use	Significant trend in risk with dose; direct relation of borderline significance with duration of drinking
				1–139.9 g/week	161	1 (reference)		
				140–279 g/week	94	1.57 (1.05–2.33)		
				280–419 g/week	29	1.13 (0.62–1.99)		
				≥420 g/week	80	1.45 (0.92–2.26) *p*-trend=0.08		

CI, confidence interval; HCFA, Health Care Financing Administration; ICD, International Classification of Diseases; MAST, Michigan alcoholism-screening test

Table 2.12 Selected case–control studies of alcoholic beverage consumption and cancer of the larynx by anatomical subsite

Reference	Amount of alcohol consumption	Relative risk (95% CI)					
		No. of cases	Epilarynx	No. of cases	Supraglottis	No. of cases	Glottis/ subglottis
Elwood *et al*. (1984)	≥20 oz/week vs <1			46	6.4	108	2.2
Olsen *et al*. (1985)	≥301 g/week vs 0–100			191	3.0	103	5.0
Brugère *et al*. (1986)	≥160 g/day vs 0–40	217	101.4 (44–233.9)	224	42.1 (20.5–86.4)	242	6.1 (3.4–10.9)
Guénel *et al*. (1988)	≥160 g/day vs ≤39 g/day			81	35.7 (19.2–66.5)	61	14.9 (8.7–25.4)
Tuyns *et al*. (1988)	≥121 g/day vs 0–20	118	10.6 (4.4–25.8)	426	2.0 (1.3–3.0)	270	3.4 (2.1–5.6)
Falk *et al*. (1989)	20 drinks/week vs non-drinkers			9	4.6 (0.6–39.1)	40	1.8 (0.8–4.0)
Maier *et al*. (1992b)	>75 g/day versus <25				11.8 (4.5–29.6)		7.9 (3.5–17.7)
Muscat & Wynder (1992)	>207 mL/day vs never/<29.6			33	9.6 (3.3–27.6)	72	2.5 (1.0–6.2)
Dosemeci *et al*. (1997)	>141 cL/week vs never drinker			385	1.3 (0.6–2.8)	183	1.5 (0.6–3.6)
Talamini *et al*. (2002)	≥56 drinks/week vs 0–13			49	11.7 (3.2–42.3)	95	4.9 (2.1–11.7)
Menvielle *et al*. (2004)	>13 glasses/day vs 1–2	13	6.6 (2.4–17.7)	12	4.1 (1.4–11.5)	14	2.9 (1.1–7.1)

CI, confidence interval

cancer of the glottis/subglottis. Conversely, other studies reported similar risks for both supraglottis and glottis/subglottis (Flanders & Rothman, 1982; Tuyns *et al*., 1988; Hedberg *et al*., 1994). In a multicentric study in France, Italy, Spain and Switzerland (Tuyns *et al*., 1988) and in two French studies (Brugère *et al*., 1986; Menvielle *et al*., 2004), a stronger effect of alcoholic beverage consumption was found for the epilarynx.

The available evidence thus indicates that the highest risks related to the consumption of alcoholic beverages tend to occur in tissues that come into close contact with both alcoholic beverages and tobacco smoke. Thus, alcoholic beverage consumption may influence the risk for laryngeal cancer particularly through its direct contact or solvent action, perhaps by enhancing the effects of tobacco or other environmental carcinogens.

2.3.4 *Types of alcoholic beverage (Table 2.13)*

Several studies have investigated whether the risk for laryngeal cancer depends on the type of alcoholic beverage consumed. In a cohort study in Hawaii (Chyou *et al*., 1995) of 93 cancers of the upper digestive and respiratory tract, no substantial difference in risk was found between the highest levels of consumption of beer (relative risk, 3.7), wine (relative risk, 3.8) or spirits (relative risk, 3.6). Another prospective study in Norway (Kjaerheim *et al*., 1998) of upper digestive and respiratory tract cancers found a higher risk for elevated consumption of beer (relative risk, 4.4) compared with that of spirits (relative risk, 2.7). However, due to the limited number of cases, specific analysis of laryngeal cancer was not possible in these two cohort studies.

Among case–control studies, a Canadian study (Burch *et al*., 1981) found an increase in risk among heavy beer drinkers (odds ratio, 4.8), but no consistent increase for spirit (odds ratio, 1.3) or wine drinkers (odds ratio, 0.5). Similarly, a case–control study from Denmark (Olsen *et al*., 1985) of 326 cases of laryngeal cancer and 1134 controls reported a higher risk in drinkers who preferably consumed beer (odds ratio, 1.4) than in those who preferred wine (odds ratio, 0.6) or spirits (odds ratio, 1.0). A case–control study in Uruguay (De Stefani *et al*., 1987) of 107 cases of laryngeal cancer and 290 controls showed a higher risk for wine (odds ratio, 7.4) than for hard liquors (odds ratio, 4.0). In an Italian study (Franceschi *et al*., 1990), wine was associated with the highest risk (odds ratio, 4.2), whereas a lower risk was reported for beer (odds ratio, 1.5) and hard liquors (odds ratio, 0.8). In a case–control study conducted in the USA (Muscat & Wynder, 1992), based on 250 cases, an increased risk for laryngeal cancer was found for heavy drinkers of beer (odds ratio, 2.7) and hard liquors (odds ratio, 2.2), but not for wine drinkers (odds ratio, 1.1). No strong differences were seen between consumption of beer, hard liquors or wine in a case–control study in Brazil (Schlecht *et al*., 2001) that included 194 cases of laryngeal cancer: the relative risk was 1.8 for high consumption of hard liquors and beer and 1.5 for that of wine. Higher risks were observed for cachaça (relative risk, 9.9), a typical Brazilian hard liquor. In a case–control study in Italy and Switzerland (Talamini *et al*., 2002),

Table 2.13 Selected case–control studies of laryngeal cancer and consumption of different types of alcohol beverage

Reference, study location	Level of alcohol intake	Relative risk (95% CI)					
		No. of cases	Beer	No. of cases	Wine	No. of cases	Hard liquors
Burch *et al.* (1981), Canada	Beer/spirits: ≥4 drinks/day versus non-drinker Wine: ever used versus never		4.8 (2.4–9.8)		0.5 (0.2–0.9)		1.3 (0.5–3.4)
Olsen *et al.* (1985), Denmark	Preferred type of alcohol		1.4 (1.1–1.9)		0.6 (0.4–0.9)		1.0 (0.6–1.8)
De Stefani *et al.* (1987), Uruguay	>201 mL/day versus non-drinker		–		7.4 (3.0–18.1)		4.0 (1.9–8.2)
Franceschi *et al.* (1990), Italy	Beer: >14 drinks/week versus 0 Wine: ≥84 versus 0–6 Hard liquors: >7 versus 0	25	1.5 (0.8–2.5)	10	4.2 (1.6–10.6)	35	0.8 (0.5–1.3)
Freudenheim *et al.* (1992), USA	Beer: ≥1873 drinks/year versus 0–32 Wine: ≥139 versus 0 Hard liquors: ≥438 versus 0	123	2.7 (1.4–5.1)	67	1.1 (0.6–2.0)	117	2.2 (1.2–4.0)
Schlecht *et al.* (2001), Brazil	>100 kg of lifetime consumption versus non-drinkers	39	1.8 (0.6–5.7)	60	1.5 (0.6–4.0)	61	1.8 (0.6–5.4)
Talamini *et al.* (2002), Italy, Switzerland	Beer: >1 drinks/week versus 0–1 Wine: ≥42 versus 0–13 Hard liquors: >3 versus 0–3	167	3.3 (1.8–6.1)	210	5.2 (2.8–9.9)	182	2.9 (1.5–5.8)
Garavello *et al.* (2006), Italy	Beer: ≥3 drinks/day Wine: ≥12 drinks/day Spirits: ≥3 drinks/day	37	1.3 (0.9–2.2)	56	5.9 (3.5–10.0)	37	1.2 (0.7–2.0)

CI, confidence interval

the risk was slightly higher for wine drinkers than for beer and hard liquor drinkers (odds ratios, 5.2, 3.2 and 2.9, respectively). Case–control studies conducted in Italy between 1986 and 2000 (Franceschi *et al*., 1990; Talamini *et al*., 2002; Garavello *et al*., 2006) included 672 cases of laryngeal cancer and 3454 hospital controls, admitted for acute, non-neoplastic conditions that were unrelated to smoking or alcoholic beverage consumption. Significant trends in risk were found for total alcoholic beverage intake, with multivariate odds ratios of 1.12 for drinkers of 3–4 drinks per day, 2.43 for 5–7, 3.65 for 8–11 and 4.83 for >12 drinks per day compared with abstainers or light drinkers. Corresponding odds ratios for wine drinkers were 1.12, 2.45, 3.29 and 5.91. After allowance was made for wine intake, the odds ratios for beer drinkers were 1.65 for 1–2 drinks per day and 1.36 for ≥3 drinks per day compared with non-beer drinkers; corresponding values for spirit drinkers were 0.88 and 1.15. Thus, in the Italian population which is characterized by frequent wine consumption, wine is the beverage most strongly related to the risk for laryngeal cancer.

Taken together, these data suggest, however, that the most frequently consumed beverage in each population tends to be that which yields the highest risk, and that ethanol is the main component of alcoholic beverages that determines the risk for cancer.

2.3.5 *Joint effects*

Several investigations have considered the combined effect of tobacco smoking and alcoholic beverage consumption on the etiology of cancer of the larynx (Flanders & Rothman, 1982; Elwood *et al*., 1984; Olsen *et al*., 1985; De Stefani *et al*., 1987; Guénel *et al*., 1988; Tuyns *et al*., 1988; Franceschi *et al*., 1990; Choi & Kahyo, 1991a; Zatonski *et al*., 1991; Maier *et al*., 1992a; Zheng *et al*., 1992; Chyou *et al*., 1995; Dosemeci *et al*., 1997; Schlecht *et al*., 1999; Bagnardi *et al*., 2001; Talamini *et al*., 2002). These studies gave risk estimates for the highest level of consumption for both factors compared with the lowest level of between approximately 10 and over 100, and indicated that a multiplicative model rather than an additive model or risk could explain the level of risk from combined exposure to both factors. Separating the effects of alcoholic beverages and tobacco remains difficult, however, since heavy drinkers tend to be heavy smokers and vice versa. Furthermore, most studies included very few cases who neither smoked nor drank.

An example of the combined effect of alcoholic beverages and tobacco on laryngeal cancer was given by Talamini *et al*. (2002). Compared with never smokers/abstainers or light drinkers, the relative risk for laryngeal cancer increased with increasing alcoholic beverage consumption in each stratum of smoking habit to reach 177.2 in heavy drinkers and smokers compared with moderate drinkers and nonsmokers. Similar results were found for smoking within strata of alcoholic beverage intake. The odds ratio for the highest level of alcoholic beverage consumption and current smoking was 177.2. In a French study (Guénel *et al*., 1988), the relative risk for combined heavy alcoholic beverage and tobacco consumption was 289.4 (95% CI, 83.0–705.8) for glottic and 1094.2

(95% CI, 185.8–2970.7) for supraglottic cancers. In a case–control study in Taiwan, China, the odds ratio for users of alcoholic beverages, betel quid and cigarettes compared with non-users was 40.3 (95% CI, 14.8–123.6) (Lee *et al*., 2005).

2.3.6 *Effect of cessation of alcoholic beverage consumption*

The risk for laryngeal cancer declines steeply with time since stopping smoking (Olsen *et al*., 1985; Guénel *et al*., 1988; Tuyns *et al*., 1988; Franceschi *et al*., 1990; Freudenheim *et al*., 1992; Kjaerheim *et al*., 1993; Bosetti *et al*., 2006). Data exist from only one study on time since stopping alcoholic beverage consumption. In a case–control study in Italy (Altieri *et al*., 2002) that included a total of 59 former drinkers, the odds ratios were 1.24 for 1–5 years, 1.29 for 6–19 years and 0.53 for ≥20 years since cessation of drinking compared with current drinking. The risk approached that of never drinkers only after 20 years since cessation (odds ratio, 0.56).

Thus, while the favourable effect of stopping smoking is evident within a few years after cessation, that of stopping drinking becomes apparent only in the long term. Among current smokers that have stopped drinking, the persistence of exposure to tobacco may play an important role in limiting the benefits from cessation of drinking. These findings must, however, be interpreted with caution, since former drinkers may represent a select group of individuals whose average alcoholic beverage intake had exceeded that of current drinkers.

2.3.7 *Effect of Alcoholic beverage consumption in nonsmokers (Table 2.14)*

An independent role of alcoholic beverages on the incidence of laryngeal cancer has been suggested, but is difficult to quantify (Austin & Reynolds, 1996). In developed countries, cancer of the larynx is rare in nonsmokers, and only a few studies have included enough cases to provide useful information on the effect of alcoholic beverages in nonsmokers.

A case–control study form Canada (Burch *et al*., 1981) of 204 cases and 204 matched controls reported an increased risk for laryngeal cancer in relation to alcoholic beverage consumption (odds ratio, 7.7 for ≥26 000 oz ethanol in a lifetime) in never smokers based, however, on three case–control pairs only. A multicentric case–control study in France, Italy, Spain and Switzerland (Tuyns *et al*., 1988) reported odds ratios of 1.7 for ≥80 g per day of alcohol among nine never-smoker cases of cancer of the endolarynx and of 6.7 for ≥40 g per day of alcohol among 22 nonsmoking cases of cancer of the epilarynx/hypopharynx. In a case–control in Italy conducted on 40 never-smoking cases, an excess risk (odds ratio, 2.5) for ≥8 drinks per day was found (Bosetti *et al*., 2002).

A pooled analysis of never-tobacco users from 11 case–control studies, including 121 cases of laryngeal cancer and 4602 controls, showed an increased risk for laryngeal

Table 2.14 Selected case–control studies of laryngeal cancer and alcoholic beverage consumption in nonsmokers

Reference, study location	Exposure Categories	Number of cases	Relative risk (95% CI)
Burch *et al*. (1981), Canada	0 oz ethanol in lifetime	3	1[a] (3)
	<10 000 oz ethanol in lifetime	3	2.0 (3)
	10 000–25 000 oz ethanol in lifetime	3	3.9 (3)
	≥26 000 oz ethanol in lifetime	3	7.7 (3)
Tuyns *et al*. (1988)[b], France, Italy, Spain, Switzerland	0–40 g/day	7	1[a] (7)
	40–80 g/day	3	1.5 (3)
	≥80 g/day	6	1.7 (6)
Bosetti *et al*. (2002), Italy, Switzerland	<8 drinks/day	31	1[a] (31)
	≥8 drinks/day	9	2.5 (9)
Hashibe *et al*. (2007b), pooled analysis	Never drinkers		1.00[a]
	<1 drink/day		0.92 (0.50–1.69)
	1–2 drinks/day		1.26 (0.77–2.07)
	3–4 drinks/day		1.24 (0.62–2.45)
	≥5 drinks/day		2.98 (1.72–5.17)
			p for trend <0.001

CI, confidence interval [a] Reference category [b] Relative risks are presented for endolarynx.

cancer with the consumption of ≥5 drinks per day (odds ratio, 2.98; 95% CI, 1.72–5.17) (Hashibe *et al*., 2007b).

Thus, these studies confirmed that, even in a population of never smokers, elevated alcoholic beverage consumption increases the risk for laryngeal cancer. There is, however, no reason to suppose that tobacco smoking is the only carcinogenic agent to which the human upper respiratory and digestive tract is exposed, and ethanol may facilitate the effect of other unrecognized carcinogenic agents in nonsmokers, just as it commonly facilitates the effect of tobacco smoking (Doll *et al*., 1999).

2.4 Cancer of the oesophagus

The evidence for the carcinogenic effects of alcoholic beverage consumption on the risk for oesophageal cancer was considered to be sufficient by a previous Working Group (IARC, 1988). Several epidemiological studies have been published since that time, and this section evaluates the risk for oesophageal cancer based on the relevant cohort and case–control studies after 1988.

The 18 cohort and 38 case–control studies conducted in Argentina, China, Denmark, Europe, India, Italy, Japan, Norway, Sweden, the United Kingdom, Uruguay and the

USA summarized in this section are described in Tables 2.15, 2.16 (literature originally in the Chinese language) and 2.17.

2.4.1 *Cohort studies (Table 2.15)*

(a) Special populations

Five cohort studies were based on either individuals who had high exposure to alcoholic beverages, such as alcoholics or workers in the brewery industry, or who had lower alcoholic beverage consumption, such as teetotalers (Carstensen *et al*., 1990; Adami *et al*., 1992b; Kjaerheim *et al*., 1993; Tønnesen *et al*., 1994; Boffetta *et al*., 2001). This type of study does not usually consider individual exposure levels. The point estimates were either the SIRs or SMRs with no adjustment for tobacco smoking. The four studies of alcoholics or brewery workers reported a statistically significant association, and the point estimates of the SIR ranged from 2.5 to 5.5 (Carstensen *et al*., 1990; Adami *et al*., 1992b; Tønnesen *et al*., 1994; Boffetta *et al*., 2001); the point estimate was 0.26 for teetotalers (Kjaerheim *et al*., 1993).

(b) General population

Thirteen cohort studies of the general population have been published, including two in the Chinese literature (Table 2.16), most of which adjusted for tobacco smoking. Ten cohort studies reported a statistically significant association between alcoholic beverage consumption and the risk for oesophageal cancer after controlling for tobacco smoking. In addition, these studies were carried out in different geographical regions of the world. The adjusted relative risks ranged from 2.8 in the USA (Thun *et al*., 1997) to 14.5 in Japan (Kono *et al*., 1987) for two or more drinks per day after adjusting for tobacco smoking. One study (Lindblad *et al*., 2005) reported a positive association for adenocarcinoma of the oesophagus with a relative risk of 1.76 (95% CI, 1.16–2.66) for heavy drinkers.

The two cohort studies in Linxian County, China, based on the same population reported a null association (Guo *et al*., 1994; Tran *et al*., 2005). The null association between alcoholic beverage consumption and oesophageal cancer in rural high-risk areas of China is probably due to the relatively low consumption of alcoholic beverages in these areas or other strong risk factor(s) which may mask or highly confound the association between alcoholic beverage consumption and oesophageal cancer. Another study from the Chinese literature (Wang *et al*., 2005a; Table 2.16) reported that an increased risk for oesophageal cancer was associated with elevated alcoholic beverage consumption (relative risk, 5.08 for >70 g/day or 5 or more drinks/day) after adjusting for tobacco smoking; however, no 95% CI was provided.

In summary, the results of the majority of the prospective cohort studies support that alcoholic beverage consumption can cause cancer of oesophagus.

Table 2.15 Cohort studies of oesophageal cancer and consumption of alcoholic beverages

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Special populations								
Kono *et al.* (1987), Japan, Japanese Physicians' Study	5130 male Japanese physicians, aged 27–89 years; followed up for 19 years, 1965–83; response rate, 51%	Self-administered questionnaire;	Oesophagus	Never and occasional Daily <2 go Daily ≥2 go		1.00 1.53 (0.14–16.83) 14.46 (3.00–69.71)	Age, smoking	No significant interaction with smoking (p>0.05); 1 go of sake ≃ 27 mL alcohol
Carstensen *et al*. (1990), Sweden	6230 men employed in the Swedish brewery industry in 1960, aged 20–69 years; followed–up 1961–79	Population census	Oesophagus	Not reported	20	2.46 (1.51–3.81)	Not reported	All Swedish men used as a reference group.
Adami *et al.* (1992b), Sweden, Uppsala Alcoholics Study	9353 (8340 men, 1013 women) with a discharge diagnosis of alcoholism in 1965–83; 94% confirmed microscopically; followed up for 19 years (mean, 7.7 years)	Record-linkage to the nationwide Registry of Causes of Death;	Oesophagus	*Years of follow-up* 1–4 5–9 10–19		**SIR** 11.7 (6.9–18.4) 3.7 (1.2–8.7) 4.6 (1.5–10.7)	Expected rates were derived from the study population.	

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Kjaerheim *et al*. (1993), Norway	5332 members of International Organization of Good Templars, Norwegian teetotalers; followed–up 1980–89	Cancer registry	Oesophagus	Not reported	1	0.26 (1–145)	Compared with that of the total Norwegian population	
Tønnesen *et al*. (1994), Denmark, Alcohol Abusers Study	18 368 non-hospitalized alcohol abusers during 1954–87; 15 214 men were observed for 12.9 years and 3093 women for 9.4 years.	Central population registry	Oesophagus	Not reported	57 2 59	Men 5.3 (4.0–6.9) $p \leq 0.01$ Women 4.9 (0.6–17.7) Total 5.3 (4.0–6.8) $p \leq 0.01$	Compared with that of Danish population	

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Boffetta *et al*. (2001), Sweden, Uppsala Alcoholics Study	173 665 patients (138 195 men, 35 470 women) with a hospital discharge diagnosis of alcoholism during1965–94, aged >20 years; followed up for 10.2 years	Linkage between the Swedish In–patient Register and the National Cancer Register	Oesophagus	Diagnosed alcoholics	 521 465 56	**SIR** *Both genders* 5.54 (5.07–6.04) *Men* 5.26 (4.79–5.76) *Women* 10.0 (7.57–13.0)		Compared with incidence in the national population
General populations								
Boffetta & Garfinkel (1990), USA, American Cancer Society Cancer Prevention Study I	276 802 white men, aged 40–59 years, volunteers for the American Cancer Society in 25 states; enrolled in 1959 and followed for 12 years	A detailed four-page questionnaire; vital status checked yearly; death certificates of deceased participants obtained from state health departments	Oesophagus	Non-drinkers Occasional 1 drink/day 2 drinks/day 3 drinks/day 4 drinks/day 5 drinks/day ≥6 drinks/day Irregular	59 9 20 18 19 19 6 22 13	1.0 1.12 (0.55–2.28) 1.37 (0.81–2.30) 1.61 (0.94–2.77) 3.52 (2.05–6.02) 5.35 (3.08–9.27) 3.53 (1.47–8.48) 5.79 (3.44–9.74) 1.64 (0.89–3.01)	Age, smoking	

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Kato *et al*. (1992c), USA, Hawaii, American Men of Japanese Ancestry Study	6701 American men of Japanese ancestry, born in 1900–19, and residing on the Hawaiian island of Oahu; 19 year follow-up survey, 1965–90	Structured interview	Oral cavity, pharynx, oesophagus, larynx	0 mL/day <30 mL/day ≥30 ml/day	13 21 36	1.0 1.2 (0.6–2.3) 5.4 (2.8–10.4)	Age, smoking	
Guo *et al*. (1994), China, Lin Xian Nutrition Intervention Trial	Nested case–control study; a cohort of 29 584 adults in a randomized intervention trial, aged 40–69 years; follow-up 1986–91; 640 cases; 3200 controls; 5 controls per case matched by age and sex	Structured interview	Oesophagus	Lifetime use of alcoholic beverages	640	Not reported	Not reported	Drinking alcoholic beverages was relatively uncommon in Lin Xian residents, but was reported by 22% of the cancer patients; no significant association between oesophageal and alcohol drinking found.

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Thun *et al.* (1997), USA, American Cancer Society Cancer Prevention Study II	490 000 (251 420 women, 238 206 men), mean age, 56 years (range, 30–104); study subjects were recruited by American Cancer Society volunteers; followed up from 1982– 91	Self-reported alcoholic beverage and tobacco use	Alcohol-related (mouth, oesophagus, pharynx, larynx, liver)		*Men*		Age, race, education, body mass index, smoking	Study subjects were recruited by American Cancer Society volunteers; they were also more likely than the general US population to be college educated, married, middle class and white; number of case or risk related to oesophageal cancer can not be determined.
				None	69	1.0		
				Less than daily	106	1.4 (1.0–1.9)		
				1 drink/day	58	1.4 (1.0–2.0)		
				2–3 drinks/ day	101	1.5 (1.1–2.1)		
				4 drinks/day	144	2.8 (2.1–3.8) $p<0.001$		
					Women			
				None	43	1.0		
				Less than daily	30	1.1 (0.7–1.8)		
				1 drink/day	10	0.8 (0.4–1.6)		
				2–3 drinks/ day	26	1.5 (0.9–2.5)		
				4 drinks/day	21	3.0 (1.7–5.3) $p<0.002$		

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Grønbaek *et al*. (1998), Denmark, The Copenhagen Centre for Prospective Population Studies	15 117 men, 13 063 women, aged 20–98 years; follow-up of 13.5 years, –1994; mean participation rate, 80%	Self–administered questionnaire; health examination	Oropharynx, oesophagus	See Tables 2.19a, b		See Tables 2.19a, b	Age, sex, smoking habits, educational level	There was a strong dose-dependent increase in risk for upper digestive tract cancer with increased alcoholic beverage intake.
Kinjo *et al*. (1998), Japan, Six-Prefecture Study	220 272 residents (100 840 men, 119 432 women), aged 40–69 years at the baseline of 1965, from 29 public health districts in six Prefectures of Japan; followed up 1966–81	Structured questionnaire	Oesophagus	None 1–3 times/ month 1–3 times/ week 4 times/week or more	149 31 76 184	1.0 0.7 (0.5–1.1) 1.1 (0.8–1.5) 2.4 (1.8–3.1) $p<0.001$	Age, Prefecture, occupation, sex	Joint effect of alcohol and tobacco, 3.9 (2.7–5.4); dose–response relationship, p for trend <0.001

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Kjaerheim *et al*. (1998), Norway, Norwegian Cohort Study	10 960 Norwegian men, born in 1893–1929, who had answered questionnaires, were alive and living in Norway on 1 January 1968 and had no diagnosis of upper aerogastric tract cancer prior to this date; mean age at start of follow-up, 59 years; followed up 1968–92; histological verification, 95.8%	Structured questionnaire; cancer registry	Oral cavity, pharynx, larynx, oesophagus	*Times/week* Never or <1 Previously 1–3 4–7	*Upper aerogastric tract cancer* 22 3 17 18	 1.0 0.8 (0.2–2.7) 1.1 (0.6–2.1) 3.2 (1.6–6.1) p=0.01	Age, smoking	

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Lindblad *et al*. (2005), United Kingdom, General Practitioner Research Database	Nested case–control study; 287 oesophageal adenocarcinomas and 10 000 controls, aged 40–84 years; controls randomly selected, frequency-matched by sex, age, same calendar year from the pool; 5 controls per case; 1994–2001	Patients reviewed by one investigator kept blinded to exposure information during the review process	Oesophagus	*Units/day* 0–2 3–15 16–34 >34 Unknown use	 294 156 54 30 375	 1.0 1.06 (0.86–1.30) 1.04 (0.76–1.43) 1.76 (1.16–2.66) 1.04 (0.82–1.32)	Sex, age, smoking, body mass index, reflux, calendar year	One unit of an alcoholic beverage = 10 mL (7.9 g) pure ethanol.

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Sakata *et al*. (2005), Japan, Japan Collaborative Cohort Study	110 792 (46 465 men, 64 327 women), aged 40–79 years; followed-up 1988– 99; a baseline survey conducted in 45 areas throughout Japan	Self-administered questionnaire; death and cause of death confirmed annually or biannually	Oesophagus	Non-drinkers	9	1.0	Age, centre	42 578 men for analysis; one unit of alcohol contains about 22 g alcohol
				<1.0 units/day	2	1.47 (0.28–7.68)		
				1.0–1.9 units/ day	16	1.58 (0.65–3.86)		
				2.0–2.9 units/ day	31	3.74 (1.62–8.66)		
				≥3.0 units/day	18	6.39 (2.54–16.12) *p*=0.028		
				Years of drinking				
				Non-drinkers	9	1.00		
				≤25.0	14	1.71 (0.64–4.60)		
				25.1–35.0	19	3.23 (1.32–7.92)		
				35.1–45.0	18	3.23 (1.33–7.81)		
				≥45.1	7	2.77 (0.85–9.03) *p*=0.100		
				Cumulative intake				
				Non-drinkers	9	1.0		
				1–29.9 unit–years	4	0.68 (0.19–2.42)		
				31.0–39.9 unit–years	6	2.31 (0.75–7.06)		
				≥40.0 unit–years	46	3.80 (1.70–8.46) *p*=0.089		

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Tran *et al.* (2005), China, Linxian Intervention Trial Study	Population-based prospective study of 29 584 adults in the Linxian General Population Trial, 40–69 years of age at baseline; follow–up, 15 years; case ascertainment considered complete and loss to follow-up minimal (*n*=176 or 1%)	Structured interviewed;	Oesophagus	Alcoholic in previous 12 months	450	0.92 (0.82–1.03)	Sex, age	No association

CI, confidence interval; ICD, International Classification of Diseases; SIR, standardized incidence

Table 2.16 Analytical studies of oesophageal cancer and alcoholic beverage consumption published in the Chinese literature

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Cohort studies	*Characteristics of the cohort*						
Zhang *et al.* (1998), Shandong, 1982–94	15 803 residents from 29 villages, aged 20 years; followed 1982-94	-	Questionnaire	*Alcoholic beverage intake (g)*		Not specified	
				0–49	1.00		
				50–149	2.05 (1.37–3.06)		
				150–249	1.20 (0.65–2.21)		
				≥250	1.03 (0.53–1.99)		
				Duration (years)			
				15–24	1.00		
				25–34	0.75 (0.27–2.10)		
				35–44	1.18 (0.44–3.20)		
				45–54	2.59 (0.99–6.73)		
				55–64	4.10 (1.52–11.08)		
				≥65	2.02 (0.51–8.06)		

Table 2.16 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Wang *et al.* (2005a), Shanghai, 1986–2002	18 244 cancer-free men; followed 1986–2000	-	Interview	*Alcoholic beverage intake (g/day)* 0 <30 30–70 >70	 1.00 1.33 2.47 5.08	Age, smoking, education	Significant result, but with no CI
Case–control studies							
Chen *et al.* (2000), Jiangsu, 1997–98	100 new cases from 11 hospitals	100 healthy controls matched on village of residence, gender, age	Questionnaire	*Alcoholic beverage consumption* <25 g/day >25 g/day	 1.00 2.09 (1.21–4.29)	Crude analysis	
Liu *et al.* (2000), TianJing, 1999	86 randomly sampled men	158 from the general population	Questionnaire	*Duration of drinking (years)* 0 1–10 10–20 >20 *Volume consumed (mL)* 0–50 50–99 100–249 ≥250	 1.00 1.85 (0.70–4.85) 2.15 (1.23–4.79) 3.10 (1.55–6.97) 1.00 1.23 (0.56–2.69) 4.31 (1.89–10.07) 18.66 (5.23–27.56)	Age, occupation, education, smoking	

Table 2.16 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Lu *et al.* (2000b), LinZhou, 1995–96	352 from cancer registry	352; matched on age, sex, neighborhood	Questionnaire	*Alcoholic beverage consumption* No Yes	 1.00 2.67 (1.04–6.81) $p<0.05$	Crude analysis	
Zhang *et al.* (2000), Ci, HeBei, 1973–97	350 hospital patients; categorized by geographical area	350 cancer-free; matched on village of residence, gender, occupation, age	Interviewer-administered questionnaire	*Alcoholic beverage consumption* No Yes	 1.0 0.62 (0.41–0.93)	Crude analysis	Alcoholic beverage consumption appears to be a protective factor for oesophageal cancer in this study.
Cui *et al.* (2001a), JiangYan, Jiangsu, 1995–99	156 living	156 healthy residents from the same community as cases, matched on age	Interviewer-administered questionnaire	*Alcoholic beverage consumption* No Yes	 1.0 3.58 (0.68–5.08)	Hot food, spicy food, smoking	
Ding *et al.* (2001a,b), TaiXing, Jiangsu, 1998–99	591 cases	591 from the same community; matched on gender, age	Interviewer-administered questionnaire	*Consumption of distilled spirits* No Yes	 1.00 2.71 (1.09–7.64)	Crude analysis	

Table 2.16 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Gao *et al.* (2001), HuaiAn, 1997–2000	141 hospital patients	223 cancer-free from the general population; matched on age	Interview	*Alcoholic beverage consumption* <1 per week ≥1 per week	 1.00 1.65 (0.90–3.03)	Gender, age, smoking	
Li *et al.* (2001), ChaoShan, Guangdong, 1997–2000	1248 from four hospitals within 3 months of diagnosis; residents of ChaoShan for over 10 years	1248 hospital patients; matched on age	Questionnaire	*Alcohol beverage consumption* No Yes	Result insignificant; number not reported		The study was primarily on smoking. A possible effect modification between smoking and alcohol beverage was detected (not significant).
Chen *et al.* (2003a), Lin Xian, 1984–97	3 periods: 1244 in 1985 640 in 1991 702 in 1997	3 periods: 1314 in 1985 3200 in 1991 702 in 1997	Interview		Result insignificant;. number not reported		Cases and controls from 3 time periods were analysed separately in this study.
Ding *et al.* (2003), Shanghai, 2000	204 hospital patients	397 healthy controls from general population	Interview	*Alcoholic beverage consumption* No Yes	 1.00 16.31 (5.57–47.77)	Education, gastritis, eating speed, smoking, drinking tea, personality	

Table 2.16 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Mu *et al*. (2003), TaiXing, Jiangsu, 2000	218	415 from the general population	Questionnaire	**Alcoholic beverage consumption stratified by green tea consumption**		Age, gender, education	
				Green tea drinker			
				Alcoholic beverages			
				No	1.00		
				Yes	1.21 (0.65–2.28)		
				Green tea non-drinker			
				Alcoholic beverages			
				No	1.00		
				Yes	1.98 (1.00–3.91)		
Wang *et al*. (2003a), XiAn	Meta-analysis; 530 cases	Meta-analysis; 4005 controls		*Alcoholic beverage consumption*			This study is a meta-analysis.
				No	1.00		
				Yes	1.72 (1.27–2.33)		

Table 2.16 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Zhao *et al.* (2003), FeiCheng	185	204 cancer-free from the general population	Interviewer-administered questionnaire	*Alcohol consumed each month (kg*years)*		Age, gender, education, smoking	
				0	1.00		
				1–280	1.00 (0.58–1.74)		
				>280	1.74 (0.88–3.42)		
Wang *et al.* (2004)	78 hospital patients	118 cancer-free from general population; matched on age	Interview	*Alcoholic beverage consumption*		Not specified	
				No	1.00		
				Yes	6.41 (2.81–14.62)		
Yan *et al.* (2004), ZhangYe, 1999–2000	125 hospital patients, residents of ZhangYe for over 20 years	145 cancer-free hospital patients	In-hospital interview with questionnaires	*Alcoholic beverage consumption*		Not specified	
				No	1.00		
				Yes	2.55 (1.47–4.43)		
Huang *et al.* (2005), Shandong	92 hospital patients	115 healthy controls from general population	Questionnaire	*Alcohol consumed each month (kg*years)*		Age, gender, smoking	
				0	1.00		
				<100	2.73 (1.04–7.20)		
				100–300	6.61 (2.34–18.67)		
				>300	23.40 (5.62–97.49)		

Table 2.16 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Wang *et al.* (2005b), Inner Mongolia, 2004	50 hospital-based	100 (1:2); matched on sex, neighbourhood, race/ethnicity, age ±5 years, time of visit	Questionnaire interview	Univariate history of alcoholic beverage consumption	4.43 (2.64–8.90)	Multivariate with years of alcoholic beverage drinking, years of smoking, difficulty in swallowing, history of psychological event, worsening of financial state, stool with blood	
				Multivariate years of alcoholic beverage consumption	5.41 (3.89–6.79)		
Zhao *et al.* (2005), Jiangsu, 2002	95 hospital patients	95; matched on gender, age	Interviewer-administered questionnaire	*Alcoholic beverage consumption*		Hot food, eating garlic, eating nuts	
				No	1.00		
				Yes	3.94 (1.81–8.59)		

CI, confidence interval

2.4.2 *Case–control studies (Table 2.17)*

Among the 38 case–control studies, 20 studies were published in the English literature and 18 in the Chinese literature. Of the 20 studies published in the English literature, 18 adjusted for tobacco smoking, 8 were population-based and 12 were hospital-based. Sixteen of the 20 studies in the English literature on alcoholic beverage consumption and the risk for oesophageal cancer reported a statistically significant association. The adjusted odds ratios ranged from 1.7 to 3.5 for ever drinkers and from 5.4 to 37.3 for heavy drinkers. Among the case–control studies identified in the Chinese literature (Table 2.16), the majority were hospital-based and 10 studies did not adjust for tobacco smoking (Chen *et al*., 2000; Lu *et al*., 2000b; Zhang *et al*., 2000; Ding *et al*., 2001a,b; Li *et al*., 2001; Mu *et al*., 2003; Wang B *et al*., 2003a; Wang *et al*., 2004; Yan *et al*., 2004; Zhao *et al*., 2005). Eight of these reported a positive association with alcoholic beverage consumption; the odds ratios ranged from 1.72 to 6.41 for ever drinkers of alcoholic beverages and from 3.1 to 23.4 for heavy drinkers. The evidence for alcoholic beverage consumption and the risk for oesophageal cancer in the Chinese literature are consistent with that in the English literature. In addition, the results from case–control studies are also consistent with those from prospective cohort studies.

2.4.3 *Histological types (Tables 2.17 and 2.18)*

Consumption of alcoholic beverages is an established cause of oesophageal cancer and is strongly associated with the risk for squamous-cell carcinoma of the oesophagus and, to a lesser degree, with the risk for oesophageal adenocarcinoma (Brown *et al*., 1994; Gammon *et al*., 1997; Lagergren *et al*., 2000; Wu *et al*., 2001; Lindblad *et al*., 2005; Hashibe *et al*., 2007a).

One prospective study of alcoholics (Boffetta *et al*., 2001), one nested case–control study (Lindblad *et al*., 2005) and eight case–control studies of adenocarcinoma of the oesophagus (Table 2.18) in relation to alcoholic beverage consumption have been published. A cohort study of alcoholics in Sweden (Boffetta *et al*., 2001) reported an SIR of 1.45 (95% CI, 0.96–2.11) for oesophageal adenocarcinoma and 6.76 (95% CI, 6.15–7.41) for oesophageal squamous-cell carcinoma. The nested case–control study on adenocarcinoma of the oesophagus observed a null association (Lindblad *et al*., 2005). Among the eight case–control studies, two reported a significant association between alcoholic beverage consumption and oesophageal adenocarcinoma. The increased risk for adenocarcinoma of oesophagus was associated with a higher level of alcoholic beverage consumption in two studies (Kabat *et al*., 1993; Vaughan *et al*., 1995), but not in the other six. Thus, the evidence for alcoholic beverage consumption and the risk for adenocarcinoma of the oesophagus was considered to be insufficient.

Table 2.17 Case–control studies of oesophageal cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
DeStefani *et al*. (1990), Uruguay, 1985–88	261 squamous-cell carcinomas (199 men, 62 women); clinical and/ or radiological diagnosis; in four main hospitals in Montevideo; response rate, 92%	522 hospital patients (398 men, 124 women), without diagnosis of tobacco- and/ or alcohol-related diseases; 1:2 matched by sex, age, hospital	Interviewer-administered standardized questionnaire	*Alcohol (mL per day)*			Sex, age, residence, smoking	Joint effect of alcoholic beverage and tobacco consumption; odds ratio for those who smoked and drank heavily compared with that of light smokers and drinkers, 22.6
					Men			
				0	26	1.00		
				1–24	16	0.85 (0.4–1.8)		
				25–49	12	0.71 (0.3–1.6)		
				50–149	50	1.37 (0.8–2.4)		
				150–249	46	3.57 (1.9–6.7)		
				≥250	49	5.27 (2.7–10.2)		
					Women			
				0	38	1.00		
				1–24	12	1.04 (0.4–2.4)		
				25–49	–			
				50–149	–			
				150–249	12	1.89 (0.7–4.9)		
				≥250	–			

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Franceschi *et al*. (1990), northern Italy, 1986–89	288 men, aged <75 years; histologically confirmed; interviews generally (90%) conducted within 2 months from diagnosis; no next-of-kin respondents; refusal rate, 2%	1272 hospital-based men; 26% non-traumatic orthopaedic conditions, 25% trauma, 17% eye disorders, 13% other illness; matched by area of residence, hospital, age; no next-of-kin respondents; refusal rate, 3%;	Interviewer-administered standardized questionnaire	≤19 drinks/week 20–34 drinks/week 35–59 drinks/week ≥60 drinks/week *Years of alcohol use* <30 30–39 ≥40	45 41 115 87 60 93 116	1.0 1.0 (0.6–1.7) 3.1 (2.0–4.7) 6.0 (3.7–10.0) p<0.01 1.0 1.1 (0.7–1.7) 0.9 (0.6–1.5) p=0.24	Age, residence, education, occupation, smoking	High level of combined alcoholic beverage and cigarette consumption increased the risk to 18 times that of the lowest levels of consumption; the effect of drinking 60 or more alcoholic drinks per week in nonsmokers was slightly stronger than that of heavy smoking in light drinkers (odds ratio, 7.9 versus 6.4).

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Castelletto *et al*. (1992), Argentina, 1985–86	170 (99 men, 71 women), >15 years old; patients from 1 hospital and 9 private clinics; patients had various gastrointestinal symptoms	226 (109 men, 117 women) with histologically normal oesophagus	Of 406 study subjects, 396 completed information on the variable under study using a simple questionnaire	**Men** *Drinking status* Non-drinkers Drinkers *Amount* 0–39 mL/day 40–79 mL/day ≥80 mL/day	 41 58 41 15 43	 1.0 2.4 (1.3–4.3) 1.0 1.9 (0.8–4.7) 2.5 (1.2–5.1)	Age, smoking	All subjects had various gastrointestinal symptoms; patients with oesophageal cancer or with severe erosions, ulcerations and stenosis associated with gastric reflux were not included.

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Cheng *et al*. (1992), Hong Kong, China, 1989–90	400 (345 men , 55 women); histologically confirmed; 85% squamous-cell carcinomas; participation rate, 86.8%	1598 (800 hospital and 798 general practice; 1378 men, 220 women); 1:4 matched by age, sex; 2 controls admitted to the same surgical departments; patients with tobacco- or alcohol-related cancers were excluded; 2 controls selected from private or general practice clinics in the area where case was originally referred to the physician; response rate, 95%	Interviewer-administered standardized questionnaire	Never drinker <50 g/week 50–99 g/week 100–199 g/week 200–299 g/week 400–599 g/week 600–799 g/week 800–999 g/week ≥1000 g/week	53 57 16 30 48 44 39 25 66	1.00 1.07 (0.66–1.75) 1.36 (0.67–2.74) 1.82 (0.99–3.35) 3.40 (1.92–6.01) 5.05 (2.72–9.39) 11.11 (5.4.–22.85) 18.07 (7.40–44.13) 9.93 (5.27–18.74)	Age, education, birthplace, smoking	Cases or controls with diabetes mellitus were excluded.

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Negri *et al*. (1992), northen Italy, 1984–90	300 (244 men, 56 women), aged 29–74 years; histologically confirmed newly diagnosed cancer of the oesophagus, admitted to the National Cancer Institute	1203 (901 men, 302 women) hospital patients, aged 25–74 years; 34% traumas, 26% non-traumatic orthopaedic conditions, 28% acute surgical disease, 12% various other diseases; diseases related to alcohol or tobacco consumption excluded	Interviewer-administered standardized questionnaire	<4 drinks/day 4–6 drinks/day >6 drinks/day	111 58 131	1.0 1.6 (1.1–2.4) 3.5 (2.5–5.1) $p<0.001$	Age, sex, education, smoking, β-carotene intake	Compared with the lowest risk category (nonsmokers, moderate alcohol drinkers and high β-carotene consumers), relative risk rose to 45.9 for men and to 36.4 for women who were heavy drinkers, heavy smokers and had a diet poor in β-carotene.

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Kabat *et al*. (1993), USA, 1981–90	Adenocarcinoma of oesophagus/ cardia (160 men, 21 women), squamous-cell carcinoma of oesophagus (122 men, 78 women) and adenocarcinoma of distal stomach (113 men, 30 women); newly diagnosed, histologically confirmed	Hospitalized patients with disease not related to smoking and of organ systems other than the gastrointestinal tract (4162 men, 2222 women); matched by age, sex, race, hospital	Interviewer-administered structured questionnaire; all subjects interviewed in 28 hospitals in 8 cities in the USA between 1981 and 1990	*Squamous-cell carcinoma* **Men** Non-drinker Occasional 1–3.9 oz WE/ day ≥4 WE/day **Women** Non-drinker Occasional 1–3.9 oz WE/ day ≥4 WE/day		 1.0 1.4 (0.6–3.5) 2.3 (1.0–5.4) 10.9 (4.9–24.4) 1.0 1.4 (0.7–2.9) 4.4 (2.2–8.7) 13.2 (6.1–28.8)	Age, education, smoking, hospital, time period (1981–84, 1985–90)	Non-drinker, <1 drink/week; occasional, ≥1 drink/week but <1 drink/day; WE = whiskey–equivalent per day; the analysis was limited to whites; joint effect of smoking and drinking (analysis limited to men), 7.6 (3.1–18.6) for squamous-cell carcinoma of oesophagus and 2.4 (1.3–4.2) for adenocarcinoma of oesophagus/ cardia

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Brown *et al*. (1994), USA, 1986–89	174 white men with adenocarcinoma of oesophagus (median age, 63 years); residents of geographical areas covered by the population-based cancer registries; response rate, 74%	750 (median age, 61 years) living in three areas of the USA selected by random-digit dialling for those aged 30–64 years (response rate, 72%) and random sampling from computerized listings of Medicare recipients (response rate, 76%)	Structured questionnaire administered by trained interviewers	*Adenocarcinoma of oesophagus and oesophagogastric junction*			Age, area, smoking, income	
				Never drank	32	1.0		
				Drank	142	0.9 (0.6–1.4)		
				<8 drinks/week	38	0.7 (0.4–1.3)		
				8–21 drinks/week	42	0.8 (0.4–1.3)		
				22–56 drinks/week	43	1.1 (0.6–1.9)		
				>56 drinks/week	18	1.5 (0.7–3.1)		

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Cheng *et al.* (1995), Hong Kong, China 1989–90	400 consecutive patients during a 21-month period in 1989–90; histologically confirmed; response rate, 87%	1598 patients from the same surgical departments as the cases and from general practices from which the cases were originally referred; matched by age, sex; response rate, 95%	Interviewer-administered structured questionnaire	Never drinkers	53	1.0	Age, sex, education, smoking	
				1–199 g/week	103	1.1 (0.7–1.8)		
				200–599 g/week	92	3.3 (2.0–5.4)		
				≥600 g/week	130	9.2 (5.4–15.7)		
				Duration				
				Never drinkers	53	1.0		
				1–19 years	24	2.0 (1.0–3.8)		
				20–39 years	175	2.1 (1.4–3.2)		
				≥40 years	131	2.4 (1.6–3.8)		
				Years since stopped drinking				
				Current drinkers	207	1.0		
				0–1 year	47	2.5 (1.4–4.4)		
				1–4 years	36	1.5 (0.9–2.6)		
				5–9 years	22	0.5 (0.3–0.9)		
				10–14 years	22	0.8 (0.4–1.5)		
				≥15 years	11	0.2 (0.1–0.6)		
				Never drinkers	33	0.6 (0.4–1.0)		

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Vaughan *et al*. (1995), western Washington, USA, 1983–90	298 adenocarcinomas (267 men, 31 women), 106 squamous-cell carcinomas (64 men, 42 women), aged 20–74 years; histologically confirmed; identified through the Cancer Surveillance System; proportion of the closest next of kin interviewed, 33%; response rate, 82.9%	724 (506 men, 218 women) population-based identified by random-digit dialling; frequency-matched on age, gender; response rate, 76.6%	Interviewer-administered standardized questionnaire	*Drinks/week* 0–6 7–13 14–20 ≥21 0–6 7–13 14–20 ≥21	 27 20 11 20 147 39 18 44	*Squamous-cell carcinoma* 1.0 6.0 (2.7–13.5) 6.3 (2.2–17.9) 9.5 (4.0–22.3) *Adenocarcinoma* 1.0 1.1 (0.7–1.8) 1.2 (0.6–2.3) 1.8 (1.1–3.1)	Cigarette use, body mass index, age, gender, race, education	Significant association between usual intake of undiluted hard liquor and adenocarcinoma (2.6; 1.4–4.6) and a weaker (not significant) association with squamous-cell carcinoma (1.7; 0.6–4.7)

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Gammon *et al*. (1997), USA, 1993–95	Oesophageal adenocarcinoma (245 men, 48 women), gastric cardia adenocarcinoma (223 men, 38 women), oesophageal squamous-cell carcinoma (176 men, 45 women), other gastric adenocarcinoma (254 men, 114 women); histologically confirmed; newly diagnosed; all cases identified by use of established rapid reporting systems	695 population-based (555 men, 140 women), aged 30–64 years; frequency-matched by age (±5years), sex; identified by use of Waksberg's random-digit dialling method; overall response rate, 70.2%	Structured questionnaire administered by trained interviewers	*Oesophageal squamous-cell carcinoma*			Age, sex, geographical centre, race, body mass index, income, cigarette smoking, all other types of alcohol use	Interviews were administered directly to subjects rather than to closest next of kin (usually the spouse) for 70.4% of target cases, 67.8% of comparison cases and 96.6% of controls.
				Never	19	1.0		
				Ever	195	3.5 (1.9–6.2)		
				<5 drinks/week	16	0.8 (0.4–1.6)		
				5–11 drinks/ week	25	1.8 (0.9–3.5)		
				12–30 drinks/ week	48	2.9 (1.5–5.4)		
				>30 drinks/week	106	7.4 (4.0–13.7)		

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Lagergren *et al*. (2000), Sweden, 1995–97	618 (81% of all eligible) patients (189 oesophageal adenocarcinoma, 262 cardia adenocarcinoma, 167 oesophageal squamous-cell carcinoma) (median ages at diagnosis, 69, 66 and 67 years, respectively); men constituted 87%, 85% and 72%, respectively	820 randomly selected population (median age, 68 years); frequency-matched on age, sex; men constituted 83%; participation rate, 73%	Structured questionnaire administered by trained interviewers	*Oesophageal squamous–cell carcinoma*			Age, sex, tobacco smoking, educational level, body mass index, reflux symptoms, intake of fruit and vegetables, energy intake, physical activity	
				Never	16	1.0		
				Ever	151	1.1 (0.6–2.1)		
				Ethanol (g) per week				
				1–15	34	0.9 (0.4–1.8)		
				16–70	39	0.8 (0.4–1.8)		
				>70	78	3.1 (1.4–6.7)		
				None		1	Age, sex, smoking	Increase in the risk of 1.95-fold (p<0.01) with habit of daily bidi smoking
				Occasional		1.36 (0.68–2.70)		
				Daily		7.81 (2.38–25.6)		

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Gallus *et al.* (2001), Italy, Switzerland	114 women aged <79 years (median age, 63 years); newly diagnosed; histologically confirmed squamous-cell oesophageal cancer; admitted to the major hospitals in the areas under study	425 women (median age, 62 years) admitted for acute, non-neoplastic conditions to the same hospitals: 40% trauma, 21% non-traumatic orthopaedic conditions, 24% acute surgical disorders, 15% miscellaneous other illnesses (including skin, eye or ear disorders); frequency-matched to cases by age, study centre; control: case ratio, 4	Interviewer-administered standardized questionnaire	<1 drink/day 1–2 drinks/day ≥3 drinks/day		1.0 1.99 (1.15–3.44) 5.40 (2.70–10.80)	Age, education, body mass index, smoking	Data from three case–control studies of squamous-cell oesophageal cancer: first conducted in 1984–93 in the provinces of Milan and Pordenone (Fioretti *et al*, 1999); second in 1992–97 in the provinces of Padua and Pordenone, and the greater Milan area, northern Italy (Franceschi *et al.*, 2000); third in 1992–99 in the Swiss Canton of Vaud (Levi *et al*., 2000).

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Wu *et al*. (2001), Los Angeles, USA, 1992–97	222 incident oesophageal adenocarcinoma (202 men, 20 women), 277 gastric cardia and 443 distal gastric adenocarcinoma, aged 30–74 years; histologically confirmed; identified by Cancer Surveillance Program	1356 multiethnic population-based (999 men, 357 women); matched by sex, race, date of birth; diagnosis of oesophageal or stomach cancer excluded; neighbourhood control sought by use of a systematic algorithm based on the address of the case patient	Interviewer-administered structured questionnaire; interviews completed by 55% of those identified and 77% of those approached	*Adenocarcinoma of oesophagus* 1–7 drinks/week 8–21 drinks/week 22–35 drinks/week ≥36 drinks/week *Alcoholic beverage* Never Former Current		 0.72 (0.5–1.2) 0.57 (0.3–0.9) 0.77 (0.4–1.4) 0.93 (0.5–1.6) *p*-trend=0.79 1.0 0.74 (0.5–1.2) 0.70 (0.5–1.1)	Age, sex, race, birthplace, education, smoking	
Znaor *et al*. (2003), Chennai and Trivandrum, South India, 1993–99	566 men; histologically confirmed	3638 men (1711 non-tobacco-related cancer controls, 1927 healthy hospital visitors); histologically confirmed	Interviewer-administered structured questionnaire	Never Ever <20 mL/day 20–50 mL/day >50 mL/day *Duration (years)* <20 20–29 30–39 ≥40	304 262 70 80 110 69 82 91 20	1.0 1.70 (1.36–2.13) 1.13 (0.83–1.55) 1.83 (1.31–2.55) 2.53 (1.85–3.46) 1.21 (0.88–1.67) 1.69 (1.23–2.34) 2.80 (1.95–4.01) 1.88 (0.98–3.59)	Age, centre, education, smoking, chewing habit	Joint effect between smoking and alcoholic beverage drinking: odds ratio, 7.33 (5.06–10.62); joint effect of smoking, chewing with tobacco and alcoholic beverage drinking: odds ratio, 8.65 (5.50–13.62) (ICD-9 150)

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Yang *et al*. (2005), Japan, 2001–04	165 (148 men, 17 women; 159 squamous-cell carcinoma, 6 adenocarcinoma), aged 18–80 years; histologically diagnosed	495 hospital-based (444 men, 51 women) randomly selected; matched 1:3 for age, sex	Interviewer-administered structured questionnaire; 7-mL of blood; 95% of eligible subjects completed the questionnaire and about 60% provided blood samples	Non-drinker Moderate drinker Heavy drinker Never Former Current	8 63 94 8 12 145	1.00 5.16 (2.33–11.4) 27.8 (12.2–63.5) 1.0 6.20 (2.34–16.4) 9.44 (4.36–20.4)	Age, sex	Significant gene–environment interaction between alcoholic beverage drinking and *ALDH2* polymorphism
Lagergren *et al*. (2006), Sweden, 1995–97	189 oesophageal adenocarcinoma (88% of all eligible), 262 adenocarcinoma (84%); all histologically classified	Controls randomly selected from the total population register; frequency-matched by age, sex; 820 (73%) interviewed in person	A computer-aided face-to-face interview	*Carbonated low-alcohol beer (times/week)* See Table 2.18		See Table 2.18	Age, sex, smoking status, socioeconomic status, dietary intake of fruits and vegetables (in quartiles), body mass index	No association between consumption of carbonated soft drinks and risk for oesophageal adenocarcinoma

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Wu *et al*. (2006a), Taiwan, China [dates not reported]	165 men (oesophageal squamous-cell carcinoma), aged 35–92 years; pathologically proven	255 hospitalized men, aged 40–92 years; none had malignant tumours or any condition known to be associated with betel chewing, cigarette smoking or alcoholic beverage consumption; refusal rate, 11.8%	Interviewer-administered structured questionnaire	*Daily quantity*			Cigarette smoking, betel chewing, age, years of education	Dose–response effects found in daily quantity of drinking and smoking; synergistic effect between alcoholic beverage intake and cigarette use (odds ratio, 108.0; 35.1–478.0)
				Non-drinker	17	1.0		
				750 mL/day	113	15.8 (8.3–31.7)		
				>750 mL/day	30	65.1 (20.0–264.8)		
						p-trend<0.001		
				Drinking status				
				Non-drinker	17	1.0		
				Former drinker	13	5.4 (1.9–15.4)		
				Current drinker	135	23.3 (12.0–47.7)		
				Starting age				
				Non-drinker	17	1.0		
				≥25 years old	103	15.7 (8.1–32.0)		
				<25 years old	43	30.8 (12.5–82.1)		
				Duration (years)				
				Non-drinker	17	1.0		
				30	75	14.9 (7.2–32.4)		
				>30	68	23.0 (10.6–52.9)		
						p-trend=0.001		
				Cumulative exposure (mL /year)				
				Non-drinker	17	1.0		
				<7500	22	6.8 (3.0–15.9)		
				7500–15 000	24	13.7 (5.3–37.8)		
				>15 000	45	37.3 (14.8–105.1)		
						p-trend<0.001		

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Wu *et al*. (2006b), Jiangsu, China, 2003–04	531 (381 men, 150 women); 45% and 72% of all newly registered cases recruited and interviewed in Dafeng (high risk area) and Ganyu (low risk area), respectively	531 population-based (381 men, 150 women); randomly selected by a computer from the demographic database of the general population; response rate, 70%	Interviewer-administered structured questionnaire; a 5-mL blood sample	*Dafeng (high-risk area)* 1–249 mL/week 250–499 mL/week 500–749 mL/week ≥750 mL/week *p*-trend=0.74 *Alcohol drinking* Never Ever *p*-trend=0.964 *Age of first drink (years)* <20 20–34 ≥35 *p*-trend=0.815 *Duration of drinking (years)* 1–24 25–34 35–44 ≥45 *p*-trend=0.834	 175 116 	 0.87 (0.49–1.54) 1.06 (0.60–1.89) 0.97 (0.52–1.79) 1.10 (0.63–1.93) 1.0 1.01 (0.70–1.46) 0.83 (0.44–1.58) 1.23 (0.79–1.91) 0.81 (0.48–1.35) 0.96 (0.56–1.59) 0.89 (0.48–1.64) 1.57 (0.92–2.70) 0.77 (0.43–1.40)	Age, gender, education, economic status, tobacco smoking	In Ganyu (low-risk area), odds ratio for oesophageal cancer versus non-drinker category was 1.71 (1.02–2.88).

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Yokoyama *et al*. (2006), Japan, 2000–04	52 women with primary oesophageal squamous-cell carcinoma at the National Cancer Center Hospital, aged 40–79 years; histological diagnosis; none of the patients refused to participate.	412 cancer-free women, aged 40–79 years; most of the controls were ordinary residents or workers living in Tokyo or neighbouring areas; 82% of the eligible subjects who were contacted were enrolled in the study.	Self-administered structured questionnaire	Never/rare Light Moderate Heavy Former drinker *Strong alcoholic beverages* Never Sometimes Frequently	24 11 6 7 4 46 4 2	1.0 1.81 (0.81–4.05) 3.97 (1.40–11.26) 15.35 (4.85–48.62) 4.58 (1.25–16.79) *p*-trend<0.0001 1.0 2.58 (0.80–8.33) 12.47 (0.97–160.06) *p*-trend=0.012	Age	Never/rare, <1 unit/week; light, 1–8.9 units/week; moderate, 9–17.9 units/week; heavy, ≥18 units/week; 1 unit=22 g ethanol

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Hashibe *et al*. (2007c), central and eastern Europe, 2000–02	192 squamous-cell carcinoma (170 men, 22 women), 35 adenocarcinoma (31 men, 4 women) of the oesophagus diagnosed at 5 centres in the Czech Republic, Poland,Romania, Russia, confirmed histologically or cytologically; recruited into the study within 3 months of diagnosis; response rate, 96%	1114 (846 men, 268 women); frequency-matched from same hospital as the cases with a recent diagnosis of disease unrelated to tobacco and alcohol; in Moscow, frequency-matched to cases by age, sex, centre, referral or residence area; in other centres, overlapped with those in study of lung cancer; interviewed more than 6 months before the beginning of recruitment of cases; response rate, 97%	Face-to-face interviews using a structured questionnaire	*Squamous-cell carcinoma* No drinking Ever drinking *Intake of ethanol (g/week)* No drinking 1–139 140–279 280–419 ≥420 *Years of drinking* No drinking 1–19 20–39 ≥40 *Cumulative consumption (grams)* No drinking 1–1399 1400–2799 2800–4199 4200–5599 ≥ 5600	 5 181 5 69 34 20 55 5 12 131 35 5 23 33 16 16 93	 1.00 2.86 (1.06–7.74) 1.00 3.08 (1.11–8.60) 4.51 (1.46–13.94) 8.14 (2.45–27.04) 9.78 (3.08–31.04) *p*-trend<0.01 1.00 2.25 (0.63–8.04) 4.80 (1.68–13.72) 2.39 (0.83–6.90) *p*-trend=0.08 1.00 1.70 (0.59–4.87) 4.91 (1.62–14.84) 3.29 (1.01–10.72) 6.62 (1.99–22.08) 7.21 (2.37–21.98) *p*-trend<0.01	Centre, age, sex, education, body mass index, fruit intake, vegetable intake, pack–years of tobacco	A synergistic interaction between tobacco and alcohol was observed for the risk for oesophageal squamous-cell carcinoma. (ICD-0-2 C 15)

ALDH, acetaldehyde dehydrogenase; CI, confidence interval; WE, whiskey equivalent

2.4.4 *Type of alcoholic beverage (Table 2.19a and Table 2.19b)*

The types of alcoholic beverage consumed were examined in several studies. Consumption of beer or hard liquor led to a higher relative risk than consumption of wine (Kato *et al*., 1992c; Brown *et al*., 1994; Gammon *et al*., 1997; Grønbaek *et al*., 1998; Kjaerheim *et al*., 1998; Lagergren *et al*., 2000), whereas two studies (Barra *et al*., 1990; Sakata *et al*., 2005) also found an excess risk for wine drinkers. Most of the studies that investigated types of alcoholic beverage showed no substantial difference in risk.

2.4.5 *Evidence of a dose–response*

The risk for oesophageal cancer was shown to increase with increasing number of drinks per day or the number of days per week on which alcoholic beverages were consumed in 10 cohort and 21 case–control studies. Some studies found a relationship between the duration of alcoholic beverage consumption in years and the risk for oesophageal cancer (Cheng *et al*., 1995; Zhang *et al*., 1998; Liu *et al*., 2000; Znaor *et al*., 2003; Sakata *et al*., 2005; Wu *et al*., 2006a; Hashibe *et al*., 2007a). Using non-drinkers as the baseline, the influence of the cumulative amount of alcoholic beverage consumed was apparent (Lagergren *et al*., 2000; Sakata *et al*., 2005; Wu *et al*., 2006a; Hashibe *et al*., 2007a). A dose–response relationship was found between the frequency of alcoholic beverage intake and the risk for oesophageal cancer (Grønbaek *et al*., 1998; Kinjo *et al*., 1998; Wu *et al*., 2006a; Hashibe *et al*., 2007a). In two studies (Yang *et al*., 2005; Wu *et al*., 2006a), the relative risks were lower in former drinkers than in current drinkers but remained significantly elevated.

2.4.6 *Effect of cessation of alcoholic beverage consumption (Table 2.20)*

Studies on the cessation of alcoholic beverage consumption may be confounded by the fact that the precursors and early malignancies of the oesophagus may lead to such cessation. Nevertheless, this type of confounding may result in an underestimation of the effect. For recent quitters, the risk for oesophageal cancer increased above that of current drinkers; as the number of years of having quit increased, however, the risk gradually decreased to below that of current drinkers or even to close to the levels of non-drinkers in some studies.

Cheng *et al*. (1995) observed that risk could decrease to nearly the levels of non-drinkers after more than 10 years of quitting. Castellsagué *et al*. (2000) showed that risk can be reduced to 50% of that of current drinkers after more than 10 years of cessation. Bosetti *et al*. (2000) observed an odds ratio of 0.37 (95% CI, 0.14–0.99) after 10 or more years of cessation. All three case–control studies suggested a reduction in risk after cessation of alcoholic beverate consumption for more than 10 years.

Table 2.18 Selected cohort and case–control studies of oesophageal cancer by histological type and alcoholic beverage intake

Reference	Exposure categories	Histological type and risks			
Cohort studies					
Boffetta *et al*. (2001)		Adenocarcinoma		Squamous-cell carcinoma	
		Cases	*SIR (95% CI)*	*Cases*	*SIR (95% CI)*
		27	1.45 (0.96–2.11)	449	6.76 (6.15–7.41)
Lindblad *et al*. (2005) (nested case–control)		Adenocarcinoma		Squamous-cell carcinoma	
	Units/day	*Cases*	*Relative Risk (95% CI)*	*Cases*	*Relative Risk (95% CI)*
	0–2	95	1.00	49	1.00
	3–15	59	1.06 (0.76–1.49)	20	1.01 (0.59–1.72)
	16–34	15	0.69 (0.39–1.20)	13	2.44 (1.26–4.71)
	>34	9	1.25 (0.61–2.55)	5	3.39 (1.28–8.99)
	Unknown use	109	1.21 (0.81–1.79)	53	0.79 (0.42–1.49)
Case–control studies					
Kabat *et al*. (1993)		Distal oesophagus/cardia		Squamous-cell carcinoma	
	Men	*Cases*	*Odds ratio (95% CI)*	*Cases*	*Odds ratio (95% CI)*
	Non-drinker	16	1.0	7	1.0
	Occasional	55	2.0 (1.1–3.5)	15	1.4 (0.6–3.5)
	1–3.9 oz WE/day	61	2.1 (1.2–3.6)	27	2.3 (1.0–5.4)
	≥4 oz WE/day	41	2.3 (1.3–4.3)	86	10.9 (4.9–24.4)
	Women				
	Non-drinker	10	1.0	16	1.0
	Occasional	5	0.6 (0.2–1.9)	17	1.4 (0.7–2.9)
	1–3.9 oz WE/day	3	0.9 (0.2–3.5)	25	4.4 (2.2–8.7)
	≥4 oz WE/day	3	3.8 (0.9–16.6)	20	13.2 (6.1–28.8)

Table 2.18 (continued)

Reference	Exposure categories	Histological type and risks			
Brown *et al.* (1994)		Adenocarcinoma of oesophagus and oesophagogastric junction			
		Cases	*Odds ratio (95% CI)*		
	Never drinker	32	1.0		
	Drinker	142	0.9 (0.6–1.4)		
	<8 drinks/week	38	0.7 (0.4–1.3)		
	8–21 drinks/week	42	08 (0.4–1.3)		
	22–56 drinks/week	43	1.1 (0.6–1.9)		
	>56 drinks/week	18	1.5 (0.7–3.1)		
Vaughan *et al.* (1995)		Adenocarcinoma		Squamous-cell carcinoma	
		Cases	*Odds ratio (95% CI)*	*Cases*	*Odds ratio (95% CI)*
	0–6 drinks/week	147	1.0	27	1.0
	7–13 drinks/week	39	1.1 (0.7–1.8)	20	6.0 (2.7–13.5)
	14–20 drinks/week	18	1.2 (0.6–2.3)	11	6.3 (2.2–17.9)
	≥21 drinks/week	44	1.8 (1.1–3.1)	30	9.5 (4.0–22.3)
Gammon *et al.* (1997)		Adenocarcinoma		Squamous-cell carcinoma	
		Cases	*Odds ratio (95% CI)*	*Cases*	*Odds ratio (95% CI)*
	Never	79	1.0	19	1.0
	Ever	210	0.7 (0.5–1.0)	195	3.5 (1.9–6.2)
	<5 drinks/week	56	0.7 (0.4–1.0)	16	0.8 (0.4–1.6)
	5–11 drinks/week	45	0.6 (0.4–0.9)	25	1.8 (0.9–3.5)
	12–30 drinks/week	57	0.7 (0.4–1.1)	48	2.9 (1.5–5.4)
	>30 drinks/week	52	0.9 (0.5–1.4)	106	7.4 (4.0–13.7)
Lagergren *et al.* (2000)		Adenocarcinoma		Squamous-cell carcinoma	
		Cases	*Odds ratio (95% CI)*	*Cases*	*Odds ratio (95% CI)*
	Never	41	1.0	16	1.0
	Ever	148	0.5 (0.3–0.9)	151	1.1 (0.6–2.1)
	1–15 g/week	54	0.6 (0.4–1.1)	34	0.9 (0.4–1.8)
	16–70 g/week	51	0.4 (0.2–0.7)	39	0.8 (0.4–1.8)
	>70 g/week	43	0.6 (0.3–1.1)	78	3.1 (1.4–6.7)

Table 2.18 (continued)

Reference	Exposure categories	Histological type and risks	
Wu *et al*. (2001)		Adenocarcinoma of oesophagus	
		Cases	*Odds ratio (95% CI)*
	1–7 drinks/week	Not	0.72 (0.5–1.2)
	8–21 drinks/week	reported	0.57 (0.3–0.9)
	22–35 drinks/week		0.77 (0.4–1.4)
	≥36 drinks/week		0.93 (0.5–1.6)
			p=0.79
	Alcohol use		
	Never		1.0
	Former		0.74 (0.5–1.2)
	Current		0.70 (0.5–1.1)
Lagergren *et al*. (2006)	*Carbonated low-alcohol beer (times/week)*	Adenocarcinoma of oesophagus	
		Cases	*Odds ratio (95% CI)*
	Unexposed (0)	40	1.00
	Low (≤1)	44	1.05 (0.60–1.83)
	Medium (>1–4)	46	1.16 (0.65–2.07)
	High (>4)	50	1.33 (0.74–2.40)
			p=0.78

Table 2.18 (continued)

Reference	Exposure categories	Histological type and risks			
Hashibe *et al*. (2007c)		Adenocarcinoma		Squamous-cell carcinoma	
		Cases	*Odds ratio (95% CI)*	*Cases*	*Odds ratio (95% CI)*
	No drinking	3	1.00	5	1.00
	Ever drinking	32	1.21 (0.31–4.77)	181	2.86 (1.06–7.74)
	1–139 g/week	13	1.06 (0.25–4.58)	69	3.08 (1.11–8.60)
	140–279 g/week	6	2.22 (0.40–12.39)	34	4.51 (1.46–13.94)
	280–419 g/week	4	5.39 (0.73–39.93)	20	8.14 (2.45–27.04)
	≥420 g/week	6	2.31 (0.30–17.58)	55	9.78 (3.08–31.04)
			p=0.20		p<0.01
	Years of drinking				
	No drinking	3	1.00	5	1.00
	1–19	1	0.38 (0.02–6.09)	12	2.25 (0.63–8.04)
	20–39	17	1.08 (0.24–4.94)	131	4.80 (1.68–13.72)
	≥40	11	1.44 (0.31–6.66)	35	2.39 (0.83–6.90)
			p=0.55		p=0.08
	Cumulative consumption (grams)				
	No drinking	3	1.00	5	1.00
	1–1399	7	1.08 (0.24–4.82)	23	1.70 (0.59–4.87)
	1400–2799	6	1.48 (0.29–7.41)	33	4.91 (1.62–14.84)
	2800–4199	4	1.16 (0.21–6.51)	16	3.29 (1.01–10.72)
	4200–5599	0	–	16	6.62 (1.99–22.08)
	≥5600	15	1.96 (0.39–9.88)	93	7.21 (2.37–21.98)
			p=0.54		p<0.01

CI, confidence interval; SIR, standardized incidence ratio; WE, whiskey equivalent

Table 2.19a. Selected cohort studies of oesophageal cancer and consumption of different types of alcoholic beverages

Reference, location, name of study	Exposure categories	Beer		Wine		Hard liquors	
		No. of exposed cases	Relative risk (95% CI)	No. of exposed cases	Relative risk (95% CI)	No. of exposed cases	Relative risk (95% CI)
Cohort studies							
Kato *et al.* (1992c), USA, Hawaii, American Men of Japanese Ancestry Study	*Alcohol intake* 0 mL/day <500 mL/day ≥500 mL/day	 24 16 30	 1.0 0.7 (0.4–1.4) 2.6 (1.5–4.6) *p* 0.01		Not reported		Not reported
Grønbaek *et al.* (1998), Denmark, The Copenhagen Centre for Prospective Population Studies	*Frequency of drinking* 0 drinks/week 1–6 drinks/week ≥7 drinks/week	 Not reported	 1.0 1.5 (0.9–2.5) 2.9 (1.8–4.8)	 Not reported	 1.0 0.8 (0.5–1.1) 0.4 (0.2 –0.8)	 Not reported	 1.0 0.7 (0.5–1.1) 1.5 (1.2–1.9)
Kjaerheim *et al.* (1998), Norway, Norwegian Cohort Study	*Frequency of drinking (times/week)* Never or <1 Previously 1–3 4–7	 37 11 8 14	*Upper aerogastric tract cancer* 1.0 1.0 (0.5–1.9) 1.4 (0.7–3.1) 4.4 (2.4–8.3) *p* 0.001	 Not reported	 Not reported	 42 15 5 5	 1.0 1.3 (0.7–2.3) 1.4 (0.6–7.0) 2.7 (1.1–7.0) *p*=0.06
Sakata *et al.* (2005), Japan, Japanese Collaborative Cohort Study		17	1.42 (0.58–3.52)	6	6.24 (1.53–25.37)	48 15 9	Sake 2.72 (1.22–6.08) Shochu 3.40 (1.33–8.68) Whisky 2.60 (0.91–7.41)

Table 2.19b Selected case–control studies of oesophageal cancer and consumption of different types of alcoholic beverages

Reference, location, name of study	Beer			Wine			Hard liquors		
	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)
Case–control studies									
Barra *et al*. (1990), northern Italy, 1986–90	≤55 drinks/ week	6	1.8 (0.7–4.5)		61	1.7 (1.1–2.7)		27	1.8 (1.0–3.1)
	56–83 drinks/ week	8	4.3 (1.6–11.3)		39	5.4 (3.1–9.3)		31	3.6 (2.0–6.4)
	≥84 drinks/ week	6	4.3 (1.5–12.4)		7	15.0 (4.6–49.1)			10.0 (4.1–24.5)
Brown *et al*. (1994), USA, 1986–89	Never	60	1.0			1.0		64	1.0
	Drank	114	6 (0.4–0.9)			0.9 (0.6-1.4)		110	1.6 (1.1–2.4)
	<8 drinks/ week	46	0.6 (0.4–1.0)	<3 drinks/ week		0.9 (0.5–1.5)	<8 drinks/ week	50	1.3 (1.0–3.2)
	8–15 drinks/ week	26	0.7 (04–1.2)	3–13 drinks/ week		0.8 (04–1.5)	8–15 drinks/ week	24	0.8 (04–1.3)
	15–28 drinks/ week	21	0.6 (0.3–1.1)	≥14 drinks/ week		1.6 (0.7–3.8)	15–28 drinks/ week	21	2.1 (1.1–4.0)
	≥29 drinks/ week	50	0.6 (0.3–1.3)				≥29 drinks/ week	13	2.8 (1.2–6.3)
Gammon *et al*. (1997), USA, 1993–95	Never	57	1.0		149	1.0		48	1.0
	Ever	164	2.2 (1.4–3.3)		72	0.6 (0.4–0.9)		173	3.1 (2.0–4.8)

Table 2.19b (continued)

Reference, location, name of study	Beer			Wine			Hard liquors		
	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)
Lagergren *et al*. (2000), Sweden, 1995–97			Strong beer						
	Never	103	1.0		68	1.0		26	1.0
	Ever	64	1.3 (0.9–2.0)		99	0.9 (0.6–1.4)		141	1.0 (0.6–1.8)
	Grams of ethanol/week								
	1–5	21	1.3 (0.7–2.3)	1–5	26	0.8 (0.5–1.5)	1–7	26	0.6 (0.3–1.2)
	6–25	21	1.0 (0.6–1.9)	6–25	29	0.9 (0.5–1.7)	8–30	39	1.1 (0.5–2.2)
	>25	22	1.2 (0.6–2.3)	>25	44	1.2 (0.7–2.1)	>30	76	2.3 (1.1–4.7)
Wu *et al*. (2001), Los Angeles, USA, 1992–97	None	Not reported	1.0		Not reported	1.0			1.0
	<7/week		0.44 (0.3–0.7)			0.86 (0.6–1.3)			0.93 (0.6–1.4)
	7–14/week		0.30 (0.2–0.5)			0.72 (0.4–1.3)			1.35 (0.8–2.3)
	≥15/week		0.57 (0.3–1.0)			1.27 (0.6–2.8)			1.34 (0.8–2.3)
Hashibe *et al*. (2007c), central and eastern Europe, 2000–02		12	0.87 (0.38–1.98)		4	0.50 (0.15–1.72)		19	Spirits 0.71 (0.39–1.29)

CI, confidence interval

Table 2.20 Case–control studies of oesophageal cancer and cessation of alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Cheng *et al*. (1995), Hong Kong, China, 1989–90	400 consecutive patients during a 21-month period in 1989–90; histologically confirmed; response rate, 87%	1598 patients from the same surgical departments as the cases and from general practices from which the cases were originally referred; matched by age, sex; response rate, 95%	Interviewer-administered structured questionnaire	Never drinkers	53	1.0	Age, sex, education, smoking	
				1–199 g/week	103	1.1 (0.7–1.8)		
				200–599 g/week	92	3.3 (2.0–5.4)		
				≥600 g/week	130	9.2 (5.4–15.7)		
				Duration				
				Never drinkers	53	1.0		
				1–19 years	24	2.0 (1.0–3.8)		
				20–39 years	175	2.1 (1.4–3.2)		
				≥ 40 years	131	2.4 (1.6–3.8)		
				Years since stopped drinking				
				Current drinkers	207	1.0		
				0–1	47	2.5 (1.4–4.4)		
				1–4	36	1.5 (0.9–2.6)		
				5–9	22	0.5 (0.3–0.9)		
				10–14	20	0.8 (0.4–1.5)		
				≥ 15	11	0.2 (0.1–0.6)		
				Never drinkers	53	0.6 (0.4–1.0)		

Table 2.20 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Bosetti *et al*. (2000), multicentre, 1992–99	404 squamous-cell cancer (356 men, 48 women), median age, 60 years (range, 34–77 years); newly diagnosed; histologically confirmed	1070 (878 men, 192 women), median age, 60 years (range, 32–77 years); patients admitted to the same hospitals for nonsmoking- or alcohol consumption-related non-neoplastic conditions	Interviewer-administered structured questionnaire	*Time since drinking cessation (years)* Current 1–9 ≥ 10		 1 1.28 (0.67–2.43) 0.37 (0.14–0.99)	Age, sex, study centre, education, alcoholic beverage and tobacco consumption	Odds ratio represents the combined effect of time since smoking and drinking cessation on risk of oesophageal cancer.
Castellsagué *et al*. (2000), 1986–92	655 men with incident squamous-cell carcinoma	1408 men; individually matched to the cases on admitting hospital, age (±5 years)	Interviewer-administered structured questionnaire	*Years of drinking cessation* Current > 1–9 > 10 *p* for trend (two-sided)	 348 176 34	 1.0 0.9 0.5 0.02	Age group, hospital, years of schooling, average amount of pure ethanol consumed	Joint effect of years of smoking and drinking cessation on oesophageal cancer; reported odds ratios adjusted for years since quitting smoking.

CI, confidence interval

2.4.7 *Effect modification*

The combined effects of smoking and alcoholic beverage consumption on the development of cancer of the oesophagus have been examined in several studies (Tables 2.17 and 2.21), which varied in the methods and approaches used to assess effect modification, and ranged from being descriptive to giving a formal estimation of interaction terms in multivariate models. Eight case–control studies (Franceschi *et al*., 1990; Negri *et al*., 1992; Kabat *et al*., 1993; Lagergren *et al*., 2000; Gallus *et al*., 2001; Znaor *et al*., 2003; Wu *et al*., 2006a; Hashibe *et al*., 2007c) and two cohort studies (Kato *et al*., 1992c; Sakata *et al*., 2005) reported the joint effect of alcoholic beverage consumption and tobacco smoking on the risk for oesophageal cancer. Overall, the studies showed that the joint effects were multiplicative rather than additive, but, since multiple logistic regression models were used in the analyses in most of these studies, some also showed them to be additive rather than multiplicative.

Some studies investigated sex-specific effects (Table 2.22), and reported similar risks for both men and women (Negri *et al*., 1992; Kabat *et al*., 1993; Kinjo *et al*., 1998). Most studies found non-significantly increased relative risks among women with oesophageal cancer, but a significant risk among men who were classified as heavy drinkers, after controlling for tobacco smoking (DeStefani *et al*., 1990; Adami *et al*., 1992b; Kinjo *et al*., 1998). The studies from Japan and Italy found a significantly increased risk for oesophageal cancer among women (Gallus *et al*., 2001; Yokoyama *et al*., 2006).

2.5 Cancer of the liver

Hepatocellular carcinoma (HCC) is the third most common cause of mortality from cancer and the sixth most common cause of cancer incidence worldwide (Parkin *et al*., 2005). Although it is relatively rare in developed countries compared to the developing world, the incidence of primary liver cancer has increased during the last few decades in the USA (Howe *et al*., 2001) and in several European countries, although it has levelled off and subsequently declined in most of southern Europe over the last decade (La Vecchia *et al*., 2000).

In 1988, the IARC Monograph on alcohol drinking concluded that there was "sufficient evidence for the carcinogenicity of alcoholic beverages" and that "the occurrence of malignant tumours of the liver is causally related to consumption of alcoholic beverages" (IARC, 1988). Since that time, further evidence has been presented on the risk of liver cancer associated with prolonged alcoholic beverage consumption, the increased risk of associated liver cancer among cirrhotics and the modifying effects of the infectious agents hepatitis B virus (HBV) and hepatitis C virus (HCV).

Table 2.21 Selected cohort and case–control studies of oesophageal cancer in nonsmokers and smokers by level of alcoholic beverage intake

Reference	Exposure categories	Nonsmokers		Smokers					
Cohort studies									
Kato *et al.* (1992c)		*Never smokers*		*Former and current smokers*					
		Cases	RR (95% CI)	Cases	RR (95% CI)				
	<30 mL/day	5	1.0	29	3.3 (1.3–8.4)				
	≥30 ml/day	3	8.6 (2.1–36.0)	34	17.3 (6.7–44.2)				
Sakata *et al.* (2005)		*Never smokers*		*Former smokers*		*Smokers*			
		Deaths	HR (95% CI)	Deaths	HR (95% CI)	Deaths	HR (95% CI)		
	Non-drinkers	4	1.0	1	0.34 (0.04–3.12)	4	0.74 (0.18–3.02)		
	Former drinkers	1	1.10 (0.12–10.24)	3	1.47 (0.31–7.08)	4	2.19 (0.51–9.40)		
	Drinkers	2	0.18 (0.03– 1.02)	21	1.39 (0.47–4.10)	60	2.37 (0.85–6.58)		
Case–control studies									
Franceschi *et al.* (1990)		*Never smokers*		*Light smokers*		*Intermediate smokers*		*Heavy smokers*	
		Cases	Odds ratio	Cases	Odds ratio	Cases	Odds ratio	Cases	Odds ratio
		9	1.0	11	1.1	47	2.7	16	6.4
		3	0.8	19	7.9	78	8.8	14	11.0
		5	7.9	13	6.4	60	16.7	6	17.5
Negri *et al.* (1992)		*Never smokers*		*Ex/Moderate smokers*		*Heavy smokers*			
		Cases	Odds ratio	Cases	Odds ratio	Cases	Odds ratio		
	<4 drinks/day	7	1.0	10	2.8	11	4.3		
	4–6 drinks/day	2	1.6	4	4.5	6	6.9		
	>6 drinks/day	1	3.5	9	3.8	12	15.3		
Kabat *et al.* (1993)		*Never smokers*		*Ever smokers*					
			Odds ratio		Odds ratio				
	Non drinker/ occasional		1.0		1.5 (0.5–4.2)				
	≥1 oz WE/day		4.3 (1.4–12.5)		7.6 (3.1–18.6)				

Table 2.21 (continued)

Reference	Exposure categories	Nonsmokers		Smokers	
Gallus *et al*. (2001)		*Never and former smokers*		*Current smokers*	
		Cases	Odds ratio (95% CI)	Cases	Odds ratio (95% CI)
	<1 drink/day	18	1.0	11	2.25 (0.95–5.33)
	1–2 drinks/week	27	1.66 (0.85–3.25)	23	5.52 (2.57–11.85)
	≥3 drinks/week	16	5.79 (2.48–13.50)	19	12.75 (5.09–31.96)
Znaor *et al*. (2003)		*No smoking*		*Smoking*	
		Cases	Odds ratio (95% CI)	Cases	Odds ratio (95% CI)
	No drinking	45	1.00	155	3.57 (2.51–5.06)
	Drinking	7	3.41 (1.46–7.99)	164	7.33 (5.06–10.62)
Wu *et al*. (2006a)		*No smoking*		*Smoking*	
		Cases	Odds ratio (95% CI)	Cases	Odds ratio (95% CI)
	No alcohol	3	1.00	11	6.5 (1.9–29.8)
	Alcohol	4	23.3 (4.3–142.2)	54	108.0 (35.1–478.0)
Hashibe *et al*. (2007c)		*Nonsmokers*		*Smokers*	
		Cases	Odds ratio (95% CI)	Cases	Odds ratio (95% CI)
	Alcohol				
	No	4	1.0	1	0.71 (0.07–7.00)
	Yes	12	0.96 (0.28–3.28)	174	6.42 (2.03–20.30)

CI, confidence interval; HR, hazard risk; RR, relative risk; WE, whiskey-equivalent

Table 2.22 Selected cohort and case–control studies of oesophageal cancer in men and women by level of alcoholic beverage intake

Reference	Exposure categories	Men		Women	
		Cases/ deaths	Relative risk (95% CI)	Cases/ deaths	Relative risk (95% CI)
Cohort studies					
Adami *et al*. (1992b)	Alcoholics	26	6.9 (4.5–10.0)	1	5.9 (0.1–32.6)
Kinjo *et al*. (1998)	None	56	1.0	93	1.0
	1–3 times/month	24	0.8 (0.5–1.3)	7	0.6 (0.3–1.3)
	1–3 times/week	67	1.1 (0.7–1.6)	9	1.3 (0.6–2.5)
	≥4 times/week	181	2.4 (1.8–3.3)	3	2.0 (0.6–6.2)
Case–control studies			**Odds ratio (95% CI)**		**Odds ratio (95% CI)**
DeStefani et al. (1990)	0 mL/day	26	1	38	1
	1–24 mL/day	16	0.85 (0.4–1.8)	12	1.04 (0.4–2.4)
	25–49 mL/day	12	0.71 (0.3–1.6)		
	50–149 mL/day	50	1.37 (0.8–2.4)		
	150–249 mL/day	46	3.57 (1.9–6.7)	12	1.89 (0.7–4.9)
	≥250 mL/day	49	5.27 (2.7–10.2)		
Negri *et al*. (1992)	<4 drinks/day	63	1	48	1
	4–6 drinks/day	50	1.5 (0.9–2.2)	8	2.2 (1.0–4.3)
	>6 drinks/day	131	3.5 (2.4–5.1)		*p*=0.05
			p<0.001		
Kabat *et al*. (1993)	Non-drinker	7	1.0	16	1.0
	Occasional	15	1.4 (0.6–3.5)	17	1.4 (0.7–2.9)
	1–3.9 oz WE/day	27	2.3 (1.0–5.4)	25	4.4 (2.2–8.7)
	≥4 oz WE/day	86	10.9 (4.9–24.4)	20	13.2 (6.1–28.8)
Gallus *et al*. (2001)	<1 drink/day			29	1.0
	1–2 drinks/day			50	1.99 (1.15–3.44)
	≥3 drinks/day			35	5.40 (2.70–10.80)
					p<0.001

Table 2.22 (continued)

Reference	Exposure categories	Men		Women	
		Cases/ deaths	Relative risk (95% CI)	Cases/ deaths	Relative risk (95% CI)
Yokoyama *et al*. (2006)	Never/rare			24	1.0
	Light			11	1.81 (0.81–4.05)
	Moderate			6	3.97 (1.40–11.26)
	Heavy			7	15.35 (4.85–48.62)
	Former drinker			4	4.58 (1.25–16.79)
					p<0.0001
	Strong alcoholic beverages				
	Never			46	1.0
	Sometimes			4	2.58 (0.80– 8.33)
	Frequently			2	12.47 (0.97–160.06)
					p=0.012

CI, confidence interval; WE, whiskey-equivalent

2.5.1 *Cohort studies*

(a) Special populations (Table 2.23)

Most HCCs occur in cirrhotic livers, and cirrhosis is a pathogenic step in liver carcinogenesis (La Vecchia *et al*., 1998). In alcoholics, prolonged, excessive alcohol consumption results in alcoholic cirrhosis. The risk of HCC has been examined among alcoholic and cirrhotic subjects. In western countries, a few cohort studies have provided information regarding these special populations. Results from these cohort studies are presented in Table 2.23. Since 1988, two cohort studies conducted in Sweden have assessed the risk of primary liver cancer. One cohort comprised alcoholic and cirrhotic subjects (Adami *et al*., 1992a) and the other cohort included male and female alcoholics (Adami *et al*., 1992b). An additional cohort study in Denmark was conducted among patients with cirrhosis (Sørensen *et al*., 1998). The number of cases ranged from four to 182 within these three populations. Each of the three studies showed evidence of a strong association between alcoholism, cirrhosis and liver cancer. Two of these studies reported statistically significant SIRs greater than 35 among alcoholics and cirrhotics (Adami *et al*., 1992a; Sørensen *et al*., 1998). The Swedish cohort, which included alcoholics and cirrhotics, was based on a total of 83 cases and the Danish cohort of cirrhotics was based on a total of 245 cases. In contrast, a cohort study of 5332 Norwegian teetotallers reported a SIR for liver cancer of 0.31. However, this was based on only one observed case (Kjaerheim *et al*., 1993).

(b) General population (Table 2.24)

Two cohort studies have been conducted among the general population since 1988 (Yuan *et al*., 1997; Wang *et al*., 2003b). Neither study observed an association between alcoholic beverage consumption and liver cancer. In a study of male residents from communities in Shanghai, Yuan *et al*. (1997) reported a non-statistically significant reduction in risk among moderate (relative risk 0.68) and heavy (relative risk 0.84) drinkers of alcohol compared with non-drinkers. Similarly, Wang *et al*. (2003b) found no significant associations with the risk for HCC among drinkers compared with non-drinkers in a study of male residents from Taiwan.

2.5.2 *Case–control studies (Table 2.25)*

Ten case–control studies published since the last evaluation (IARC, 1988) provide information related to alcoholic beverage consumption and liver cancer: four were conducted in Italy (La Vecchia *et al*., 1998; Donato *et al*., 2002; Gelatti *et al*., 2005; Franceschi *et al*., 2006), two in the USA (Yuan *et al*., 2004; Marrero *et al*., 2005), and one each in Greece (Kuper *et al*., 2000a), Japan (Tanaka *et al*., 1992), South Africa (Mohamed *et al*., 1992) and Spain (Vall Mayans *et al*., 1990). All of these studies, with the exception of Yuan *et al*. (2004), used hospital-based controls. Tanaka *et al*. (1992) used city residents who visited a local public health centre for a routine health

Table 2.23 Cohort studies of liver cancer and alcoholic beverage consumption in special populations

Reference, location, study name	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment	Comments
Adami *et al* (1992a), Sweden	Cohorts were selected from the in-patient registry containing diagnostic codes for alcoholism and/ or liver cirrhosis; 12 942 patients included in the study. 8511 alcoholics (7609 men, 911 women), 3589 cirrhotics (1961 men, 1628 women), 836 alcoholics/ cirrhotics (734 men, 102 women); follow-up 1965–1983; 90% histology confirmed	Hospital discharge-diagnosis	Liver (155.0, 155.1, 155.2, 155.3, 155.8, 155.9)			**SIR**	Age, sex	Risk for liver cancer 10 times higher among cirrhotics than among alcoholics
				Alcoholics	13	3.1 (1.6–5.3)		
				Cirrhotics	59	35.1 (26.7–45.3)		
				Alcoholics and cirrhotics	11	34.3 (17.1–61.3)		

Table 2.23 (continued)

Reference, location, study name	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment	Comments
Kjaerheim *et al*. (1993)	5332 members of the International Organization of Good Templars, Norwegian teetotalers; followed-up 1980–1989	Cancer Registry	Liver (155.0)	Teetotalers		**SIR** 0.31 (0.1–1.7)	Age, sex	
Adami *et al*. (1992b), Sweden	Population-based cohort of 9353 (8340 men; 1013 women) alcoholics diagnosed in 1965–1983, followed-up for 19 years; 90% diagnosed	Discharge diagnosis of alcoholism	Liver (ICD-7 307, 322; ICD-8 291, 303	Alcoholics (men, women)	Men 23 Women 4	5.4 (3.4–8.1) 12.5 (3.4–32.0)	Age, years follow-up	No age related trends were seen with relation to liver cancer. Patients without a discharge diagnosis of cirrhosis experienced a 3-fold increase in risk for primary liver cancer.

Table 2.23 (continued)

Reference, location, study name	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment	Comments
Sørensen *et al*. (1998), Denmark	Danish National Registry of Patients; patients with a diagnosis of alcoholic cirrhosis, primary biliary cirrhosis, non-specified cirrhosis, chronic hepatitis or other type of cirrhosis, alcoholism not indicated between 1977 and 1989; 205 cases (182 men, 103 women); follow-up until 1993	Discharged diagnosis	Liver (ICD-8 571.09, 571.90, 571.92, 571.93, 571.99, 303)	Cirrhotics	Men 82 Women 63 Both 245	 40.2 (NG) $p<0.05$ 27.8 (NG) $p<0.05$ 36 (31.6–40.8)	Age, sex	Excess risk for liver cancer observed among cirrhotics: 40-fold increase risk among men and 28-fold increase among women; risk further exaggerated among cases of hepatocellular carcinoma

CI, confidence interval; ICD, International Classification of Diseases; NG, not given; SIR, standardized incidence ratio

Table 2.24 Cohort studies of liver cancer and alcoholic beverage consumption

Reference, location, study name	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment	Comments
Yuan *et al.* (1997), Shanghai, China, 1986–1989	18 244 male residents living in 4 small communities in the city of Shanghai, aged 45–64 years; no history of cancer; follow-up until 1995	Structured questionnaire	Liver (ICD-9 155)	Non-drinkers 1–28 drinks/ week ≥29 drinks/ week	61 32 9	1.0 0.68 0.84	Age, level of education, cigarette smoking	No association between alcohol consumption and risk for liver cancer in men; CI not given, *p* values not given
Wang et al. (2003b); Taiwan 1990-2000	Residents of seven townships in Taiwan; 11 937 born between 1926 and 1960; follow-up until 2000	Personal interview; serum samples	Liver	Non-drinkers Drinkers	84 31	1.00 1.46 (0.97–2.21)	Age, residence, HBV, HCV markers	Elevated risk for HCC among users of alcohol although not significant

CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD, International Classification of Diseases

Table 2.25 Case–control studies of liver cancer and alcoholic beverage consumption

Reference, location, study name	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment	Comments
Mayans *et al*. (1990), Catalonia, Spain, 1986-88	96 hospital-based cases were diagnosed with primary liver cancer in 1986–88; 77% histologically confirmed as HCC	190 matched 2:1 on age (within 5 years), sex; selected from same hospital as cases	Structured interview	Non-drinker 1–20 g/day 21–40 g/day 41–60 g/day 61–80 g/day >80 g/day	3 27 16 18 12 20	1.00 1.78 1.97 6.22 7.89 12.0 $p<0.001$	Age, sex, HBV status	Alcohol consumption significantly associated with HCC; risk did not significantly change with HBV status; CI not given
Yuan *et al*. (2004), Los Angeles County, CA, USA, 1984-2002	Population-based; 295 HCC cases, 18–74 years old; LA County Cancer Surveillance Program (1984–2002); 100% histologically confirmed	435 (age, gender, race) controls; Hispanic and non-Hispanic 2% match; age (within 5 years)	Personal interview; blood specimen	Non-drinker >0–2 drinks/day >2–4 drinks/day >4 drinks/day	91 66 43 95	1.00 0.6 (0.4–0.9) 1.4 (0.8–2.4) 3.2 (1.9–5.3) $p<0.001$	Age, gender, race, level of education, smoking status, history of diabetes	Risk for HCC increased with increased drinking: reduction in risk for patients that consumed >2 drinks/day (40% reduction)

Table 2.25 (continued)

Reference, location, study name	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment	Comments
Gelatti *et al*. (2005), Brescia and Pordenone, Italy	200 cases of HCC, up to age 79 years; born in Italy; Caucasian	400 hospitalized for other reasons not related to liver disease, neoplasms, tobacco- or alcohol-related disease; frequency-matched with cases on age (± 5 years), sex, date of hospital admission	Interview; blood sample	0–60 g/day 61–100 g/day >100 g/day	86 48 66	1.00 1.2 (0.8–1.9) 2.6 (1.7–4.0)	Age, sex, HBV and HCV markers, area of recruitment	Heavy alcohol consumption related to increased risk for HCC; no other alcohol related findings reported
Franceschi *et al*. (2006), Pordenone and Naples, Italy, 1999–2002	279 cases, aged 43–84 years; diagnosed with HCC without treatment; 78.2% histologically confirmed; enrolled from hospitals and cancer institutes in Naples and Pordenone (1999–2002)	431 hospital-based 40–83 years old; admitted for reasons other than alcohol- and tobacco-related use or hepatitis; distribution matched on age, sex	Questionnaire; HBV, HCV testing	Never <7 drinks/ week 7–13 drinks/ week 14–20 drinks/ week 21–34 drinks/ week ≥35 drinks/ week	20 16 26 38 53 76	1 1.67 (0.55–5.13) 0.81 (0.35–2.38) 1.04 (0.41–2.65) 1.61 (0.61–4.29) 5.94 (2.25–15.67)	Gender, age, center, education, HBV, HCV markers	Significant increase in risk for HCC among heaviest drinkers

Table 2.25 (continued)

Reference, location, study name	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment	Comments
Marrero *et al*. (2005), Michigan, USA, 2002–03	70 cases of HCC from liver or general medicine clinics; 81.4% histologically confirmed	70 with cirrhosis and 70 with no liver disease; 2:1 match on age (± 5 years) and sex: 80% histologically confirmed for cirrhosis controls	Validated questionnaire by trained interviewer	None <1500 g–years ≥1500 g–years	11 11 48	1.0 1.4 (0.8–1.9) 23.8 (7.3–79)	Body mass index, smoking, age	24-fold increased risk for HCC among heavy consumers of alcohol (HCC versus no liver disease); risk not as excessive in comparison with cirrhotics
Kuper *et al*. (2000a); Athens, Greece, 1995-98	333 cases enrolled from 3 teaching hospitals in Athens (283 men, 50 women); 99% confirmed diagnosis	360 (298 men, 62 women) hospital controls; matched 1:1 on gender, age (±5 years)	Hospital interview; blood test	Non-drinkers <20 glasses/week 20–39glasses/week ≥40 glasses/week	135 71 46 81	1.0 0.8 (0.4–1.4) 0.7 (0.3–1.5) 1.9 (0.9–3.9) *p*=0.13	Age, gender, years of education, HBV, HCV markers	Increased risk of HCC among heavy consumers of alcohol not significant.

Table 2.25 (continued)

Reference, location, study name	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment	Comments
Mohamed *et al*. (1992), Johannesburg, South Africa	101 (77 men, 24 women) Southern African blacks with HCC, 20–87 years old; enrolled from a hospital outside Johannesburg;	101 controls; 1:1 matched on ethnic origin, sex, age (±2 years); same hospital as cases with diagnosis other than HCC	Interview	*Men* Non-drinkers Light/ moderate Heavy *Women* Non-drinkers Light/ moderate Heavy	 Not reported 18 39 Not reported 1 7	 0.8 (0.2–2.6) 4.4 (1.4–14.1) p=0.0005 0.6 (0.0–8.8) 1.4 (0.3–9.3) p=0.81	HBV status, smoking	Significant increased risk for HCC found only among men >40 years of age

Table 2.25 (continued)

Reference, location, study name	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment	Comments
Tanaka *et al*. (1992), Fukuoka, Japan, 1985–89	204 HCC patients aged 40–69 (168 men, 36 women); residents of Fukuoka or Saga Prefecture, Japanese nationality, enrolled from Kyushu University Hospital; 40% histologically confirmed enrolled in 1985–89	410 residents (291 men, 119 women) of Fukuoka city who visited a public health center near Kyushu University Hospital between January 1986 and July 1989 for a health examination; matched on age, sex	In-person interview; blood sample	*Men* Non-drinker 0.1–33.9 drink–years 34.0–76.6 drink–years >76.6 drink–years *Women* Non-drinkers 0.1–33.9 drink–years 34.0–76.6 drink–years >76.6 drink–years	 37 31 36 64 27 5 2 2	 1.0 (reference) 0.9 (0.5–1.6) 0.9 (0.5–1.7) 1.7 (1.0–2.9) *p*=0.03 1.0 (reference) 2.1 (0.6–7.0) – 2.4 (0.6–9.1) *p*=0.11	Age, sex	History of heavy drinking significantly associated with increased risk for HCC
La Vecchia *et al*. (1998), Milan, Italy, 1984–96	499 (276 men, 123 women) with HCC, aged 23–74 recruited from major teaching and general hospitals in the greater Milan area	1552 (1141 men, 411 women); aged 20–74 years; patients admitted to area hospitals; with no history of cancer	Interview	0 drink/day 1–4 drinks/day >4 drinks/day (cases with history of cirrhosis)	26 24 37	13.4 (4.1–43.8) 15.2 (3.2–72.9) 24.9 (8.2–76.0)	Age, sex, tobacco smoking, hepatitis, diabetes, body mass index, family history	Association between heavy alcohol consumption and HCC among patients with a history of cirrhosis

Table 2.25 (continued)

Reference, location, study name	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment	Comments
Donato *et al*. (2002), Brescia, Italy, 1995–2000	464 (380 men, 84 women) patients with first diagnosis of HCC admitted between 1995–2000; aged <76 years; Italian, lived in province of Brescia	Hospital-based; 824 (686 men, 138 women), aged <76 years; no liver disease or cancer; frequency-matched with cases on age (±5 years), sex, date or hospital admission; from Brescia, Italia	Questionnaire; blood sample	*Men*			Age, residence, HBV, HCV markers	For women, categories of alcohol consumption above 80 g/day were omitted; higher levels of alcohol consumption (>81 g/day) associated with HCC in men.
				Non-drinkers	8	1.0 (reference)		
				1–20 g/day	24	2.3 (0.7–7.2)		
				21–40 g/day	27	0.9 (0.3–2.7)		
				41–60 g/day	44	1.6 (0.5–4.6)		
				61–80 g/day	33	2.4 (0.8–7.1)		
				81–100 g/day	62	4.2 (1.5–11.7)		
				101–120 g/day	47	7.7 (2.7–22.7)		
				121–140 g/day	48	9.8 (3.3–29.1)		
				>140 g/day	87	11.0 (3.9–31.0)		
				Women				
				Non-drinkers	24	1.0 (reference)		
				1-20 g/day	22	0.6 (0.2–1.7)		
				21-40 g/day	15	1.4 (0.4–5.4)		
				41-60 g/day	11	1.9 (0.4–8.1)		
				61-80 g/day	4	3.1 (0.3–29.7)		
				>80 g/day	8	16.5 (3.0–90.1)		

CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus

examination. Significantly higher relative risks were reported among heavy drinkers compared with non-, light or moderate drinkers in nine studies (Vall Mayans *et al*., 1990; Mohamed *et al*., 1992; Tanaka *et al*., 1992; La Vecchia *et al*., 1998; Donato *et al*., 2002; Yuan *et al*., 2004; Gelatti *et al*., 2005; Marrero *et al*., 2005; Franceschi *et al*., 2006). In these studies, the magnitude of the association ranged from 2.6 for intake of more than 100 g/day compared with 60 g/day or less (Gelatti *et al*., 2005); to 24.9 for those who consumed more than four drinks per day compared to those who consumed no drinks per day (La Vecchia *et al*., 1998). Tanaka *et al*. (1992) found a significant 1.7-fold increase in risk among men whose cumulative alcohol consumption was greater than 76.6 drink–years. No significant associations were observed among women. However, despite the number of studies that have demonstrated evidence of an association between heavy alcoholic beverage consumption and liver cancer, a clear, consistent dose–response relationship between light or moderate drinking and HCC risk has not yet been established.

2.5.3 *Meta-analyses (Table 2.26)*

Two meta-analyses have examined the association between alcoholic beverage consumption and liver cancer. A meta-analysis of 229 studies that evaluated the association between alcohol drinking and risk for cancer included data from 17 case–control and three cohort studies and 2294 cases of HCC. These 20 studies reported a direct trend in risk for HCC with increasing alcoholic beverage consumption. The reported relative risks were 1.17 (95% CI, 1.11–1.23) for consumption of 25 g alcohol per day, 1.36 (95% CI, 1.23–1.51) for 50 g per day and 1.86 (95% CI, 1.53–2.27) for 100 g per day (Bagnardi *et al*., 2001). An additional review of the Chinese literature included a meta-analysis of 55 case–control studies that investigated the risk factors for primary liver cancer in China. Twenty-two of these 55 studies assessed the effect of exposure to alcohol. A total of 3207 cases of primary liver cancer and 3983 controls were identified (Luo *et al*., 2005). The combined odds ratio reported from these 22 studies was 1.88 (95% CI, 1.53–2.32) for alcoholic beverage drinkers versus non-drinkers. No information regarding the dose–risk relationship was given. [The Working Group could not determine whether there was possible overlap between the individual cohort and case–control studies listed and the studies included in the meta-analyses conducted by Bagnardi *et al*. (2001) and Luo *et al*. (2005), because the individual studies included in the meta-analyses were not identified.]

2.5.4 *Interaction with hepatitis viral infection (Table 2.27)*

The impact of alcohol on primary liver cancer is difficult to measure because of the existence of other factors, in particular chronic infection with HBV and HCV—which have already been shown to be important determinants for HCC worldwide, and may modify the relationship between alcoholic beverage consumption and liver cancer.

Table 2.26 Meta-analyses of liver cancer and alcoholic beverage consumption

Reference, description, study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment	Comments
Luo *et al*. (2005); meta-analysis of 55 case–control studies from China	Database search of Chinese biomedical literature database (1979–2003), China Hospital Knowledge Database (1999–2003) and Medline (1966–2003); inclusion criteria were: case–control studies investigating risk factors for PLC in Chinese population.	22 studies assessed exposure to alcohol	Non-drinkers Drinkers	Not reported 3207	1.0 1.88 (1.53–2.32) $p<0.001$	Not reported	Studies of alcohol showed significant heterogeneity
Bagnardi *et al*. (2001); meta-analysis of 229 cohort and case–control studies	3 cohort and 16 case–control studies on liver cancer; total of 1961 cases	Exposure to alcohol	25 g/day 50 g/day 100 g/day		1.20 (1.13–1.27) 1.41 (1.26–1.56) 1.83 (1.53–2.19) p-trend <0.01	Gender	A gender effect was also observed (p-trend<0.05)

CI, confidence interval; PLC, primary liver cancer

Table 2.27 Selected cohort and case–control studies of liver cancer by alcoholic beverage consumption and infection with hepatitis B virus (HBV) and hepatitic C virus (HCV)

Study design	Odds ratio (95% CI) of risk for liver cancer by alcoholic beverage intake			
Cohort study				
Wang *et al*. (2003b)	*None*	*Light/moderate*		
HBV-negative	1	1.64 (0.74–3.64)		
HBV-positive	13.12 (7.82–22.01)	17.93 (9.58–33.68)		
Case–control studies				
Kuper *et al*. (2000a)	*None*	*<20 drinks/week*	*20–39 drinks/week*	*≥40 drinks/week*
HBV/HCV	1	1.0 (0.2–4.1)	1.4 (0.3–7.9)	5.4 (0.6–50.3)
No infection	1	0.7 (0.3–1.3)	0.6 (0.2–1.4)	1.6 (0.8–3.4)
Donato *et al*. (2002)		*<60 g/day*	*>60 g/day*	
No infection		1	7.0 (4.5–11.1)	
HCV		55.0 (29.9–101)	109 (50.9–233)	
HBV		22.8 (12.1–42.8)	48.6 (24.1–98.0)	
Yuan *et al*. (2004)		*<4 drinks/day*	*>4 drinks/day*	
No infection		1	2.6 (1.3–5.1)	
HBV/HCV		8.1 (4.6–14.4)	48.3 (11.0–212.1)	
Franceschi *et al*. (2006)		*<14 drinks/week*	*14–34 drinks/week*	*≥35 drinks/week*
No infection		1	0.68 (0.26–1.76)	4.96 (2.19–11.24)
HBV/HCV		28.82 (12.84–64.69)	47.6 (20.76–109)	74.36 (22.89–242)

CI, confidence interval

Chronic infections with HBV and HCV have been shown to increase the risk for HCC by approximately 20-fold (Parkin, 2006). Five studies examined the association between alcoholic beverage consumption and the risk for liver cancer among patients with chronic infection with HBV and HCV; one cohort study (Wang *et al*., 2003b) and four case–control studies (Kuper *et al*., 2000a; Donato *et al*., 2002; Yuan *et al*., 2004; Franceschi *et al*., 2006). The cohort study reported a relative risk of 13.12 among non-drinkers with chronic HBV infection. Light to moderate drinking and heavy drinking further increased the relative risk to 17.93. All four case–control studies showed an increased risk for HCC with increased alcoholic beverage consumption among subjects infected with HBV or HCV. Three of these studies showed a significant increase in risk. However, the study by Kuper *et al*. (2000a), based on 333 cases of HCC and 360 controls, did not indicate the same significant trend in increased risk for HCC.

2.5.5 *Interaction with tobacco smoking*

The interaction between alcoholic beverage consumption and tobacco smoking—another recognized risk factor for HCC (IARC, 2004)—was considered in case–control studies in Greece (Kuper *et al*., 2000a) and the USA (Yuan *et al*., 2004; Marrero *et al*., 2005). In the Greek study (Kuper *et al*., 2000a), the relative risk was 5.6 (95% CI, 1.70–19.0) for heavy drinkers and heavy smokers compared with never smokers and non- and light drinkers. In a US dataset (Marrero *et al*., 2005), the relative risk was 7.2 (95% CI, 2.2–14.1) for combined exposure to alcoholic beverages and tobacco compared with cirrhotic subjects. In another US dataset (Yuan *et al*., 2004), the corresponding relative risk for exposure to both factors was 5.9 (95% CI, 3.3–10.4).

2.6 Breast cancer

Overall, more than 100 epidemiological studies—two thirds case–control and one third cohort—have evaluated the association between the consumption of alcoholic beverages and the risk for breast cancer. In addition, two pooled analyses, the largest of which included data from more than 50 studies, have been conducted. For ease of presentation, the data from the individual studies that were included in this pooled analysis are not presented in Tables 2.28 or 2.29, except for studies that examined detailed exposure effects, such as duration of alcoholic beverage consumption, that were not considered in the pooled analysis.

2.6.1 *Pooled and meta-analyses*

The pooling of data from many epidemiological studies permits the use of uniform definitions across studies and reduces the inevitable statistical variability in the findings from one study to another. This is particularly important when the associated risks are relatively small and individual studies lack statistical power. Hamajima *et al*.

(2002) (The Collaborative Group on Hormonal Factors on Breast Cancer) collated and re-analysed individual data from 53 studies on 58 515 women who had breast cancer, which constituted most of the evidence available worldwide at that time. Results from this pooled analysis showed a linear increase in risk for breast cancer with increasing levels of alcoholic beverage consumption, with a relative risk of 1.46 (95% CI, 1.34–1.60) for women who drank ≥ 45 g alcohol per day (median, 58 g per day) compared with non-drinkers. This corresponds to an increase of 7.1% (95% CI, 5.5–8.7%) per 10 g per day (Table 2.28; see Figure 2.1). The results were consistent across studies and between cohort and case–control studies included in the analysis (Figure 2.2).

A previous meta-analysis of 38 case–control and cohort studies (Longnecker, 1994), most of which were included in the Collaborative Group analysis, and a pooled analysis of six cohort studies, based on 4330 incident cases of breast cancer (Smith-Warner *et al*., 1998), reported results consistent with the findings of the Collaborative Group (Hamajima *et al*., 2002). The latter study showed a 9% increase in risk per 10 g intake of alcohol per day (8% after correction for measurement error), which was adjusted for a wide range of potential confounding factors (Smith-Warner *et al*., 1998).

2.6.2 *Additional cohort studies*

Two cohort studies were conducted among women who had a high intake of alcoholic beverages; both were conducted in Sweden and reported a significant increase in incidence rates for breast cancer among alcoholics compared with national incidence rates (Sigvardsson *et al*., 1996; Kuper *et al*., 2000b) (Table 2.29). However, neither of these studies provided information on individual exposures, or adjusted for potential confounders.

The majority of the 21 additional cohort studies conducted in the general population also showed an increase in risk for breast cancer with increased alcoholic beverage consumption (Table 2.30). The largest of these studies, conducted by the European Prospective Investigation into Cancer and Nutrition (EPIC) and based on 4300 cases, reported a significant 13% increase in risk for breast cancer for intakes of ≥ 20 g alcohol per day, which corresponds to an increase in risk of 3% per 10 g intake of alcohol per day (95% CI, 1–5%) (Tjønneland *et al*., 2007).

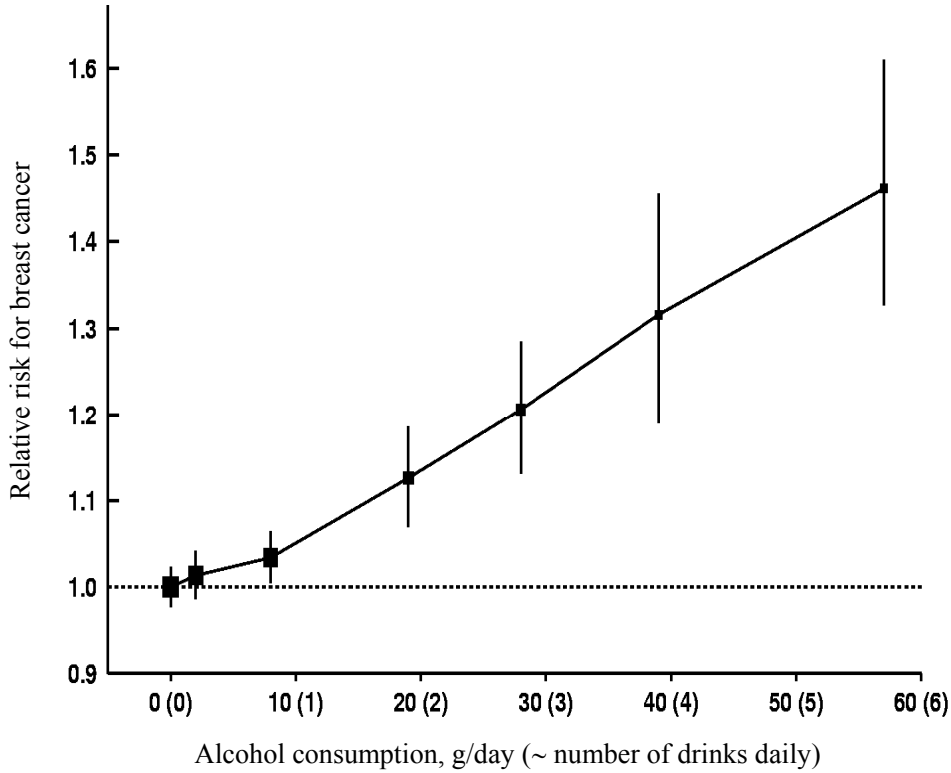
2.6.3 *Additional case–control studies*

The majority of the 35 case–control studies that were not included in the pooled analyses have reported positive associations with increasing alcoholic beverage intake, which were statistically significant in 14 studies (Table 2.31).

2.6.4 *Measurements of alcoholic beverage intake*

Taken together, all of the results from these studies suggest that low to moderate alcoholic beverage intake (i.e. in the order of one drink per day) is associated with

Figure 2.1. Relative risk for breast cancer in relation to reported alcoholic beverage consumption (adjusted by study, age, parity, age at first birth and tobacco smoking).
Pooled analysis of data from 53 studies that included 58 515 women with breast cancer



From Hamajima *et al.* (2002)

Figure 2.2. Details of and results from studies on the relation between alcohol consumption and breast cancer. Relative risks are stratified by age, parity, age at first birth and smoking history.

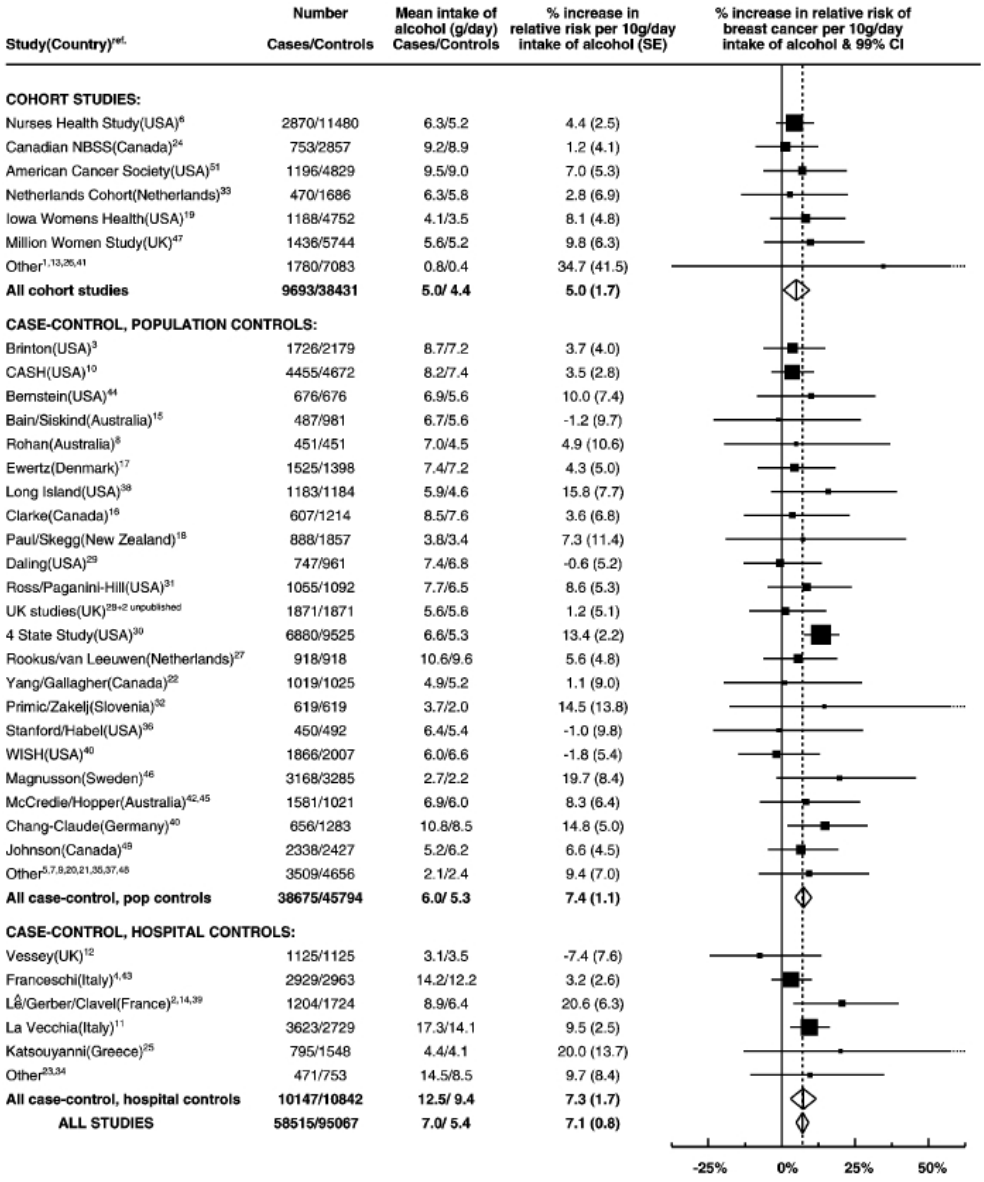


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Table 2.28 Pooled and meta-analyses of female breast cancer and alcoholic beverage consumption

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Longnecker (1994)	Meta-analysis of 38 case–control and cohort studies	Varied	*Alcohol intake (drinks/day)* Non-drinker 1 2 3	Not stated	 1.0 1.11 (1.07–1.16) 1.24 (1.15–1.34) 1.38 (1.23–1.55)	As defined per study	Variation across studies found
Smith-Warner *et al*. (1998), pooling project	Pooled analysis of six cohort studies; 322 647 women followed up for up to 11 years; 4335 cases of invasive breast cancer identified	Self-administered questionnaire	*Average intake (g/day)* Non-drinker >0–<1.5 1.5–4.9 5.0–14.9 15–29.9 30–59.9 ≥60 *p* for trend *Per 10 g/day* Uncorrected Corrected Beer Wine Spirits	 1462 680 882 727 360 194 30	 1.0 1.07 (0.96–1.19) 0.99 (0.90–1.10) 1.06 (0.96–1.17) 1.16 (0.98–1.38) 1.41 (1.18–1.69) 1.31 (0.86–1.98) <0.001 1.09 (1.04–1.13) 1.08 (1.0–1.16) 1.11 (1.04–1.19) 1.05 (0.98–1.12) 1.05 (1.01–1.10)	Age at menarche, parity, age at first birth, menopausal status, history of benign breast disease, hormone replacement therapy use, oral contraceptive use, family history, smoking, education, body mass index, height, fat intake, fibre intake, energy intake	Correction for measurement error made little difference to the estimate; similar associations found for beer, wine and spirits; no difference by subgroup of menopausal status, family history, hormone-replacement therapy use or body mass index

Table 2.28 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Bagnardi *et al.* (2001)	Meta-analysis of 49 studies (12 cohort, 37 case–control, with a total of 44 033 cases)	Varied	*Alcohol intake (g/day)* 25 50 100	244 033	 1.31 (1.27–1.36) 1.67 (1.56–1.78) 2.71 (2.33–3.08)	As per study	Significant heterogeneity between the studies
Hamajima *et al.* (2002), Collaborative Group on Hormonal Factors in Breast Cancer	Pooled analysis of 53 case–control and cohort studies; 58 515 invasive breast cancers; 95 067 controls	Varied	*Alcohol intake (g/day)* 0 <5 5–14 15–24 25–34 34–44 ≥45 Increase per 10 g/day	58 515	Relative risk (floated SE) 1.0 (0.012) 1.01 (0.014) 1.03 (0.015) 1.13 (0.028) 1.21 (0.036) 1.32 (0.059) 1.46 (0.060) 7.1% (SE, 0.8%)	Study, age, parity, age at first birth, smoking	No differences by subgroup of age at diagnosis, race, family history, menopausal status, parity, age at first birth, breastfeeding, education, age at menarche, height, weight, hormone replacement therapy use, oral contraceptive use, smoking
	Pooled analysis of 42 case–control studies		*Increase per 10 g/day* Population controls Hospital controls	 38 675 10 147	 7.4% (SE, 1.1%) 7.3% (SE, 1.7%)		
	Pooled analysis of 11 cohort studies		Increase per 10 g/day	9 693	5.0% (SE, 1.7%)		

CI, confidence interval; SE, standard error

Table 2.29 Cohort studies of breast cancer and alcoholic beverage consumption among special populations

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Standardized incidence ratio (95% CI)	Adjustment factors	Comments
Sigvardsson *et al.* (1996), Sweden, Alcoholics	Analytical cohort of 15 508 alcoholics (identified via Temperence Board records) in 1944–77; comparison group of 15 500 women, matched by age and region (identified via population register); follow-up not stated; 268 cases identified through cancer registry	Alcoholics	Comparison group (expected) Alcoholics (observed)	191 268	1.0 1.4 (1.2–1.7)	Age, region	Excluded ~6000 older women with no identification number; large changes in alcohol availability and attitudes during follow-up; not adjusted for potential confounders; no individual exposure data
Kuper *et al.* (2000b), Sweden, Hospital Discharge Records for Alcoholism	Analytical cohort of 36 856 women diagnosed with alcoholism from hospital discharge data, 1965–95; compared with national incidence rates; matched by age, sex, calendar time; excluding first year of follow-up; 514 cases identified through cancer registry	Hospital discharge related to alcoholism	National rates (expected) Alcoholics (observed)	Not stated 514	1.0 1.15 (1.05–1.25)	Age, sex, calendar time	No individual exposure information; no adjustment for potential confounders; no association found with age at diagnosis or menopausal status

CI, confidence interval

Table 2.30 Cohort and nested case–control studies of breast cancer and alcoholic beverage consumption in the general population

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Schatzkin *et al.* (1987), USA, NHANES I Epidemiologic Follow-up Study	Analytical cohort of 7188 women, aged 25–74 years; recruited 1971–75; median follow-up, 10 years; 121 cases identified through hospital records or death certificates	Interviewer-administered questionnaire	*Intake (g/day)* Non-drinker Any >0–1.2 1.3–4.9 ≥5	 57 64 25 19 20	 1.0 1.5 (1.1–2.2) 1.4 (0.9–2.3) 1.5 (0.9–2.6) 1.6 (1.0–2.7)	Age	Results presented for age-adjusted relative risks only; multivariate adjustment gave similar results, but based on fewer numbers (complete-case analysis); risk for any drinking versus none higher among younger versus older women, pre- versus post-menopausal women and lean versus overweight women; no differences in risk by subgroup of age at first birth, parity, age at menarche, family history, fat intake, smoking

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Dupont & Page (1985), USA, Nashville hospitals (retrospective cohort study)	Analytical cohort study of 3303 women with benign breast disease (100% histological confirmation); aged >20 years; recruited 1958-68 (response rate 84%); follow-up for a median of 17 years; 135 cases identified from death certificates and verified by pathology records	Self-administered questionnaire to patients or their next-of-kin; or via telephone interview.	*Alcohol* No Yes	 76 37	 1.3 (1.1–1.7) 1.7 (1.2–2.3)	Age, length of follow-up	Risk compared to women in the Third National Cancer Survey (Atlanta); mortality only; cohort of women with benign breast disease
Garfinkel *et al.* (1988), USA, American Cancer Society	Analytical cohort of 581 321 women across the USA, 1959–60, aged ≥30 years; mortality follow-up until 1972; 2933 deaths identified from death certificates	Self-administered questionnaire	*Intake (drinks/day)* None Occasional 1 2 3 4 5 ≥6	 2334 153 236 110 45 23 12 20	 1.00 1.00 (0.82–1.13) 1.18 (1.03–1.36) 1.06 (0.86–1.30) 1.28 (0.95–1.74) 1.36 (0.90–2.07) 2.10 (1.18–3.72) 1.60 (1.00–2.56)	Age, education, age at first birth, family history, meat intake, smoking	Based on mortality only

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Simon *et al.* (1991), USA, Tecumseh Community Health Study	Analytical cohort of 1954 women recruited in 1959–60, aged ≥21 years years; follow-up for 28 years; 87 self-reported cases verified by pathology and medical records	Interviewer-administered questionnaire	Overall *No. of drinks/day* Never Former 0–<1 1–1.9 ≥2	87	 1.0 0.93 (0.40–2.18) 1.08 (0.64–1.82) 1.23 (0.49–3.10) 1.12 (0.25–5.01)	Age, body mass index, subscapular and triceps skinfold measurements, education, smoking, family history, age at menarche, parity, age at first birth	No difference in risk by menopausal status (but low numbers)
Høyer & Engholm (1992), Denmark, Glostrup Population Study	Analytical cohort of 5207 women recruited 1964–86, aged 30–80 years; follow-up until 1989; 51 cases identified through registry	Self-administered questionnaire	*Intake (drinks/week)* 0 1–3 4–8 ≥9 *p* for trend	51	 1.0 0.7 (0.3–1.6) 1.3 (0.7–2.5) 0.8 (0.3–2.0) 0.2	None stated	

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Boice *et al.* (1995), USA, American Registry of Radiologic Technologists	Nested case–control study of 79 016 women recruited 1926–82, aged 23–90 years; follow-up for mean of 29 years; 528 cases matched with 2628 controls on age, year of diagnosis, follow-up time	Self-administered questionnaire	*Intake (drinks/week)*			Age at menarche, age at menopause, age at first birth, family history, breast biopsy	
			None	133	1.0		
			<1	183	0.86 (0.67–1.10)		
			1–6	135	0.91 (0.69–1.20)		
			7–13	57	0.86 (0.61–1.22)		
			≥14	13	2.12 (1.06–4.27)		
			Unknown	7	1.91 (0.74–4.92)		

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Holmberg *et al.* (1995); Suzuki *et al.* (2005), Sweden, Swedish Mammography Cohort	Holmberg *et al.* (1995): nested case–control study of screening cohort, recruited 1987–90, aged 40–70 years; 380 cases ascertained through pathology departments and screening programme (response rate, 73%); 525 controls matched by age, date of diagnosis, region (response rate, 86%)	Self-administered questionnaire	Never Ever *Intake (g/day)* Never <0.76 0.76–2 ≥2	71 205 71 54 79 72	1.0 1.7 (0.2–2.4) 1.0 1.2 (0.8–1.8) 1.9 (1.2–2.9) 1.6 (1.0–2.4)	Family history, parity, age at first birth, education, body mass index	Stronger association for ever versus never drinking in women >50 versus <50 years; risk increased with increasing duration of drinking; no significant association with age at first started drinking

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Holmberg *et al.* (1995); Suzuki *et al*. (2005) (contd)	Suzuki *et al*. (2005): analytical cohort of 51 847 women, recruited 1987–90, aged 55–70 years;; follow-up until 2004 through cancer registry, verified by pathology and medical records; 1284 cases		*Intake in last 6 months (based on intake in 1987 and 1997; g/day)* None <3.4 3.4–9.9 ≥10 *p* for trend	 314 476 343 151	 1.0 1.08 (0.94–1.25) 1.10 (0.94–1.29) 1.43 (1.16–1.76) 0.012	Age, body mass index, height, education, parity, age at first birth, age at menarche, age at menopause, type of menopause, oral contraceptive use, hormone replacement use, family history, benign breast disease, energy intake, fibre and fat intake	Results also by receptor status (see accompanying table)

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Goodman *et al.* (1997a), Japan, Life Span Study	Analytical cohort of 22 000 residents of Hiroshima and Nagasaki in 1945, recruited 1979–1981, age range not stated; follow-up until 1989; 161 cases identified through cancer registry; 98% histologically confirmed	Self-administered questionnaire	*Alcohol use* Never Drinker	 106 40	 1.0 0.91 (0.61–1.31)	City, age, age at the time of the bombings, radiation dose to the breast	No association in women who drank beer, sake or other alcoholic beverages
Lucas *et al.* (1998), USA, Study of Osteoporotic Fractures	Analytical cohort of 7250 women recruited 1986–88, aged ≥65 years; follow-up 3 years after interview; 104 self-reported cases confirmed by medical records or through cancer registry	Self-administered questionnaire administered 1 year after recruitment; alcoholic beverage intake adjusted for atypical drinking (i.e. heavy drinking in past 30 days)	*Average no. of drinks per week* None <2 2–7 ≥8	 21 38 17 8	*No family history of breast cancer* 1.0 1.13 (0.66–1.93) 1.41 (0.74–2.67) 1.70 (0.75–3.84)	No adjustment	Includes 4 cases with in-situ cancer; no association in women with a positive family history, but few cases (n=20)

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Zhang *et al.* (1999), USA, Framingham Study	Analytical cohort of 2764 women recruited in 1948, aged 28–62 years; plus 2284 recruited in 1971 in offspring cohort; follow-up until 1993; 287 cases (221 in original cohort, 66 in offspring cohort) identified through hospital admissions data and death certificates; verified from pathology and medical records (98% in original cohort and 100% in offspring cohort)	Self-administered questionnaire; intake assessed at several time points	*Average intake (g/day)* None 0.1–4.9 5–14.9 ≥15	 69 110 55 53	 1.0 0.8 (0.6–1.1) 0.7 (0.5–1.1) 0.7 (0.5–1.1)	Age, education, height, body mass index, physical activity, age at first birth, parity, age menarche, age at menopause, smoking, hormone replacement therapy use	Similar risks for each cohort separately; no association with type of drink

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Vachon *et al.* (2001), USA, Minnesota Breast Cancer Family Study	Cohort of 426 families with breast cancer (probands, family members and their spouses; *n*=9032), recruited 1944–52, aged ≥18 years; follow-up until 1990; 558 cases identified from self-report and through death certificates	Telephone interviews (surrogate and self-reported)	Overall *Lifetime intake* Never < Weekly Weekly Daily	558	 1.0 1.23 (1.00–1.51) 1.14 (0.86–1.51) 1.28 (0.85–1.91)	Age, birth cohort, familial clustering, type of respondent, smoking	Higher risk in first-degree relatives for daily versus never drinkers; validation study verified 136 of 138 breast cancers through medical and pathology records
Tjønneland *et al.* (2003, 2004), Denmark, Diet, Cancer and Health Study	Analytical cohort of 23 778 women, recruited 1993–97, aged 50–64 years; follow-up until 2000; 425 cases identified through registry	Self-administered questionnaire	*Intake (g/day)* None <6 6–12 13–24 25–60 ≥61 Occasional	 10 122 9 93 93 9 9	 1.21 (0.64–2.31) 1.0 0.97 (0.74–1.28) 1.18 (0.90–1.56) 1.45 (1.10–1.92) 1.35 (0.68–2.66) 1.32 (0.67–2.60)	Parity, age at first birth, benign breast disease, education, hormone replacement therapy use and duration, body mass index.	No significant difference by beverage type or frequency of intake (days per week) for a given alcohol intake; association for 10 g/day intake similar by hormone replacement therapy use, although only significant in past users.
			Recent intake (per 10 g/day)	423	1.09 (1.00–1.18)	As above plus intake earlier in life	No association with intake earlier in life or cumulative intake

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Dumeaux *et al.* (2004), Norway, Norwegian Women and Cancer Study	Analytical cohort of 86 948 women recruited 1991–97, aged 30–70 years; follow-up until 2001; 1130 cases identified through registries and death certificates	Self-administered questionnaire	*Intake in last year (g/day)* None 0.1–4.9 5–9.9 ≥10 *p* for trend	 244 554 188 96	 1.0 1.24 (1.06–1.44) 1.35 (1.11–1.64) 1.69 (0.32–2.15) <0.0001	Age, breast screening, age at menarche, parity, age at first birth, family history, menopausal status, hormone replacement therapy use, body mass index	Interaction with oral contraceptive use; increased risk among long-term users who consumed >10 g/day alcohol versus non-drinkers who had never used oral contraceptives; stronger association for high alcohol intake (≥10 g/day) in post- versus pre-menopausal women

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Horn-Ross *et al.* (2004), USA, California Teachers Study	Analytical cohort of 103 460 women recruited 1995–96, aged 21–84 years; follow-up until 2001; 1742 invasive cases, ascertained through cancer registry and death certificates	Self-administered questionnaire	*Intake in past year (g/day)*		*Pre-/ perimenopausal*	Age, race, energy intake, family history, age at menarche, parity, age at first birth, physical activity, body mass index, hormone replacement use and duration	Overall risk ≥20 g/day versus none, 1.28 (1.06–1.54); differences by menopausal status not significant; no clear pattern for age at started drinking; increased risk for ≥20 g/day among ever users of hormone replacement therapy versus non-drinkers who were never users; increased risk for ≥20 g/day among postmenopausal women who had a history of benign breast disease versus non-drinkers with no benign breast disease; no differences by subgroups of family history, body mass index, parity, physical activity
			Non-drinkers	95	1.0		
			<5	53	0.93 (0.66–1.30)		
			5–9	55	1.05 (0.75–1.47)		
			10–14	42	1.09 (0.75–1.57)		
			15–19	27	1.28 (0.83–1.97)		
			≥20	23	1.21 (0.76–1.92)		
					Postmenopausal		
			Non-drinkers	311	1.0		
			<5	181	1.03 (0.86–1.24)		
			5–9	150	1.04 (0.86–1.27)		
			10–14	126	1.08 (0.88–1.33)		
			15–19	82	0.91 (0.71–1.16)		
			≥20	123	1.32 (1.06–1.63)		

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Mattisson *et al.* (2004), Sweden, Malmö Diet and Cancer Cohort	Analytical cohort of 11 726 women, recruited 1991–96, aged ≥50 years; follow-up until 2001; 342 cases (312 invasive; 30 *in situ*) identified through cancer registry	Interviewer-administered diet history (7-day diary)	*Intake (g/day)* None <15 15–29 ≥30	 22 257 39 11	 0.89 (0.57–1.39) 1.0 0.88 (0.62–1.24) 1.68 (0.91–3.12)	Interviewer, method version, season, age, energy, change in dietary habits, height, waist, hormone use, age at first birth, age at menarche, physical activity, smoking, education	Adjustment for energy from fat made little difference; association with high intake of wine (>20.8 cl/day versus <2.9 cl/day, relative risk for 2.1; 95% CI, 1.24–3.60)

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Petri *et al.* (2004), Denmark, Copenhagen City Heart Study and Glostrup Population Study (data for Glostrup Study also presented in Høyer & Engholm, 1992)	Analytical cohort of 13 074 women, aged 20–97 years; dates of recruitment not stated; followed-up until 1996; 473 cases identified through cancer registry	Self-administered questionnaire	*Average intake (drinks/week)*			Age, cohort, parity, hormone replacement therapy use	No difference by beverage type overall; stronger association for high intakes among premenopausal women, but based on very small numbers; positive association for spirits in postmenopausal women, but not for wine or beer (but again based on small numbers)
			<1	148	0.91 (0.73–1.13)		
			1–6	207	1.0		
			7–13	72	1.11 (0.85–1.45)		
			14–27	36	1.10 (0.77–1.57)		
			≥28	10	1.19 (0.58–2.41)		
			Premenopausal				
			<1	17	1.17 (0.66–2.07)		
			1–6	36	1.0		
			7–13	12	1.22 (0.66–2.25)		
			14–27	5	0.86 (0.33–2.21)		
			≥28	6	3.49 (1.36–8.99)		
			Postmenopausal				
			<1	131	0.87 (0.69–1.10)		
			1–6	171	1.0		
			7–13	60	1.09 (0.81–1.47)		
			14–27	31	1.15 (0.78–1.69)		
			≥28	4	0.57 (0.18–1.78)		

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Baglietto *et al.* (2005), Australia, Melbourne Collaborative Cohort Study	Analytical cohort of 17 447 women recruited 1990–94, aged 40–69 years; follow-up until 2003; 537 cases identified through registries and histologically verified	Structured interview	*Intake in last year (g/day)* Never Former 1–19 20–39 ≥40	 171 16 286 43 21	 1.0 1.03 (0.62–1.73) 1.12 (0.93–1.36) 0.87 (0.62–1.22) 1.41 (0.90–2.33)	Age, energy and folate intake	Adjustment for education, body mass index, age at menarche, parity, hormone replacement therapy, multivitamins had little effect; stronger association for high alcohol intake (≥40 g/day) among women with low folate intake; no association with alcoholic beverages at higher folate intake
Lin *et al.* (2005), Japan, Japanese Collaborative Cohort	35 844 women recruited 1988–90, aged 40–79 years; follow-up until 1997; 151 cases ascertained through registries	Self-administered questionnaire	*Current intake (g/day)* Non-drinker Former drinker Current 0.1–4.9 5–14.9 ≥15 *p* for trend	151 103 3 45 13 5 11	 1.0 0.82 (0.20–3.33) 1.27 (0.87–1.84) 1.07 (0.57–2.00) 0.83 (0.34–2.04) 2.93 (1.55–5.54) 0.01	Age, body mass index, study area, family history, walking, hormone replacement therapy, age at menarche, parity, age at first birth, age at menopause	Significant association for binge drinking (>23 g/day on one occasion); no association for age at started drinking or frequency of consumption

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Hirvonen *et al.* (2006), France, Supplementation and Vitamins and Minerals Antioxidant Study	Analytical cohort of 4396 women recruited in 1994, aged 35–60 years; followed-up until 2002; 95 cases identified through clinical examination every 2 years and via self-report; validated through medical and pathology records	3 or more telephone-administered 24-hour recalls completed during the first year following recruitment	*Red wine (mL/day)* 0 1–149 ≥150 *p* for trend *White wine or rose (mL/day)* 0 1–149 ≥150 *p* for trend	 39 25 31 62 14 19 	 1.0 1.06 (0.64–1.76) 1.24 (0.76–2.03) 0.39 1.0 0.87 (0.49–1.56) 1.09 (0.64–1.84) 0.88	Age, smoking, parity, oral contraceptive use, family history, menopausal status	
Stolzenberg-Solomon *et al.* (2006), USA, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	Analytical cohort of 25 400 women, recruited 1993–2001 into screening arm, aged 55–74 years; follow-up until 2003; 691 self-reported cases (including 96 *in situ*), 72% verified by pathology and medical records, and through cancer registry	Self-administered questionnaire	*Intake (g/day)* <0.01 >0.01–0.43 >0.43–1.39 >1.39–7.62 >7.62 *p* for trend	 104 138 158 118 173 	 1.0 1.23 (0.95–1.58) 1.20 (0.94–1.54) 0.97 (0.75–1.26) 1.37 (1.08–1.76) 0.02	Age, education (best fit model)	Stronger association for high alcohol intake (>7.62 g/day) among women with low folate intake; no association with alcoholic beverages at higher folate intake

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Tjønneland *et al.* (2007), European Prospective Investigation into Cancer and Nutrition	Analytical cohort of 274 688 women, recruited 1993–2000, aged 35–70 years; follow-up for 6.4 years; 4285 incident cases (all invasive) identified through registries and active follow-up	Self-administered questionnaire	*Recent intake (g/day)*			Height, weight, age at menarche, parity, oral contraceptive use, hormone replacement use, menopausal status, smoking, education	No differences by subgroups of body mass index or hormonal replacement therapy use; no association for age started drinking; similar association for wine, beer and spirits
			None	612	1.01 (0.91–1.13)		
			>0–1.5	701	1.0		
			1.6–4.7	723	0.98 (0.89–1.09)		
			4.8–10	731	0.97 (0.88–1.08)		
			10.1–19	759	1.07 (0.96–1.19)		
			≥20	765	1.13 (1.01–1.25)		
			20–23.6	211	1.08 (0.92–1.26)		
			23.7–29.9	154	1.03 (0.86–1.23)		
			30–37.1	194	1.36 (1.15–1.60)		
			≥37.2	206	1.09 (0.93–1.28)		
			Increase per 10 g/day		1.03 (1.01–1.05)		
			Lifetime alcohol				
			Increase per 10 g/day		1.02 (0.99–1.06)		

CI, confidence interval

Table 2.31 Case–control studies of breast cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Williams & Horm (1977), USA, Third National Cancer Survey, 1969–71	7518 (all sites, men and women), aged ≥35 years; histological confirmation not stated; 57% randomly selected	Randomly selected patients with cancer of other non-related sites	Interviewer-administered questionnaire	*Total alcohol (oz/year)* None 1 2	 1.0 1.28 (significant) 1.55 (significant)	Age, race, smoking	Increased risk for wine (low intake only) and hard liquor (low and high intake); no association with beer
Byers & Funch (1982), New York, USA, 1957–65	1314, aged 30–69 years; all admitted to hospital; response rate not stated	770 hospital-based (non-malignant); not matched; response rate not stated	Interviewer-administered questionnaire	*Drinks/month* Never Former <3 3–8 9–25 ≥26	 1.0 0.59 1.11 1.02 1.09 1.13 all non-significant	Age	No differences by type of drink; no association for lifetime alcoholic beverage intake; few heavy drinkers
Rosenberg *et al.* (1982), Canada, Israel, USA, 1976–80	1152, aged 30–69 years; verification by hospital discharge records or pathology records; response rate, 94% overall (cases and controls)	2702 hospital-based (519 endometrial/ovarian cancer; 2702 non-malignant); matching criteria not stated	Interviewer-administered questionnaire	*Intake in previous year (days/week)* Never Former <4 ≥4	 1.0 1.6 (1.1–2.4) 1.9 (1.5–2.4) 2.5 (1.9–3.4)	Age, region	Results presented using non-malignant controls; similar association using cancer controls; increased risk seen for beer, wine and spirits among regular drinkers

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Begg *et al.* (1983), Canada, USA, 1982, survey of cancer patients	997 overall (cases and controls); response rate not stated	730 hospital-based (other cancers excluding head and neck and uncertain origin); matching criteria not stated	Interviewer-administered questionnaire	*Drinks/week* None 1–7 >7	 1.0 0.9 (0.8–1.1) 1.4 (0.9–2.0)	Age, smoking	
O'Connell *et al.* (1987), North Carolina, USA, 1977–78	276, aged ≥30 years; 100% histologically confirmed; response rate, 93%	1519 population-based (selected from a stratified sample of households); response rate, 85%	Interviewer-administered questionnaire	*Usual intake (drinks/week)* None or <1 ≥1	 1.0 1.45 (0.99–2.12)	Age, race, smoking, hormone replacement therapy use, oral contraceptive use	Higher risk in white versus black women, and in pre- versus postmenopausal women
Harris & Wynder (1988) 20 sites, USA, 1969–84	1467, ages not stated; verified by medical records and pathology reports; response rate not stated	10 178 hospital-based (non-malignant and not related to alcohol or tobacco); matched by age; response rate not stated	Interviewer-administered questionnaire	*Usual intake (g/day)* Never <5 5–15 >15	 1.0 1.03 0.97 0.96	Education, occupation, marital status, smoking, age at diagnosis, year of interview	No association by subgroup of body mass index

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Cusimano *et al.* (1989a), Sicily, 1983–85	143, aged ≥30 years; 100% histologically confirmed; response rate, 68%	260 hospital-based (non-malignant); matched by age, health service; response rate, 91%	Interviewer-administered questionnaire	No Yes	1.0 1.68 (1.10–2.56)	Socioeconomic status	Stronger association in women with a family history of breast cancer
Kato *et al.* (1989), Japan, 1980–86	1740, aged ≥20 years; ascertained through registry; response rate not stated	8920 hospital-based (other cancers not related to alcohol); not matched; response rate not stated	Not stated; exposure information obtained at the hospital	<Daily Daily *p* for trend	1.0 1.35 (1.01–1.80) <0.01	Age, smoking, marital status, residence, occupation, family history	Higher risk for post- versus premenopausal women, and for beer versus sake or whisky
Iscovich *et al.* (1989), Argentina, 1984–88	150, all ages; 100% histologically confirmed; response rate, 99%	150 population-based (same neighbourhood, not on a special diet) and hospital-based (in- and out patients); matched by age; response rate not stated	Interviewer-administered questionnaire	*Quartile of intake* 1 2 3 4	 1.0 0.37 1.10 0.60		Results presented for population controls; similar results when using hospital-based controls

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Toniolo *et al*. (1989), Italy, 1983–86	250, aged 25–75 years; 100% histologically confirmed; response rate, 91%	499 population-based (electoral roll); matched by age; response rate, 79%	Interviewer-administered questionnaire	*Usual intake (g/day)* None >0–10 >10–20 >20–30 >30–40 >40 *p* for trend	 1.0 0.9 (0.5–1.5) 1.2 (0.7–1.9) 1.0 (0.7–1.6) 1.2 (0.6–2.4) 1.6 (0.9–2.9) 0.17	Age, body mass index, menopausal status, non-alcohol energy intake	Increased risk also for wine-only drinkers; few women with high intakes (>30 g/day)
Van't Veer *et al*. (1989), Netherlands, 1985–87	120, aged 25–44 years (*n*=47) and 55–64 years (*n*=73); 96% histologically confirmed; response rate, 80%	164 population-based (population registry surrounding hospitals); matched by age; response rate, 55%	Interviewer-administered questionnaire	*Usual intake (g/day)* *Premenopausal* None 1–4 5–14 15–29 ≥30 ≥30 vs 1–4 *p* for trend *Postmenopausal* None 1–4 5–14 15–29 ≥30 30 vs 1–4 *p* for trend	 1.0 0.3 (0.0–1.7) 0.5 (0.1–2.9) 0.8 (0.1–4.9) 2.3 (0.3–19.1) 8.5 (1.1–65.1) 0.04 1.0 0.8 (0.3–2.3) 1.0 (0.3–3.6) 1.1 (0.3–4.3) 0.9 (0.2–4.5) 1.1 (0.5–2.4) 0.37	Age, region, season, reproductive factors, education, family history, smoking, body mass index, fat intake	Increased risk if started drinking aged <25 years versus older ages, and in post- versus premenopausal women

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Young (1989), Wisconsin, USA, 1981–82	277, aged 35–89 years; identified through hospital registry; response rate, 64%.	372 population-based (drivers' licence records); response rate, 57%; 433 hospital-based; (no alcohol-related disease); matched by age; response rate, 61%	Self-administered questionnaire	*Drinks/week aged 18–35 years* None 1–5 ≥6 *Drinks/week aged >35 years* None 1–5 ≥6	 1.0 1.74 (1.37-2.21) 3.17 (2.20-4.57) 1.0 1.13 (0.87–1.46) 2.67 (1.91–3.71)	None; adjustments made little difference	Results presented using population controls; weaker, but still significant association when cancer controls used; slightly stronger association if started drinking <35 years
Nasca *et al.* (1990) NY State, USA, 1982–84	1617, aged 20–79 years; verified by pathology reports; response rate, 79%	1617 population-based (drivers' licence files); matched by age, region; response rate, 72%	Interviewer-administered questionnaire (telephone)	*Usual intake (g/day)* None <1.5 1.5–4.9 5.0–14.9 ≥15	 1.0 1.07 (0.83–1.36) 1.04 (0.78–1.39) 1.10 (0.87–1.39) 1.26 (0.98–1.64)	Age, race, age at first birth, menopausal status, benign breast disease, family history	Increased risk for later age at starting (i.e. ≥31 years); no association for duration of use

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Zaridze *et al.* (1991), Moscow, 1987–89	139, aged <41–≥71 years; verification not stated; response rate, 99%	139 hospital-based (outpatients); matched by age, region; response rate, 94%	Interviewer-administered questionnaire	*Alcohol intake (g/week)* *Premenopausal* 0 <0.93 0.93–2.12 2.13–6.46 ≥6.46 *p* for trend *Postmenopausal* 0 <0.93 0.93–2.12 2.13–6.46 ≥6.46 *p* for trend	 1.0 4.60 (0.46–46.14) 4.58 (0.38–55.89) 6.37 (0.72–56.34) 7.98 (0.79–80.47) 0.08 1.0 2.26 (0.66–7.76) 7.06 (1.70–29.40) 3.10 (0.83–11.55) 0.78 (0.06–8.89) 0.003	 Age at menarche, age at first birth Age at menarche, education	
Harris *et al.* (1992), New York, USA, 1987–89	604, all ages; verified by pathology and medical records; response rate not stated	520 hospital-based (unrelated to risk factors); matched by age, date of diagnosis, hospital; response rate not stated	Interviewer-administered questionnaire	*Premenopausal (n=192)* 0 g/day 1–15 g/day ≥16 g/day *Postmenopausal (n=412)* 0 g/day 1–15 g/day ≥16 g/day	 1.0 1.2 (0.7–1.9) 0.7 (0.3–1.5) 1.0 1.1 (0.8–1.6) 0.8 (0.5–1.3)	Age, family history, age at menarche, parity, age at first birth, breastfeeding, smoking, oral contraceptive use	

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Kato *et al.* (1992d), Japan, 1990–91	908, aged ≥20 years; 100% histologically confirmed; response rate not stated	908 (244 breast cancer screening and 664 hospital-based [including benign breast disease and excluding hormone-related cancers]); matched by age; response rate not stated	Self-administered questionnaire	None Occasional Daily *p* for trend	1.0 0.99 (0.80–1.22) 0.97 (0.71–1.33) 0.64	None stated	~20% of controls had benign breast disease or gynaecological diseases
Pawlega (1992), Poland, 1987	127, aged ≥35 years; 100% histologically confirmed; response rate, 75%	250 population-based (electoral roll); matched by age, place of residence	Mailed self-administered questionnaire	**Intake 20 years ago** *<50 years* Never vodka Ever vodka *≥50 years* Never vodka Ever vodka	 1.0 4.4 (1.6–12.4) 1.0 1.2 (0.8–2.6)	Age, education, social class, marital status, no. of people in household, body mass index, smoking	

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Martin-Moreno *et al.* (1993), Spain, 1990–91	762, aged 18–75 years; 100% histologically confirmed; response rate, 89%	988 population-based (municipal rolls); matched by age; response rate, 82%	Interviewer-administered questionnaire	*Intake (g/day)* None <2.41 2.41–7.60 7.61–20.40 ≥20.41 *p* for trend	 1.0 1.2 (0.9–1.6) 1.5 (1.1–2.1) 1.7 (1.2–2.3) 1.7 (1.3–2.3) 0.001	Age, region, socioeconomic status, body mass index, family history, age at menarche, menopausal status, age at menopause, age at first birth, energy intake	Increased risk for wine, sherry and spirits; no association with beer or liqueurs; slightly higher risk in post- versus premenopausal women

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Wakai *et al.* (1994), Japan, 1990-91	314, aged >25 years; 100% histologically confirmed; response rate not stated	900 hospital-based (outpatients at department of breast surgery; included women with benign breast disease); matched by age; response rate not stated	Self-administered questionnaire	*Current alcohol drinking* No Yes	 1.0 1.04 (0.77–1.39)	Age, menopausal status, family history, history of benign breast disease, age at menarche, age at menopause, regularity of menstrual cycles, duration of menstrual cycles, age at first birth, parity, breastfeeding, smoking, height, weight	No significant association in pre- or postmenopausal women

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Freudenheim *et al.* (1995, 1999), New York, USA, 1986–91	740, aged 40–85 years; 100% histologically confirmed; response rate, 58%	810 population-based (drivers' licence and HCFA records); matched by age; response rate, 50%	Interviewer-administered questionnaire	*Total drink intake over 20 years* 0–479 480–1300 1301–4560 4561–6719 ≥6720 *p* for trend	 1.0 1.13 (0.84–1.53) 0.99 (0.73–1.35) 0.95 (0.59–1.52) 0.86 (0.61–1.21) 0.76	Age, education, menopausal status, age at menarche, age at first birth, family history, benign breast disease, body mass index, energy intake, fat, carotenoids, vitamin C, α-tocopherol, folic acid, fibre	No association for cumulative intake by beverage type; no association for drinking 2, 10 or 20 years or at 16 years old; weak association with beer; Freudenheim *et al.* (1999) reported slight increased risk in premenopausal (*n*=134) versus postmenopausal (*n*=181), but not significant; results for alcohol intake 2, 10 and 20 years ago very similar

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Gomes *et al.* (1995), Brazil, 1978–87	300, aged 25–75 years; 100% histologically confirmed	600 hospital-based (300 outpatients, 300 gynaecology patients); matched by age, date of diagnosis	Information from patient records	*Current intake* No Yes	 1.0 1.16 (0.68–1.97)	No adjustment	
Longnecker *et al.* (1995), USA, 1988–91 [included in Collaborative Project, but incorporated here for details on lifetime exposure]	6662, aged <75 years; ascertained through cancer registry; response rate, 80%	9163 population-based (drivers'licence records and HCFA records); matched by age; response rate, 84%	Interviewer-administered questionnaire (via telephone) Lifetime intake (age 16 years to baseline [recent past])	*Most recent intake (g/day)* 0 >0–5 6–11 12–18 19–32 33–45 ≥46 per 13 g/day *p* for trend *Lifetime intake (g/day)* 0 >0–5 6–11 12–18 19–32 33–45 ≥ 46 per 13 g/day *p* for trend	 1.0 1.08 (0.98–1.19) 1.09 (0.96–1.23) 1.17 (1.01–1.37) 1.49 (1.24–1.79) 1.95 (1.42–2.66) 1.96 (1.43–2.67) 1.24 (1.15–1.33) <0.0001 1.0 1.13 (1.01–1.26) 1.24 (1.08–1.42) 1.39 (1.16–1.67) 1.69 (1.36–2.10) 2.30 (1.51–3.51) 1.75 (1.16-2.64) 1.31 (1.20–1.43) <0.001	Age, state, age at first birth, parity, body mass index, age at menarche, education, benign breast cancer, family history	Slightly stronger association in post- versus premenopausal women (but both statistically significant); no association for intake when aged <30 years, especially among older women; similar association found for beer, wine and spirits

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Haile *et al.* (1996), Canada, USA, 1935–89 (Connecticut), 1970–89 (Los Angeles), 1975–89 (Canada)	144 premenopausal bilateral cases, aged <50 years; 100% histologically confirmed; response rate, 55%	232 sister controls; response rate, 55%	Mailed self-administered questionnaire	*Drinks/week* None 1–3 ≥3	 1.0 1.2 (0.6–2.3) 1.8 (1.0–3.4)	Age, body mass index	Premenopausal bilateral breast cancer only; no difference according to family history of breast cancer
Royo-Bordonada *et al.* (1997), EURAMIC study, Europe (5 countries), 1991–92	315, aged 50–74 years; 100% histologically confirmed; response rate, 86%	364 population-based (population registries, GP records); matched by age, centre; response rate, 41%	Interviewer-administered questionnaire	*Alcohol intake (tertiles)* Never Former 1 2 3 *p* for trend	 1.0 1.73 (1.07–2.79) 1.00 (0.60–1.67) 1.01 (0.60–1.73) 1.18 (0.69–2.03) 0.81	Age, centre, body mass index, smoking, parity, age at first birth, age at menopause, age at menarche, hormone replacement therapy, family history, benign breast disease	Higher risk for age started drinking <40 years versus ≥ 40 years; no difference by subgroup of body mass index

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Viel *et al.* (1997), France, 1986–89	154, aged 30–50 years; 100% histologically confirmed; response rate, 90%	154 population-based (women who attended a preventative health clinic); matched by age, socioeconomic status; response rate, 100%	Self-administered questionnaire; verified by interviewer	*Alcohol intake (kcal/day)* None 1–60 ≥60 *p* for trend	 1.0 0.77 (0.41–1.47) 2.69 (1.40–5.17) 0.007	Parity, total energy intake	Premenopausal only; increased risk for amount of red wine and duration of red wine intake; no association with white wine, beer or fortified wine (but very low intake)
Tung *et al.* (1999), Japan, 1990-95	376, aged ≥29 years; histological confirmation not stated; response rate, 47%	430 hospital-based (non-malignant, non-endocrine, not related to nutritional or metabolic disease); matching criteria not stated; response rate, 77%	Self-administered questionnaire	*Drinking* None Former Current	 1.0 0.42 (0.19–0.95) 0.86 (0.61–1.22)	Age at menarche, age at first birth, weight, height, smoking, education	No association in pre- or postmenopausal women

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Huang *et al.* (2000); Kinney *et al.* (2000); Marcus *et al.* (2000), North Carolina Breast Cancer Study, 1993–96	Huang *et al.* (2000): 862, aged 20–74 years; 100% histologically confirmed; response rate, 77%	790 population-based (drivers' licence and HCFA records); matched by age, race; response rate, 68%	Interviewer-administered questionnaire	*Drank alcohol recently* No Yes	 1.0 1.0 (0.8–1.2)	Age, race, sampling design	Results also by receptor status (see accompanying table)
	Marcus *et al.* (2000): 864; recent intake	790		*Recent intake (drinks/week)* None 0.1–6.9 7–13.9 ≥14	 1.0 0.9 (0.8–1.2) 1.2 (0.8–1.8) 1.2 (0.8–1.8)		No association with age at started drinking
	Kinney *et al.* (2000): 890; lifetime intake	841		*Lifetime intake* (<25, 25–49, ≥50 years, g/week) Never <13 13–90.0 91–181.0 ≥182 *p* for trend	 1.0 0.9 (0.7–1.2) 1.0 (0.7–1.3) 1.2 (0.8–1.9) 0.8 (0.5–1.3) 0.96	Age, race, family history, age at menarche, parity, previous breast biopsy, body mass index, education, smoking	No association for type of beverage; no significant association with binge drinking; no differences by race, age, menopausal status, use of hormone replacement therapy or body mass index

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Männistö *et al*. (2000), Finland, 1990–95	301 (113 pre-, 188 postmenopausal), aged 25–75 years; 100% histologicaly confirmed; response rate not stated	443 population-based (national register); matched by urban/rural residence, age; response rate, 72%	Interviewer-administered and self-administered questionnaire	*Intake (g/week)* *Premenopausal* Never 1–12 13–36 ≥37 Former *Postmenopausal* Never 1–12 13–29 ≥30 Former	 1.0 0.8 (0.4–1.9) 0.9 (0.4–1.9) 1.0 (0.4–2.2) 1.4 (0.3–6.2) 1.0 0.9 (0.5–1.6) 0.6 (0.3–1.2) 0.8 (0.4–1.6) 0.6 (0.2–1.7)	Age, area, age at menarche, age at first birth, oral contraceptive use, hormone replacement therapy use, family history, benign breast disease, education, smoking, physical activity, body mass index, waist-hip ratio	Results are presented for alcohol as measured from interviewer-administered questionnaire; no association from self-reported questionnaire either; no association with age at first use, or cumulative intake < age 30 years or over lifetime

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Baumgartner *et al.* (2002), New Mexico, 1992–94	712 (332 Hispanic, 380 white), aged 30–74 years; ascertained through registry; response rate, 68% (Hispanics) and 77% (white)	844 population-based (random-digit dialling); matched by age, race, area; response rate, 76% (Hispanic) and 86% (white)	Interviewer-administered questionnaire	*Recent intake (g/week or drinks/week)* Non-drinker <8 8–20 (1 drink) 21–41 (2 drinks) 42–84 (2–4 drinks) 85–147 (5–7 drinks) Non-drinker <8 8–20 (1 drink) 21–41 (2 drinks) 42–84 (2–4 drinks) 85–147 (5–7 drinks) ≥148 (≥8 drinks)	*Hispanic* 1.0 1.21 (0.68–2.15) 1.00 (0.54–1.85) 0.75 (0.37–1.53) 1.24 (0.52–2.93) 1.35 (0.63–2.93) *White* 1.0 0.49 (0.28–0.85) 0.46 (0.27–0.79) 0.44 (0.25–0.77) 0.60 (0.35–1.05) 0.49 (0.24–1.00) 1.56 (0.85–2.86)	Age, area, education, age at menarche, menopausal status, parity, age at first birth, breastfeeding, oral contraceptive use, benign breast disease, family history, smoking, body mass index, physical activity, energy intake, fat intake	Increased risks in postmenopausal women at high intakes (≥42 drinks) for both races (but not significant); no association for age at first use or duration of drinking; results also by receptor status (see accompanying table)

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Gammon *et al*. (2002); Terry *et al*. (2006), Long Island Breast Cancer Study Project, 1996–97	Gammon *et al.* (2002): 1508 (*in situ* and invasive), aged 20–98 years; verified by medical records; response rate, 82% Terry *et al.* (2006) current alcohol (g/day)	1556 population-based (random-digit dialling and HCFA records); matched by age; response rate, 63%	Interviewer-administered questionnaire	*Intake* Never Ever *Current intake (g/day)* None <0.5 0.5–5 5–15 ≥15 *p* for trend *Lifetime intake (g/day)* None <15 15–30 ≥30 *p* for trend	 1.0 1.00 (0.86–1.15) 1.0 0.67 (0.50–0.91) 0.83 (0.63–1.11) 0.99 (0.75–1.31) 1.04 (0.74–1.45) 0.2 1.0 1.12 (0.88–1.42) 1.35 (0.96–1.91) 0.81 (0.55–1.19) 0.5	Age Age, race, education, body mass index, lifetime intake Age, race, education, body mass index, current intake	No association when stratified by body mass index, menopausal status or hormone replacement therapy use; no association with drinking at specific ages; results also for receptor status (see accompanying table); no difference by subgroups of body mass index, menopausal status or hormone-replacement therapy use

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Lenz *et al.* (2002), Canada, 1996–97	556, aged 50–75; identified through pathology departments and cancer registry; 100% histologically confirmed; response rate, 81%	577 hospital-based (other cancers not related to alcohol); response rate, 76%	Interviewer-administered questionnaire	*Use* Never Ever Infrequent Regular Current regular (i.e. weekly or daily)	 1.0 1.2 (0.9–1.7) 1.2 (0.8–1.8) 1.3 (0.9–1.8) 1.5 (1.0–2.2)	Age, family history, age at oophorectomy, education, marital status, race, age at menarche, oral contraceptive use, hormone replacement therapy use, breast feeding, smoking, body mass index, age at first birth, proxy respondent status	Similar association for type of drink (slightly higher for wine drinkers with long duration of intake); no association with age at first started drinking, duration of intake or lifetime alcoholic beverage intake

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Althuis *et al.* (2003), USA (Atlanta, Seattle and New Jersey), 1990–92	1750 premenopausal women, aged 20–54 years; includes in-situ and invasive cancers identified through hospital records; response rate, 86%	1557 population-based (random-digit dialling); all premenopausal women; no matching criteria; response rate, 78%	Interviewer-administered questionnaire	**Alcohol intake (drinks/week)** *Aged <35 years (n=265)* None <3 3–6.9 7–13.9 ≥14 *Aged 35–44 years (n=1214)* None <3 3–6.9 7–13.9 ≥14 *Aged 45–54 years (n=271)* None <3 3–6.9 7–13.9 ≥14	 1.0 1.33 (0.8–2.2) 0.99 (0.6–1.7) 1.29 (0.6–2.7) 1.71 (0.7–4.0) 1.0 1.04 (0.3–1.3) 1.00 (0.8–1.3) 1.04 (0.7–1.5) 1.95 (1.2–3.3) 1.0 1.98 (1.2–3.2) 1.95 (1.1–3.4) 1.84 (1.0–3.5) 4.24 (1.2–14.6)	Study site, screening history, age, race, oral contraceptive use, parity, age at first birth, family history, age at menarche, body mass index	No significant difference by age group; overall relative risk for ≥14 drinks/week versus none, 2.06 (95% CI, 1.4–3.1)

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Choi *et al.* (2003), Republic of Korea, 1995–2001	346, all ages; verification not stated; response rate not stated	332 hospital-based (non-malignant and no hormone-related or benign breast disease); response rate not stated	Interviewer-administered questionnaire	*Use* <1 month ≥1 month	 1.0 1.4 (0.99–2.11)	Age, family history	Association stronger in post- versus premenopausal (no results stated)
Wrensch *et al.* (2003), Marin County, CA, USA, 1997–99	285, all ages; identified through cancer registry; verification not stated; response rate, 71%	286 population-based (random-digit dialling); matched by race, age; response rate, 87%	Interviewer-administered questionnaire	*Intake (aged ≥ 21, drinks/week)* <1 1–1.9 2 ≥3 *p* for trend	 1.0 1.1 (0.7–1.8) 2.3 (1.2–4.4) 3.6 (1.2–11.5) 0.004	Smoking, socioeconomic status, religion, parity, breastfeeding, oral contraceptive use, hormone replacement therapy use, body mass index, screening history, family history, benign breast disease, radiation treatment, age at menarche, menopausal status	Stronger association for age started drinking >21 years versus <21 years; slightly stronger association in women aged <50 versus ≥50 years

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
McDonald *et al.* (2004), CARE Study, 5 centres in the USA, 1994–98	4575, aged 35–64 years; response rate, 77%	4682 population-based (random-digit dialling), matched by site, race, age; response rate, 65%	Interviewer-administered questionnaire	*Drinks/week 2 years ago* None <7 >7 7–<14 >14 Odds ratio for trend	 1.0 1.0 (0.9–1.1) 1.2 (1.0–1.3) 1.2 (1.0-1.4) 1.2 (1.0-1.5) 1.1 (1.0–1.1)	Site, race, age, menopausal status, age at menarche, age at menopause, parity, age at first birth, body mass index, family history, oral contraceptive use, hormone replacement therapy use	Similar association for intake 1–10 years before recruitment; no significant difference by menopausal status; slightly stronger association for wine than for beer or spirits; stronger association for older women drinking >14 drinks/ week

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Ma *et al.* (2006), Los Angeles, USA, 2000–03	1725, aged 20–49 years; 100% histologically confirmed; response rate, 62%	440 population-based (neighbourhood walk algorithm); matched by age, race; response rate, 74%	Interviewer-administered questionnaire	*Drinks/week in last 5 years* Never <3 3–5 6–11 >12 *p* for trend	 1.0 1.01 (0.76–1.35) 0.93 (0.63–1.37) 1.16 (0.75–1.81) 1.77 (1.01–3.08) 0.12	Age, race, education, family history, age at menarche, parity, body mass index, oral contraceptive use, menopausal status, hormone replacement use	Results also by receptor status (see accompanying table)

CI, confidence interval; HCFA, Health Care Finance and Administration

an increased risk for breast cancer, and that the risk increases with increasing intake (Figure 2.1). Hamajima *et al.* (2002) (The Collaborative Group on Hormonal Factors in Breast Cancer) found a significantly increased risk (relative risk, 1.13; 95% CI, 1.07–1.20) for an intake of 18 g alcohol per day. No single study was large enough to estimate reliably the risk for breast cancer at such low levels of intake.

Several studies have examined the effect of lifetime alcoholic beverage intake by total amount (Freudenheim *et al*., 1995; Longnecker *et al*., 1995; Kinney *et al*., 2000; Gammon *et al*., 2002) or by 10 g intake of alcohol per day (Longnecker *et al*., 1995; Smith-Warner *et al*., 1998; Hamajima *et al*. 2002; Tjønneland *et al*., 2003) on the risk for breast cancer. One large case–control study, based on more than 6000 cases, reported an increase in risk of 31% per 13 g intake of alcohol per day (Longnecker *et al*., 1995). In contrast, the EPIC cohort found no association with lifetime alcoholic beverage intake after adjustment was made for current alcoholic beverage intake (Tjønneland *et al*., 2007).

Most studies that examined the age at which a woman started to drink in relation to risk for breast cancer reported no association (Freudenheim *et al*., 1995; Holmberg *et al*., 1995; Lenz *et al*., 2002; Horn-Ross *et al*., 2004; Tjønneland *et al*., 2004; Lin *et al*., 2005; Terry *et al*., 2006; Tjønneland *et al*., 2007).

One large case–control study found that, among women who had not recently consumed alcoholic beverages, consumption before the age of 30 years was positively associated with risk for breast cancer, which suggests a continuing increased risk with past consumption (Longnecker *et al*., 1995). Overall, however, there is limited information on the association between cessation of drinking and subsequent risk for breast cancer, and therefore no firm conclusions can be drawn.

2.6.5 *Tumour type*

Three cohort (Table 2.32) and 12 case–control studies (Table 2.33) examined whether the association between alcoholic beverage intake and risk for breast cancer differed by estrogen receptor (ER) or progesterone receptor (PR) status.

Three cohort studies (Potter *et al*., 1995; Colditz *et al*., 2004; Suzuki *et al*., 2005) (see Table 2.32) evaluated the association of alcoholic beverage intake according to receptor status. All three studies reported a significant association between alcoholic beverage consumption and risk for breast cancer for the most common subgroup of ER+ tumours; the small number of cases in the other subgroups may limit the power to detect significant differences between different subgroups of tumours. The Iowa Women's Health Study (Gapstur *et al*., 1995; Potter *et al*., 1995; Sellers *et al*., 2002) reported a higher risk with increasing alcoholic beverage intake for ER–/PR– tumours and the Swedish Mammography Cohort Study found a higher risk for ER+/PR+ and ER+/PR– tumours (Suzuki *et al*., 2005); both studies found stronger associations for users of hormone replacement therapy compared with non-users, although these were based on small numbers of cases and should be interpreted with caution.

Table 2.32 Cohort studies of alcoholic beverage intake and breast cancer by hormone-receptor status

Reference, name of study	Cohort description	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Gapstur *et al.* (1995); Potter *et al.* (1995); Sellers *et al.* (2002), Iowa Women's Health Study	37 105 women, aged 55–69 years; recruited in 1986; follow-up until 1992 through registry; 939 cases identified through cancer registry (610 had receptor status)	*Intake in last year* None Any None Any None Any	*ER+/PR+ (414)* 1.0 1.17 (0.95-1.44) *ER–/PR+ (99)* 1.0 1.23 (0.81–1.87) *ER–/PR– (80)* 1.0 1.37 (0.86–2.18)	Age at menopause, hormone replacement therapy use, current body mass index and at age 18 years, waist:hip ratio, age at menarche, type of menopause, family history, parity, age at first birth, oral contraceptive use	Gapstur *et al.* (1995) found higher risk for women who consumed ≥ 4 g/day and had ever used hormone replacement therapy versus non-drinkers who had never used hormone replacement therapy for ER+/PR+ and ER–/PR– tumours; no association with other tumour subtypes; also interaction by family history and body mass index. Sellers *et al.* (2002) reported higher risk for women who consumed ≥ 4 g/day and had a low folate intake for ER– tumours; no association with other tumour subtypes

Table 2.32 (continued)

Reference, name of study	Cohort description	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Colditz *et al.* (2004), Nurses Health Study	66 145 women; aged 30–55 years; recruited in 1976; follow-up from 1980 until 2000; 2096 self-reported invasive cancers verified through medical and pathology records with ER/PR status	*Cumulative intake before menopause* β coefficient (SE) *p* for trend β coefficient (SE) *p* for trend β coefficient (SE) *p* for trend β coefficient (SE) *p* for trend	*ER+/PR+ (1281)* 0.0003 (0.00009) 0.001 *ER+/PR– (318)* 0.0002 (0.0002) 0.20 *ER–/PR– (417)* –0.00003 (0.0002) 0.86 *ER–/PR+ (80)* 0.0002 (0.0004) 0.68	Not clearly stated	No strong association with alcoholic beverage intake after menopause for any tumour subgroup; no difference by hormone replacement therapy use for any tumour subgroup

Table 2.32 (continued)

Reference, name of study	Cohort description	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Suzuki *et al.* (2005), Swedish Mammography Cohort	51 847 women, aged 55–70 years; recruited 1987–90; follow-up until 2004 through cancer registry; verified by pathology and medical records; 1188 invasive cases with ER/PR status	*Intake in last 6 months (1987 and 1997; g/day)* None <3.4 3.4–9.9 ≥10 *p* for trend None <3.4 3.4–9.9 ≥10 *p* for trend None <3.4 3.4–9.9 ≥10 *p* for trend None <3.4 3.4–9.9 ≥10 *p* for trend	*ER+/PR+ (716)* 1.0 1.07 (0.89–1.30) 1.09 (0.88–1.35) 1.35 (1.02–1.80) 0.05 *ER+/PR– (279)* 1.0 1.10 (0.78–1.55) 1.30 (0.91–1.87) 2.36 (1.56–3.56 <0.01 *ER–/PR– (143)* 1.0 1.11 (0.72–1.71) 1.09 (0.68–1.75) 0.80 (0.38–1.67) 0.45 *ER–/PR+ (50)* 1.0 1.27 (0.63–2.57) 1.30 (0.58–2.89) 0.62 (0.13–2.90) 0.57	Age, body mass index, height, education, parity, age at first birth, age at menarche, age at menopause, type of menopause, oral contraceptive use, hormone replacement therapy use, family history, benign breast disease, energy intake, fibre and fat intake	Stronger association with increasing alcohol intake in hormone replacement therapy users versus never users for ER+/PR+ tumours; no difference for other tumour subtypes

CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; SE, standard error; +, positive; –, negative

Table 2.33 Case–control studies of alcoholic beverage intake and breast cancer by hormone-receptor status

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
McTiernan *et al.* (1986), Cancer and Steroid Hormone Study, Washington, USA, 1981–82	329 (240 with receptor status) identified through cancer registry, aged 25–54 years; 100% histologically confirmed; response rate, 79%	332 population-based (random-digit dialling); matched by age, all in same region; response rate, 87%	Interviewer-administered questionnaire	*No. of drinks/week* Never/rarely 1–6 ≥7 Never/rarely 1–6 ≥7	*ER+ (143)* 1.0 1.2 (0.7–1.9) 1.7 (1.1–2.8) *ER– (97)* 1.0 1.1 (0.6–2.0) 2.1 (1.1–3.6)	Adjusted for age, age at menarche, benign breast disease, age at first birth, parity
Nasca *et al.* (1994) NY State, USA, 1982–84	1152, aged 20–79 years; verified by pathology reports; response rate, 79%	1617 population-based (drivers' licence records); matched by age, region; response rate, 72%	Interviewer-administered questionnaire (telephone)	*Intake (g/day)* None <1.5 1.5–4.9 5.0–14.9 ≥15 *p* for trend None <1.5 1.5–4.9 5.0–14.9 ≥15 *p* for trend	*ER+ (794)* 1.0 1.18 (0.88–1.57) 1.28 (0.91–1.80) 1.28 (0.96–1.70) 1.35 (0.99–1.85) 0.07 *ER– (358)* 1.0 0.92 (0.62–1.36) 1.19 (0.77–1.83) 0.94 (0.64–1.35) 1.05 (0.70–1.59) 0.73	Unadjusted results shown; adjustment for age, menopausal status, smoking, race, age at menopause, age at first birth, history of benign breast disease and family history made no difference to the risk estimates.

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Yoo *et al*. (1997), Japan, 1988–92	1154 (455 had receptor status), aged ≥25 years; 100% histologically confirmed; response rate not stated	21 714 hospital-based (non-malignant); response rate not stated	Self-administered questionnaire	*Intake* Never Ever *ER+/PR– (114)* Never Ever *ER–/PR– (141)* Never Ever *ER–/PR+ (24)* Never Ever	*ER+/PR+ (176)* 1.0 1.0 (0.71–1.41) 1.0 0.96 (0.60–1.52) 1.0 0.68 (0.44–1.05) 1.0 0.80 (0.32–2.02)	Adjusted for age, occupation, family history, age at menarche, menstrual regularity, age at menopause, parity, age at first birth, breastfeeding, smoking

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Enger *et al.* (1999), 2 studies in Los Angeles, USA, 1983–89	424 premenopausal, aged <41 years; response rate, 77%; 760 postmenopausal, aged 55–64 years; response rate, 67%; 100% histologically confirmed; included invasive and in-situ cancers	760 premenopausal population-based; matched by region, parity, age; response rate, 79%; 1506 postmenopausal; response rate, 80%; all controls identified through a neighbourhood walk algorithm	Interviewer-administered questionnaire	**Intake (g/day)** *Premenopausal* 0 1–5 6–13 ≥14 *p* for trend Increase per 13 g/day 0 1–5 6–13 ≥14 *p* for trend Increase per 13 g/day 0 1–5 6–13 ≥14 *p* for trend Increase per 13 g/day	 *ER+/PR+ (205)* 1.0 0.73 (0.46–1.15) 1.07 (0.69–1.65) 1.10 (0.67–1.80) 0.56 1.10 (0.91–1.32) *ER+/PR- (52)* 1.0 0.45 (0.18–1.10) 0.16 (0.04–0.69) 0.71 (0.30–1.68) 0.21 0.88 (0.59–1.30) *ER–/PR– (149)* 1.0 0.68 (0.40–1.16) 0.90 (0.53–1.51) 1.04 (0.60–1.81) 0.84 1.08 (0.89–1.31)	Adjusted for age, socioeconomic status, education, age at menarche, age at first birth, parity, breastfeeding, physical activity, family history (premenopausal, also oral contraceptive use); insufficient data for ER–/PR+; no differences by subgroup of body mass index or hormone replacement therapy use among ER+/PR+ cases

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Enger *et al.* (1999) (contd)				*Postmenopausal*	*ER+/PR+ (450)*	
				0	1.0	
				1–13	0.97 (0.74–1.27)	
				14–26	1.18 (0.80–1.75)	
				≥27	1.76 (1.14–2.71)	
				p for trend	0.03	
					ER+/PR- (159)	
				0	1.0	
				1–13	0.75 (0.49–1.14)	
				14–26	1.36 (0.80–2.33)	
				≥27	1.10 (0.53–2.26)	
				p for trend	0.65	
				Increase per 13 g/day	1.05 (0.90–1.24)	
					ER–/PR– (127)	
				0	1.0	
				1–13	0.81 (0.52–1.26)	
				14–26	0.91 (0.47–1.75)	
				≥27	1.37 (0.68–2.76)	
				p for trend	0.77	

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Gammon *et al,* (1999), USA, New Jersey, 1990–92 [data also reported in Althuis *et al.* (2003)]	509 in-situ and invasive cancers, aged 20–44 years; identified through hospital records; 401 had tissue blood material for assessment of HER-2 amplification; response rate, 83%	462 population-based (random-digit dialling); matched by age; response rate, 77%	Interviewer-administered questionnaire	*Alcohol intake (drinks/week)* None <7 ≥7 None <7 ≥7	*HER2+ (159)* 1.0 0.95 (0.65–1.40) 1.24 (0.65–2.36) *HER2- (212)* 1.0 1.43 (1.00–2.04) 1.54 (0.84–2.80)	Adjusted for age; premenopausal women only
Huang *et al.* (2000), North Carolina Breast Cancer Study, 1993–96	862, aged 20–74 years; 100% histologically confirmed; response rate, 77%	790 population-based (drivers' licence and HCFA records), matched by age, race; response rate, 68%	Interviewer-administered questionnaire	*Most recent intake* No Yes No Yes No Yes No Yes	*ER+/PR+ (381)* 1.0 0.8 (0.6–1.1) *ER+/PR– (78)* 1.0 1.5 (0.9–2.8) *ER–/PR– (262)* 1.0 0.9 (0.6–1.2) *ER–/PR+ (64)* 1.0 1.5 (0.8–2.8)	Adjusted for age, race, age at menarche, parity/age at first birth, breastfeeding, abortion/miscarriage, body mass index, waist:hip ratio, oral contraceptive use, hormone replacement therapy use, family history, chest X-ray, smoking, education; no significant difference by menopausal status

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Baumgartner *et al*. (2002), New Mexico, 1992–94	281 (128 Hispanic, 153 white), aged 30–74 years; response rate, 68% (Hispanics) and 77% (white); ascertained through registry	532 population-based (random digit dialling); matched by age, race, area; response rate, 76% (Hispanic) and 86% (white)	Interviewer-administered questionnaire		ER+/PR+	Adjusted for age, area, education, age at menarche, menopausal status, parity, age at first birth, breastfeeding, oral contraceptive use, benign breast disease, family history, smoking, body mass index, physical activity, energy intake, fat intake; too few cases for ER+/PR– and ER–/PR+
				Recent intake (g/week)	*Hispanic*	
				Non-drinker	1.0	
				<8	0.83 (0.35–1.98)	
				8–41 (1–2 drinks)	0.97 (0.49–1.91)	
				≥42 (≥3 drinks)	1.78 (0.86–3.68)	
					White	
				Non-drinker	1.0	
				<148 (<8 drinks)	0.46 (0.28–0.74)	
				≥148 (≥8 drinks)	2.13 (1.03–4.43)	
					ER–/PR–	
					Hispanic	
				Non-drinker	1.0	
				<8	1.04 (0.39–2.79)	
				8–41 (1–2 drinks)	0.39 (0.17–1.08)	
				≥42 (≥3 drinks)	1.43 (0.55–3.74)	
					White	
				Non-drinker	1.0	
				<148 (<8 drinks)	0.37 (0.19–0.73)	
				≥148 (≥8 drinks)	1.62 (0.51–5.18)	

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Britton *et al.* (2002), Women's Interview Study of Health, multi-site USA, 1990–92	1556 (1212 had receptor status); aged 20–44 years; identified through registry and medical records; response rate, 86%	1397 population-based (random-digit dialling); matched by age, region; response rate, 79%	Interviewer-administered questionnaire	*Usual intake (drinks/week)* None <7 ≥7 None <7 ≥7 None <7 ≥7 None <7 ≥7	*ER+/PR+ (615)* 1.0 1.11 (0.88–1.41) 1.33 (0.94–1.87) *ER+/PR– (117)* 1.0 0.86 (0.55–1.35) 0.94 (0.47–1.86) *ER–/PR– (360)* 1.0 1.08 (0.81–1.43) 1.38 (0.93–2.06) *ER-/PR+ (118)* 1.0 0.87 (0.55–1.39) 1.64 (0.90–2.98)	Adjusted for site, age, race, education, body mass index, waist:hip ratio, parity, age at first birth, breastfeeding, oral contraceptive use, smoking, physical activity, age at menarche, family history, menopausal status

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Cotterchio *et al.* (2003), 2 studies in Canada (ECSS, WHS), 1995–98	3748 (2638 had receptor status), aged 25–74 years; confirmed by pathology reports; response rate, 86% for ECSS, 73% for WHS	373 population (Ministry of Finance rolls); matched by age, all in same region; response rate, 80% for ECSS, 61% for WHS	Self-administered questionnaire	Drinks/week *Premenopausal* 0 ≤1 1.5–3 ≥3.5 *Postmenopausal* 0 ≤1 1.5–3 ≥3.5 *Premenopausal* 0 ≤1 1.5–3 ≥3.5 *Postmenopausal* 0 ≤1 1.5–3 ≥3.5	 *ER+/PR+ (479)* 1.0 1.08 (0.72–1.60) 0.84 (0.55–1.28) 1.38 (0.91–2.10) *(1332)* 1.0 1.03 (0.23–1.30) 0.90 (0.69–1.15) 1.27 (1.00–1.64) *ER–/PR– (256)* 1.0 1.31 (0.78–2.19) 1.36 (0.81–2.28) 0.92 (0.51–1.68) *(442)* 1.0 1.06 (0.75–1.50) 0.90 (0.62–1.32) 1.13 (0.79–1.64)	Adjusted for age at menarche, parity, age at first birth, oral contraceptive use, age at menopause, hormone replacement therapy use, body mass index, smoking, breastfeeding, benign breast disease, family history, age, oopherectomy; significant difference for ER+/PR+ versus ER–/PR– in premenopausal women; no significant differences for postmenopausal women

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Li *et al.* (2003), 3 sites in Seattle, USA, 1997–99	975; aged 65–79 years; cases identified through cancer registry and verified by medical and pathology records; response rate, 81%	998 population-based (HCFA records); matched by date; response rate, 74%	Interviewer-administered questionnaire	*Intake in last 20 years (g/day)*	*ER+ (789)*	Adjusted for age, family history, body mass index; no significant association with alcohol intake overall
				Never	1.0	
				Ever	1.3 (1.0–1.6)	
				<1.5	1.2 (0.8–1.8)	
				1.5–4.9	1.6 (1.0–1.8)	
				5–14.0	1.2 (0.9–1.6)	
				15–29.9	1.2 (0.9–1.8)	
				≥30	1.7 (1.1–2.7)	
				p for trend	0.71	
					PR+ (648)	
				Never	1.0	
				Ever	1.3 (1.1–1.7)	
				<1.5	1.2 (0.8–1.9)	
				1.5–4.9	1.4 (1.0–2.0)	
				5–14.0	1.2 (0.9–1.6)	
				15–29.9	1.3 (0.9–1.9)	
				≥30	1.8 (1.1–2.8)	
				p for trend	1.0	
					ER– (106)	
				Never	1.0	
				Ever	1.1 (0.7–1.7)	
				<1.5	1.1 (0.4–2.7)	
				1.5–4.9	1.1 (0.5–2.1)	
				5–14.0	1.0 (0.6–1.9)	
				15–29.9	1.4 (0.7–2.7)	
				≥30	1.2 (0.5–3.2)	
				p for trend	0.54	

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Li *et al.* (2003) (contd)					*PR– (244)*	
				Never	1.0	
				Ever	1.1 (0.8–1.4)	
				<1.5	1.0 (0.5–1.9)	
				1.5–4.9	1.0.(0.6–1.6)	
				5–14.0	1.1 (0.7–1.6)	
				15–29.9	1.1 (0.6–1.8)	
				≥30	1.4 (0.7–2.7)	
				p for trend	0.71	
McDonald *et al.* (2004), CARE Study, multisite, USA, 1994–98	4575, aged 35–64 years; response rate, 77%	4685 population-based (random-digit dialling); matched by site, race, age; response rate, 65%	Interviewer-administered questionnaire	*Drinks/week*	*ER+/PR+ (2155)*	Adjusted for site, race, age, menopausal status, age at menarche, age at menopause, parity, age at first birth, body mass index, family history, hormone replacement therapy use, oral contraceptive use; slightly stronger association in postmenopausal women across all subtypes, except for ER–/PR–
				None	1.0	
				<7	1.0 (0.9–1.1)	
				≥7	1.2 (1.0–1.4)	
					ER+/PR– (370)	
				None	1.0	
				<7	1.3 (1.04–1.70)	
				≥7	1.6 (1.2–2.3)	
					ER–/PR– (1071)	
				None	1.0	
				<7	0.9 (0.8–1.1)	
				≥7	1.0 (0.8–1.2)	
					ER–/PR+ (202)	
				None	1.0	
				<7	0.8 (0.5–1.1)	
				≥7	1.4 (0.98–2.1)	

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Ma *et al*. (2006), Los Angeles, USA, 2000–03	1725 (1419 had receptor status), aged 20–49 years; 100% histologically confirmed; response rate, 62%	440 population-based (neighbourhood walk algorithm); matched by age, race; response rate, 74%	Interviewer-administered questionnaire	*Intake in last 5 years (drinks/week)* Never <3 3–5 6–11 >12 *p* for trend Never <3 3–5 6–11 >12 *p* for trend	*ER+/PR+ (739)* 1.0 1.11 (0.81–1.53) 1.01 (0.66–1.54) 1.26 (0.78–2.03) 2.10 (1.17–3.79) 0.03 *ER–/PR– (334)* 1.0 0.89 (0.61–1.30) 0.76 (0.45–1.28) 1.06 (0.60–1.86) 1.71 (0.87–3.38) 0.42	Adjusted for age, race, education, family history, age at menarche, parity, body mass index, oral contraceptive use, menopausal status, hormone replacement therapy use; differences not statistically significant between ER–/PR– and ER+/PR+; data not shown for ER–/PR+ or ER+/PR–

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Terry *et al.* (2006), Long Island Breast Cancer Study Project, 1996–97	1508 (ER status for 66%), aged 20–98 years; verified by pathology reports; response rate, 82%; included in-situ and invasive cancers	1556 population-based (HCFA records and random-digit dialling); matched by age; response rate, 63%	Interviewer-administered questionnaire	*Lifetime intake (g/day)*		Adjusted for age, race, education, body mass index; alcohol not associated with risk overall; stronger association for ≥15 g/day intake for ER+ cases among lean women (body mass index <25); no association among overweight women
					ER+ (730)	
				None	1.0	
				<15	1.04 (0.85–1.27)	
				≥15	1.14 (0.86–1.51)	
					PR+ (636)	
				None	1.0	
				<15	1.08 (0.89–1.33)	
				≥15	0.97 (0.71–1.32)	
					ER+/PR+ (583)	
				None	1.0	
				<15	1.06 (0.86–1.32)	
				≥15	0.98 (0.72–1.35)	
					ER– (265)	
				None	1.0	
				<15	1.03 (0.77–1.39)	
				≥15	1.27 (0.85–1.90)	
					PR– (355)	
				None	1.0	
				<15	0.97 (0.75–1.27)	
				≥15	1.52 (1.08–2.14)	
					ER–/PR– (212)	
				None	1.0	
				<15	0.99 (0.71–1.37)	
				≥15	1.41 (0.92–2.16)	

CI, confidence interval; ECSS, Enhanced Cancer Surveillance Study; ER, estrogen receptor; HCFA, Health Care Finance and Administration records; PR, progesterone receptor; WHS, Women Health Study ;+, positive; –, negative

Of the case–control studies, only one reported a stronger association for ER+/PR+ tumours than for ER–/PR– tumours in premenopausal women (relative risks, 1.4 and 0.9, respectively, for ≥3.5 drinks per week versus non-drinkers), although no significant difference was found in postmenopausal women (Cotterchio *et al*., 2003).

2.6.6 *Types of alcoholic beverage*

Results from studies that have looked at the type of alcoholic beverage consumed and risk for breast cancer have suggested an increased risk with increasing alcoholic beverage consumption regardless of the beverage type. Estimates from a pooled analysis of six cohort studies showed risks of 11%, 5% and 5% per 10 g intake of beer, wine and spirits per day, respectively (Smith-Warner *et al*., 1998), which suggests that the effect is principally due to the presence of alcohol.

2.6.7 *Subgroups of women*

Evidence of whether the association of alcoholic beverage intake and risk for breast cancer varied by lifestyle and other factors was available in the study of Hamajima *et al*. (2002) (Collaborative Group on Hormonal Factors in Breast Cancer). This pooled analysis indicated that the association of alcoholic beverages with the risk for breast cancer was not modified by tobacco smoking, age at diagnosis, reproductive factors, having a mother or sister with a history of breast cancer, use of oral contraceptives or use of hormone replacement therapy (see Fig. 2.3).

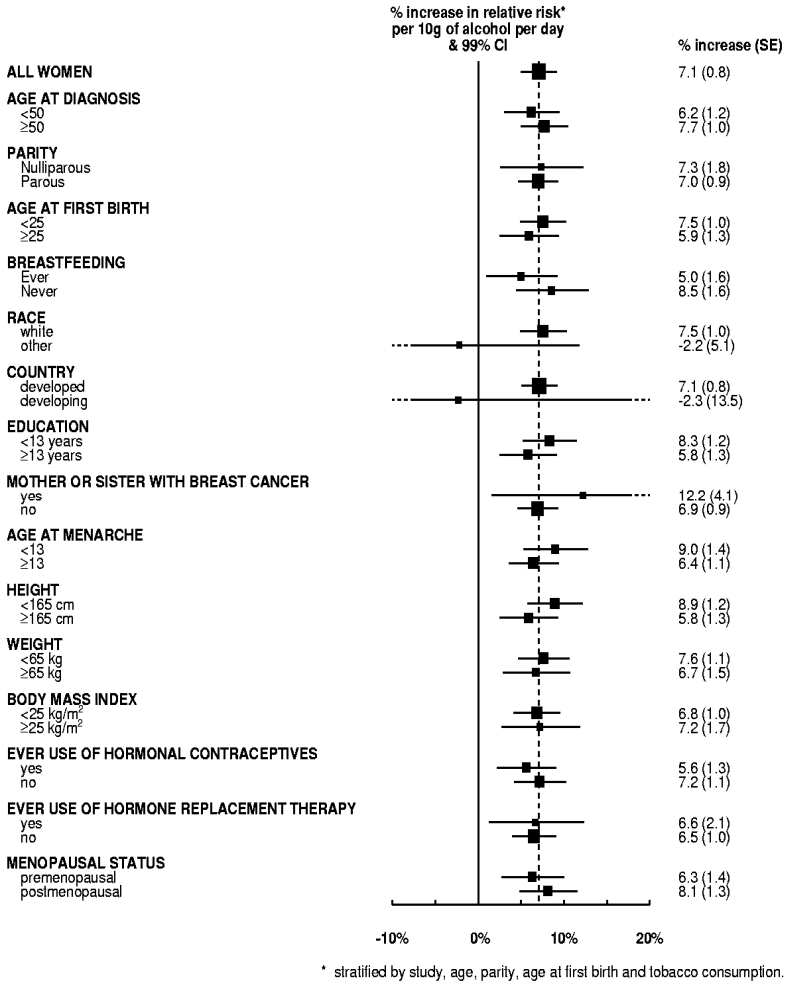
2.6.8 *Male breast cancer*

Overall, one cohort study (Table 2.34) and eight case–control studies (Table 2.35) have evaluated the association between consumption of alcoholic beverages and the risk for male breast cancer.

One cohort study of male alcoholics in Sweden has reported on the relationship with male breast cancer; this study found no difference in the rates of male breast cancer between alcoholics and the general population, based on 13 cases (Weiderpass *et al*., 2001c; Table 2.34).

Two case–control studies were based on a population of alcoholics as reported from hospital records. One study reported a significant twofold increased risk for alcoholics (Olsson & Ranstam, 1988) and the other found no association (Keller, 1967). [Both studies included small numbers of exposed cases, had a high proportion of cases for whom data were missing and, in Olsson and Ranstam (1988), different risk estimates were produced when different groups of controls were used.] A European case–control study, based on 74 cases, found a sixfold increase in risk in the highest category of alcoholic beverage consumption (>90 g alcohol per day) compared with light drinkers and non-drinkers, corresponding to an increase in risk per 10 g intake of alcohol per day of 17% for beer and wine, but not spirits (Guénel *et al*., 2004). All other studies

Figure 2.3. Percentage increase in the relative risk for breast cancer per 10 g of alcoholic beverage consumption per day in various subgroups of women (adjusted by study, age, parity, age at first birth and tobacco smoking).
Pooled analysis of data from 53 studies that included 58 515 women with breast cancer



From Hamajima et al. (2002)

Table 2.34 Cohort study of male breast cancer and alcoholic beverage consumption

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Standardized incidence ratio (95% CI)	Adjustment factors	Comments
Weiderpass *et al.* (2001c), Cohort of Alcoholics (hospital discharge records)	145 811 men diagnosed as alcoholics in hospital records; recruited 1965–95; follow-up through linkage with cancer registry; comparison with national incidence rates; matched by age, sex, calendar time	Incidence rates in alcoholics compared with national rates	Comparison group Alcoholics	13	1.0 1.1 (0.6–2.0)	Age, calendar time	No individual exposure information; no adjustment factor

CI, confidence interval

Table 2.35 Case–control studies of male breast cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Keller (1967), Veterans Administration hospitals, USA, 1958–63	181 (adenocarcinoma), aged 26–88 years	Group 1: 181 hospital-based (discharge lists of medical procedures); matched by age, place of residence; Group 2: 181 hospital-based (bladder or kidney cancer); matched by age, place of residence, hospital characteristics	Indication of alcoholism abstracted from medical records	*Chronic alcoholism* No Yes	No data, but similar proportions of cases and controls were alcoholics.		14 cases, 10 group 1 controls and 9 group 2 controls were alcoholics; information on alcoholic beverage intake was missing for >50%.
Mabuchi *et al.* (1985a), New York, USA, 1972–75	52 identified through hospital medical and pathology records; 100% histologically confirmed; response rate, 81%	52 hospital-based; matched by age, sex, race, marital status (selected from hospital lists); response rate not stated	Interviewer-administered questionnaire	Usual intake of ≥1 glass/day	No relative risk reported (no association with wine, beer, mixed drink, whisky)		

Table 2.35 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Casagrande *et al.* (1988), Los Angeles, USA, 1978–85	75, aged 20–74 years; 100% histologically confirmed; response rate, 61%	75 population-based (neighbourhood survey); matched by age, race; response rate not stated	Interviewer-administered questionnaire	Alcohol drinks intake (oz/week)	No relative risk reported; 12.2 oz/wk in cases and 12.8 oz/wk in controls; p=0.81		No significant difference by wine, beer and spirits
Olsson & Ranstam (1988), Sweden, 1970–86	95 identified through registry, aged 21–99 years; verified through medical records	383 hospital-based (lung cancer and non-Hodgkin lymphoma); matched on hospital	Indication of alcoholism abstracted from medical records	*Chronic alcoholism* No Yes	 1.0 2.3 (not significant; using lung cancer controls) 13.5 (significant; using non-Hodgkin lymphoma controls)		Only 8 cases were alcoholics

Table 2.35 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Thomas *et al.* (1992); Rosenblatt *et al.* (1999), 10 states, USA, 1983–86	227 identified through registry, all ages; 100% histologically confirmed; response rate, 75%	300 population-based (random-digit dialling and HCFA records); matched by age, cancer registry area; response rate, 45%	Interviewer-administered questionnaire	*Lifetime intake (no. of drinks)* None 1–2314 2315–7774 7775–20 878 ≥20 879	 1.0 0.6 (0.3–1.3) 1.2 (0.6–2.2) 1.0 (0.6–1.9) 0.9 (0.5–1.7)	Matching factors	Thomas *et al.* (1992): No association with current intake or intake during period of life when one drank the most, or with age at which one started drinking
Hsing *et al.* (1998b), USA, 1985–86. National (US) Mortality Followback Survey	178 identified from death certificates, aged 25–74 years; response rate, 88%	512 decedants of other causes, excluding smoking- or alcohol-related causes; matched by age, race; response rate not stated	Questionnaire completed by next of kin	*Intake (drinks/day)* None Ever 1 2 3–4 ≥5	 1.0 0.9 (0.6–1.6) 0.8 (0.5–1.6) 1.1 (0.6–2.0) 0.9 (0.5–1.8) 0.9 (0.5–1.8)	Age at death, socioeconomic status	Exposure information taken from next of kin; drinking could be overascertained in the controls.
Petridou et al. (2000), Greece, 1996–97	23 identified in 2 hospitals; 100% histologically confirmed; response rate not stated	76 hospital-based, matched by age, sex (visitors and patients of trauma unit); response rate not stated	Interviewer-administered questionnaire	*Drinks/week* None <7 ≥7 *p* for trend	 1.0 1.15 (0.26-6.07) 0.44 (0.09-2.48) 0.12	None	

Table 2.35 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Johnson *et al.* (2002), Canada, National Cancer Surveillance System 1994–98	81 identified through cancer registry, aged 42–74 years; 100% histologically confirmed; response rate, 68%	1905 population-based (health insurance records and random-digit dialling); matched by age, sex; response rate, 65%	Self-administered questionnaire	*Intake (servings/week)* None < 3 3–9 ≥10 *p* for trend	 1.0 0.66 (0.35–1.26) 0.91 (0.50–1.65) 0.63 (0.33–1.23) 0.3	Age, marital status, coffee, physical activity, body mass index, area	
Guénel *et al.* (2004), multisite, Europe, 1995–97	74 identified through pathology and clinical departments; aged 35–70 years; 100% histologically verified; response rate, 87%	1432 population (population registers and electoral roll); matched by age, sex, region; response rate, 52%–78% by region	Interviewer-administered questionnaire	*Intake 5 years ago (g/day)* 0–15 16–30 31–45 46–60 61–75 76–90 >90 Per 10 g/day	 1.0 0.87 (0.30–2.47) 1.37 (0.46–4.08) 2.28 (0.73–7.11) 4.45 (1.12–17.7) 4.68 (1.07–20.6) 5.62 (1.54–20.6) 1.17 (1.05–1.30)	Age, region, smoking, gynaecomastia, diabetes, fertility problems, head injury, body mass index	Increased risk for wine and beer, but not spirits; similar results found when using hospital-based controls (rare cancers); adjustment for confounders made little difference to the estimates.

CI, confidence interval; HCFA, Health Care Finance and Administration

have found no association (Mabuchi *et al*., 1985a; Casagrande *et al*., 1988; Hsing *et al*., 1998b; Rosenblatt *et al*., 1999; Petridou *et al*., 2000; Johnson *et al*., 2002).

2.7 Cancer of the stomach

A possible relationship between alcoholic beverage consumption and risk for stomach cancer has long been hypothesized, but epidemiological evidence has been considered uncertain (IARC, 1988). This section evaluates the human evidence related to the risk for stomach cancer based on relevant publications from cohort and case–control studies published since 1988. Because a large proportion of cases of stomach cancer occur in China (accounting for 38% throughout the world), papers published in the Chinese literature are also included in this review.

The effects of total alcoholic beverage consumption on the risk for stomach cancer are summarized in Table 2.36 (cohort studies), Table 2.37 (cohort studies in the Chinese literature), Table 2.38 (case–control studies) and Table 2.39 (case–control studies in the Chinese literature). The effects of alcoholic beverage consumption and risk for stomach cancer by anatomic subtypes (cardia and distal cancer) are shown in Table 2.40, the effects of alcoholic beverage types are presented in Table 2.41 and the effects of alcoholic beverage consumption and the risk for stomach cancer stratified by gender are given in Table 2.42.

2.7.1 *Cohort studies*

(a) Special populations (Table 2.36)

In the Danish cohort study of 18 368 alcohol abusers conducted in Copenhagen in 1954–87, 64 cases of stomach cancers occurred during follow-up (Tønnesen *et al*., 1994). The SIR for stomach cancer was slightly increased and marginally significant (SIR, 1.3; 95% CI, 1.0–1.7). In the Swedish cohort of alcoholics (Adami *et al*., 1992a), a total of 25 cases resulted in a null association and an SIR of 0.9 (95% CI, 0.6–1.4) for men and 0.7 (95% CI, 0.0–4.0) for women.

(b) General population (Tables 2.36 and 2.37)

A total of 12 cohort studies of the general population that were conducted in Japan, the USA, Sweden, China, Denmark and the United Kingdom have examined the association between alcoholic beverage consumption and stomach cancer; three studies reported a significant association. Two cohort studies reported a statistically significant association between alcoholic beverage consumption and the risk for stomach cancer (Kato *et al*., 1992b; Fan *et al*., 1996) and one study with a large sample size reported an inverse relationship (Tran *et al*., 2005). Nine studies reported either a non-statistically significant association or no association.

Table 2.36 Cohort studies of stomach cancer and alcoholic beverage consumption

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Special populations								
Kono *et al.* (1987), Japan, Japanese Physicians' Study	5130 male Japanese physicians, aged 27–89 years; followed up for 19 years; 1965–	Self-administered questionnaire	ICD-8 (155) Primary liver cancer ICD-8 (151)	Never Occasional Daily (<2 g/ day) Daily (≥2 g/ day)	Total: 116 deaths	1.00 1.11 (0.69–1.79) 1.30 (0.79–2.12) 1.17 (0.66–2.07)	Age, smoking	Daily consumption of alcohol (1'go' sake) 1'go' =180 mL; 1'go' sake ≈ 27 mL alcohol
Adami *et al.* (1992a), Sweden, Uppsala Alcoholics Study	9353 (8340 men, 1013 women) selected from the Uppsala Inpatients Register with a discharge diagnosis containing a diagnostic code for alcoholism during 1965–83; follow-up, 19 years (mean, 7.7)	Follow–up was by record linkage to the nationwide Cause of Death Registry and the Swedish Cancer registry.	ICD-7 (155.0) Liver cancer; ICD-7 (307,322) ICD-8 (291,303)		Total, 24 cases 23 men 1 woman	**SIR** 0.9 (0.6–1.4) 0.7 (0.0–4.0)	-	Expected numbers of cancers computed from cancer incidence in the study population (Uppsala health care region) to compare with the observed

Table 2.36 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Tønnesen *et al*. (1994), Denmark, Alcohol Abusers Study	18 368 alcoholics from Copenhagen who entered a public outpatient clinic for free treatment in 1954–87; 15 214 men observed for 12.9 years on average and 3093 women observed for an average of 9.4 years	Records of cohort members linked to the Danish Cancer Registry to obtain cancer morbidity information		Alcohol abuse (male, female alcoholics)	64 cases 60 men 4 women	**SIR** 1.3 (1.0–1.6) $p \leq 0.05$ 1.8 (0.5–4.6) $p \leq 0.05$	Age, sex	Observed cancer incidence compared with that expected in the Danish population

Table 2.36 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Nomura *et al.* (1995), Hawaii, USA, American Men of Japanese Ancestry Study	8006 men born in 1900–19, and residing on the Hawaiian island of Oahu; followed up for 25 years examined between 1965–1968 at all hospitals on Oahu and the Hawaian Tumor Registry	Interviewed; surveillance to identify incident cases		Non–drinker <5 oz/month 5–14 oz/ month 15–39 oz/ month ≥40 oz/month	86 cases 43 41 39 36	1.0 0.9 (0.6–1.3) 1.1 (0.8–1.6) 1.0 (0.7–1.5) 1.2 (0.8–1.8) *p*=0.20	Age, smoking history	

Table 2.36 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
General population								
Kneller *et al*. (1991), USA	17 633 white American men insurance policy holders, largely of Scandinavian and German descent, aged ≥35 years; follow-up, 1966–86	Mailed questionnaire		Alcoholic beverage consumption (data not presented)	75 deaths	No association	-	Data regarding alcohol use and risk for stomach cancer not presented
Kato *et al*. (1992a), Japan	3914 subjects who underwent gastroscopic examination; 4.4 years of follow-up on average (1985–89)	Self-recorded questionnaire, cancer registry and death certificate	Organ site (ICD code)	None Past Occasional Daily	12 cases 6 11 16 Total: 45 (35 men, 10 women)	1.00 2.19 (0.78–6.19) 1.10 (0.47–2.60) 1.51 (0.65–3.54)	Sex , age, residence	Non-significant increase in risk for stomach cancer among past and daily drinkers

Table 2.36 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Kato *et al*. (1992b), Japan	9753 Japanese men and women, aged ≥40 and ≥30 years, respectively; follow-up, 1986–91; response rate, 85.9%	Baseline survey using a mailed questionnaire; death certificate		None Occasional Daily <50 mL Daily ≥50 mL	26 cases 12 7 12 Total: 57 (33 men, 22 women)	1.0 1.75 (0.84–3.61) 1.20 (0.48–3.00) 3.05 (1.35–6.91)	Sex, age	Association between alcohol intake and stomach cancer slightly weakened when smoking status, diet and family history of stomach cancer were included in the multivariate analysis.

Table 2.36 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Guo *et al*. (1994), China, Lin Xian Nutrition Intervention Trial	Nested case–control study; 29 584 adults who participated in a randomized intervention trial, aged 40–69 years; follow-up, 1986–91; 539 cases, 2695 controls, 5 controls per case; matched by age, sex	Structured interview		Lifetime consumption of alcoholic beverages (data not presented)	539 cases			Drinking alcoholic beverages was relatively uncommon in this area, but was reported by 22% of the cancer patients; no significant association (data not presented)

Table 2.36 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Murata *et al.* (1996), Japan, Chiba Center Association Study	Nested case–control study; 887 cases and 1774 controls, selected from a cohort of 17 200 male participants of a gastric mass survey in 1984; followed up for 9 years; 2 controls per case; matched by sex, birth year, first digit of the address code	Self-administered questionnaire		0 (cup/day) 0.1–1.0 (cups/day) 1.1–2.0 (cups/day) ≥2.1 (cups/day)	101 cases 82 51 12	1.0 1.1; $p>0.05$ 1.1; $p>0.05$ 0.5; $p>0.05$	Smoking	No 95% CI provided; a cup of 180 mL Japanese sake contains 27 mL ethanol.

Table 2.36 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Yuan *et al.* (1997), China, Shanghai Men's Study	18 244 male residents of Shanghai, enrolled between 1986 and 1989 (80% of eligible subjects); only 50 subjects lost to follow-up until 1993	Structured interviewed; cancer incidence ascertained through the population-based Shanghai Cancer Registry and vital status ascertained by inspection of the Shanghai death certificate records		Non-drinkers 1–28 drinks/ week ≥29 drinks/ week	48 deaths 33 10	1.0 0.98 1.37	Age, education, smoking	95% CI not given; non-significant 30–40% increase in risks of death from cancers of the stomach observed in heavy drinkers.

Table 2.36 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Terry *et al.* (1998), Sweden, Swedish Twin Registry Study	11 546 individuals born in 1886–1925 in the Swedish Twin Registry, and both still living in Sweden in 1961; followed up, 1967–92; 98% follow-up	Mailed questionnaire, record linkage to the National Cancer and Death Registers.	Organ site (ICD code)	None Light Moderate	116 cases	1.00 1.51 (0.89–2.55) 1.36 (0.83–2.24)	Fruit and vegetable intake, age, gender, body mass index, socioeconomic status, smoking	Alcoholic beverage consumption was assessed as number of drinks per week (data not presented); no. of cases per drinking category not given.
Sasazuki *et al.* (2002), Japan, The Japan Public Health Center Study Cohort I	19 657 men, born in 1930–49, aged 40–59 years at baseline; followed up, 1990–99; response rate: men, 76%; women, 82%	Self-administered questionnaire, death certificates, cancer registry	ICD-9 (151)	0–3 days/ month 0–161.0 g/ week 162.0–322.0 g/week 322.5 g/week	68 deaths 54 77 74	1.0 0.8 (0.6–1.2) 1.1 (0.8–1.5) 1.1 (0.8–1.6)	Age, area, smoking habit, consumption of fruit, green or yellow vegetables, salted cod roe or fish gut, body mass index	Reference group (0–3 days/month) included drinkers; data for women collected but not presented

Table 2.36 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Tran *et al.* (2005), China, Linxian General Population Trial	29 584 adults who participated in the Linxian General Population Trial, 40–69 years of age at baseline; follow-up, 15 years (1984–98)	Structured interview; case ascertainment considered complete and loss to follow–up minimal (176 or 1%)		Alcoholic beverage consumption (data not presented)	1089 363	Gastric cardia cancer 0.84 (0.72–0.97); Gastric non-cardia cancer 0.79 (0.61–1.02)	Age, sex	Alcoholic beverage drinking defined as any in previous 12 months

CI, confidence interval; ICD, International Classification of Diseases; SIR, standardized incidence ratio

Table 2.37 Cohort studies of stomach cancer and alcoholic beverage consumption published in the Chinese literature[a]

Reference, study location, period	Characteristics of cases	Characteristics of cohort	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Fan *et al.* (1996), Sifang County, Shichiuan, 1985–90	128 digestive tract cancers identified from the Disease Surveillance Spot, including stomach, liver, colorectal and oesophageal cancer; 97% diagnosed by county level hospitals	29 929 farmers, aged >35 years; age and sex distribution not provided; loss to follow-up not described	Interviewer-administered questionnaire (once a year)	*Cumulative alcohol consumption (kg)* Non-drinkers *Men* 1–125 125–500 ≥500 *Women* 1–125 125–500 ≥500	(Stomach cancer only) 1.0 2.53 (0.74–8.70) 3.89 (1.55–9.74) 6.28 (1.11–12.97) 0.69 (0.17–2.73) 1.67 (0.34–8.20) 1.81 (0.70–4.68)	Not mentioned	Relative risk for death from stomach cancer
Wang *et al.* (2005a), Shanghai, 1986–2002	18 244 cancer-free men followed from 1986 to 2002		Interview	*Alcoholic beverages (g/day)* 0 <30 30–70 >70	 1.00 1.00 1.16 1.42 (p-value>0.05)	Age, smoking, education	

CI, confidence interval

There was evidence of an association between alcohol consumption and an increased risk stomach cancer in the two cohort studies conducted in Japan (57 cases; Kato *et al.,* 1992b) and China (128 cases; Fan *et al*., 1996). The relative risks for stomach cancer were 3.05 (95% CI, 1.35–6.91) for 50 mL or more alcohol per day (three or more drinks per day) when adjusted for age and gender (Kato *et al*., 1992b) and 6.28 (95% CI, 1.11–12.97) for men who had a cumulative alcoholic beverage consumption of 500 kg or more (Fan *et al*., 1996). One cohort study in China with a large sample size (1089 cardia cancer and 363 non-cardia cancer) reported inverse associations with alcoholic beverage consumption, with relative risks of 0.84 (95% CI, 0.72–0.97) for cardia cancer and 0.79 (95% CI, 0.61–1.02) for non-cardia cancer (Tran *et al*., 2005). The two studies that reported a positive association (Kato *et al*., 1992b; Fan *et al*., 1996) adjusted for age and gender, but it is not clear what confounding factors were adjusted for in the study by .Tran *et al*.,(2005).

A positive, but not statistically significant, association was observed in five studies (Kono *et al*., 1987; Kato *et al*., 1992a; Yuan *et al*., 1997 Terry *et al*., 1998; Wang *et al*., 2005a) and null results were reported in three studies with relatively large sample sizes ranging from 75 to 493 cases (Kneller *et al*., 1991; Nomura *et al*., 1995; Murata *et al*., 1996; Sasazuki *et al*., 2002).

2.7.2 *Case–control studies (Tables 2.38 and 2.39)*

Several case–control studies have reported results on the influence of alcoholic beverage consumption on the risk for stomach cancer. More than 50% of the studies reported a positive association between alcoholic beverage consumption and stomach cancer: 60% of the studies that adjusted for confounding factors and 52% of the studies that did not also report a positive association. The proportion of positive associations was 71% in the Chinese literature and 44% in the English literature.

In more than half of the studies, the odds ratios were adjusted for variables such as sex, age, residence, education, diet, socioeconomic status and cigarette smoking. Odds ratios were adjusted for *Helicobacter pylori* status in one study (Kikuchi *et al*., 2002). In 25 case–control studies, of which 11 were published in English (Lee *et al*., 1990; Boeing *et al*., 1991; Jedrychowski *et al*., 1993; Falcao *et al*., 1994; Inoue *et al*., 1994; Ji *et al*., 1996; De Stefani *et al*., 1998a; Zaridze *et al*., 2000; Muñoz *et al*., 2001; Kikuchi *et al*., 2002; Shen *et al*., 2004), an association was found between stomach cancer and alcoholic beverage consumption. The point estimates of adjusted odds ratios for an association between alcoholic beverage consumption and the risk for stomach cancer were between 2.4 and 2.8 for 2–3 drinks per day.

2.7.3 *Anatomic subsite and histological type (Table 2.40)*

Among 12 case–control studies of both cardia cancer and distal stomach cancer, eight demonstrated a stronger association for cardia cancer than for distal stomach

Table 2.38 Case–control studies of stomach cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Lee *et al*. (1990), Taiwan, China, 1954–88	210 (123 men, 87 women); histologically confirmed; adenocarcinoma, 97.7%; other type of carcinoma, 2.3%; participation rate, 90%; death certificate from Taiwan Provincial Department of Health	810 (478 men, 332 women) from ophthalmic service in four major hospitals in Taibei; matched with cases on hospital, age, sex; participation rate, 96%	Interviewer-administered structured questionnaire		*Days/week* None 1–3 ≥4	 150 21 39	 1.0 0.93 1.51; $p<0.05$	Smoking; green tea drinking, salted meat consumption, fried food consumption, fermented bean consumption, milk consumption	Frequency and duration of alcoholic beverage drinking both associated with stomach cancer; dose–response relationship
Boeing *et al*. (1991), Germany, 1985–88	143 incident, almost equal number of men and women, aged 32–80 years; histologically confirmed; patients from 5 hospitals in Germany	579 hospital patients and visitors; matched by 2:1 match by age (±3 years), sex	Interviewer-administered standardized questionnaire		*Beer* None <100 g/day 100–500 g/day >500 g/day *Wine* None <20 g/day >20 g/day *Liquor* None <2 g/day >2 g/day	 37 24 50 32 69 53 21 107 22 14	 1.0 1.12 (0.62–2.01) 2.22 (1.30–3.77) 1.82 (0.95–3.50) $p<0.05$ 1.0 0.94 (0.61–1.45) 0.52 (0.30–0.93) $p<0.05$ 1.0 0.75 (0.43–1.29) 0.52 (0.27–1.00) $p<0.05$	Age, sex, hospital	Beer is the dominant alcoholic beverage in the study area.

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Hoshiyama & Sasaba (1992a,b), Saitama, Japan, 1984–90	216 single and 35 multiple, newly diagnosed stomach adenocarcinomas (men); participation rate, 73%	483 randomly selected from electoral roll; stratification by sex, age; participation rate, 28%	Interviewer-administered standardized questionnaire		**Single stomach cancer**			Age, smoking status	No association between single and multiple stomach cancer risk and alcoholic beverage consumption
					Never	33	1.0		
					Past	11	1.0 (0.4–2.2)		
					Occasional	48	1.0 (0.6–1.7)		
					Daily	124	1.0 (0.6–1.6)		
							p=0.56		
					Total alcohol consumption (mL/lifetime)				
					Non-drinker		1.0		
					<500 000		0.9 (0.6–1.6)		
					≥500 000		1.1 (0.7–1.9)		
					Multiple stomach cancer				
					Never		1.0		
					Past		4.7 (1.0–21.6)		
					Occasional		2.6 (0.7–9.6)		
					Daily		1.4 (0.4–5.2)		
					Total alcohol consumption (mL/lifetime)				
					Non-drinker		1.0		
					<500 000		1.7 (0.4–6.4)		
					≥500 000		2.5 (0.7–9.3)		

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Jedrychowski *et al*. (1993), Poland, 1986–90	520 men, aged <75 years; histologically confirmed, classified according to the Lauren criteria; 137 cardia (58% intestinal, 20% diffuse type), 383 non-cardia (51.2% intestinal, 36% diffuse type); participation rate, 100%	520 men from nine university hospitals in Poland admitted mostly for accidents, orthopaedic problems or general surgery; matched by age (±5 years); disease of gastrointestinal tract and other cancers excluded; participation rate, 100%	Interviewer-administered standardized questionnaire		*Average quantity of vodka per occasion* Non-drinker 100 g 250 g >250 g *Frequency of vodka drinking* Non-drinker Very rare (<1/month) 1–3/month ≥1/week *Vodka drinking on an empty stomach* Non-drinker Not drinking before breakfast Drinking before breakfast	 68 85 208 159 68 132 205 115 68 401 51	 1.0 1.99 (1.23–3.23) 2.01 (1.33–3.05) 2.43 (1.57–3.75) $p<0.001$ 1.0 1.83 (1.18–2.83) 2.09 (1.38–3.16) 3.06 (1.90–4.95) $p<0.001$ 1.0 2.09 (1.42–3.08) 2.98 (1.60–5.53) $p<0.001$	Hospital, age, sex, occupation, education, sausage consumption, fruit/vegetable consumption, smoking	Non-drinkers: abstainers or who reported drinking vodka occasionally but less than 100 g at a time; those who drank vodka before breakfast had a nearly threefold elevated risk; findings on alcoholic beverages other than vodka not reported.

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Kabat *et al*. (1993), USA, 1981–90	Adenocarcinoma of the oesophagus/ cardia (160 men, 21 women), squamous-cell carcinoma of the oesophagus (122 men, 78 women), adenocarcinama of distal stomach (113 men, 30 women); newly diagnosed, histologically confirmed	Hospitalized patients with disease not related to smoking and of organ systems other than the gastrointestinal tract (4162 men, 2222 women); matched by age (±5 years), sex, race, hospital	Interviewer-administered structured questionnaire; all subjects were interviewed in 28 hospitals in eight cities in the USA between 1981 and 1990	ICD-9 (150, 151.0, 151.1–151.9)	**Adenocarcinama of distal stomach** *Men* Non-drinker Occasional 1–3.9 oz WE/day ≥4 WE/day *Women* Non-drinker Occasional 1–3.9 oz WE/day ≥4 WE/day		 1.0 1.0 (0.6–1.7) 0.5 (0.3–0.9) 0.7 (0.4–1.3) 1.0 0.6 (0.3–1.4) 0.6 (0.2–1.8) 0.9 (0.3–3.1)	Age education, smoking, hospital, time period (1981–84, 1985–90)	Non-drinker: less than 1 drink per week; occasional: ≥ 1 drink per week but < 1 drink per day; WE: whiskey-equivalent; analysis limited to whites; joint effect of smoking and drinking (analysis limited to men), 0.9 (0.5–1.5) for adenocarcinama of distal stomach and 2.4 (1.3–4.2) for oesophagus/ cardia
D'Avanzo *et al*. (1994), Milan, Italy, 1985–93	746 (457 men, 289 women), aged 19–74 years; histologically confirmed incident; refusal rate, 5%; admitted to National Cancer Institute; 5 major hospitals in Milan	2053 hospitalized (1205 men, 848 women) for acute non-neoplastic non-digestive tract disease, aged 19–74; >90% from Italy; refusal rate, 5%;	Interviewer-administered standardized questionnaire		Non-drinkers <2 drinks/day 2<4 drinks/day 4<6 drinks/day 6<8 drinks/day ≥8 drinks/day *Duration (years)* Non-drinkers <30 ≥30	187 115 199 109 52 84 187 132 427	1.0 1.1 (0.9–1.5) 1.1 (0.9–1.4) 1.1 (0.8–1.5) 1.3 (0.9–1.9) 1.6 (1.1–2.2) p<0.05 1.0 1.1 (0.9–1.4) 1.2 (1.0–1.6) p<0.05	Sex, age, education	Conditions of controls: traumatic diseases, 47%; non-traumatic orthopaedic, 20%; acute surgical, 19%; other miscellaneous disorders, 14%

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Falcao *et al*. (1994), Portugal	74 selected from patients undergoing gastroscopy; histologically confirmed	193 patients undergoing gastroscopy or colonoscopy or other recto-sigmoidal procedure; patients accompanying patients; matched for age (± 5 years), sex	Interviewer-administered structured questionnaire		*Red wine consumed per week (g of alcohol)* <187 187–372 373–559 ≥560		 1.0 1.36 (0.64–2.93) 1.77 (0.63–4.98) 3.67 (1.42–9.49)		
Hansson *et al*. (1994), central and northern Sweden, 1989–92	338 (218 men, 120 women), aged 40–79 years; histologically confirmed; 74.1% of original sample	679 randomly selected from population registers; mean age, 67 years; 1:2 frequency-matched by age strata, sex; participation rate, 77.3%	Interviewer-administered structured questionnaire		*Total alcohol consumption (mL 100% alcohol/ month)* Non-drinkers 1–35 36–160 >160	 83 95 87 73	 1.0 1.17 (0.81–1.70) 1.11 (0.75–1.64) 0.92 (0.60–1.42) p=0.64	Age, gender, socioeconomic status	High alcohol intake tended to increase the risk associated with tobacco use; among non-drinkers, odds ratio for tobacco use was 0.53 (0.25–1.12) and, among drinkers, was 1.77 (1.22–2.57) (p=0.0073)

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Inoue *et al*. (1994), Nagoya, Japan, 1988–91	668 (420 men , 248 women); histologically confirmed; 123 cardia, 218 middle (body), 256 antrum, 71 unclassified	668 (420 men , 248 women) with no history of cancer or any other specific disease, randomly selected from outpatients at same hospital; matched by sex, age (± 2 years), time of hospital visit	Common self-administered questionnaire	ICD-9 (151.0–151.9)	Drinker (versus non-drinker) Current drinker Former drinker <1 year after quitting ≥1 year after quitting		1.23 (0.92–1.65) 1.16 (0.86–1.56) 1.87 (1.11–3.15) $p<0.05$ 2.60 (1.09–6.19) $p<0.05$ 1.60 (0.87–2.94)	Sex	Joint effect of smoking and drinking: 1.97 (1.14–3.42); especially in the development of cardia cancer, 4.70 (1.10–20.2) ; drinkers included ‘ex-drinkers’; only data for men were presented.

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Gajalakshmi & Shanta (1996), India, 1988–90	388 incident (287 men, 101 women); 75% confirmed histologically, 25% by barium meal, exploratory surgery or endoscopy	287 men and 101 women cancer patients from Cancer Institute, diagnosed in 1988–90; site of cancer: penis, 23.5%; bone and connective tissue, 15.2%; skin, 13.1%; cervix, 11.9%; leukaemia, 6.2%; prostate, 6.2%; breast, 5.2%; other sites, 18.7%; 1:1 matched by age (± 5 years), sex, religion, mother tongue; cancers of gastrointestinal tract, bladder and pancreas and smoking-related cancers excluded	Interviewer-administered standardized questionnaire		Non–drinkers Former drinkers Current drinkers Former and current	285 37 66 103	1.0 1.4 (0.54–3.40) 0.8 (0.41–1.77) 1.1 (0.58–1.95)	Chewing habit, income group, education, residence (multivariate model)	Controls were cancer patients.

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Ji *et al.* (1996), Shanghai, China, 1988–89	1124 (770 men, 354 women), aged 20–69 years; 52.1% confirmed histologically, 48% by surgery, endoscopy, X–rays or ultrasound as cancer of cardia (16%), distal stomach (70%) or unclassified (14%); participation rate, 65.5%	1451 (819 men, 632 women) randomly selected permanent residents in Shanghai; frequency-matched for age, sex; participation rate, 85.8%	Interviewer-administered structured questionnaire	ICD-9 (151.0, 151.1–151.8, 151.9)	*Ethanol intake (g/week)*		*Men*	Age, income, education, smoking	Risk for distal cancer among men increased more than twofold (odds ratio, 2.21; 95% CI, 1.28–3.82) for users of both tobacco and alcohol relative to non-users but no statistically significant interaction between lifetime amounts of smoking and alcoholic beverage drinking; data for women not presented.
					<175	75	1.02 (0.71–1.49)		
					175–349	80	1.00 (0.70–1.43)		
					350–524	79	1.08 (0.75–1.53)		
					≥525	79	1.19 (0.84–1.68)		
							p=0.36		
					Non-drinker	483	1.0		
					Former drinker	27	1.91 (1.16–3.15)		
					Current drinker	307	1.04 (0.84–1.30)		
					Duration (years)				
					<15	100	0.80 (0.57–1.13)		
					15–< 34	113	1.21 (0.90–1.63)		
					≥35	121	1.30 (0.96–1.75)		
							p=0.06		
					Lifetime ethanol intake (g/week × years)				
					<2450	76	0.68 (0.46–1.02)		
					2450–7462	79	1.37 (0.98–1.93)		
					7463–15 399	79	0.87 (0.60–1.25)		
					≥15 400	78	1.39 (0.99–1.95)		
							p=0.12		

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Zhang *et al*. (1996), USA, 1992–94	95 (79 men, 16 women) incident with pathological diagnosis of adenocarcinomas of oesophagus and gastric cardia, 67 (43 men, 24 women) with adenocarcinoma of the distal stomach; participation rate, 81%	132 (62 men, 70 women) consecutive patients scheduled to have an upper gastrointestinal endoscopy in the cancer centre and later classified as cancer-free; participation rate, 81%	Self-administered modified National Cancer Institute Health Habits History Questionnaire	ICD-0 (150.0–150.9; 151.0, 151.1–151.9)	*ACDS* No ≤1/week >1/week *ACOGC* No ≤1/week >1/week	 20 20 27 14 26 55	 1.00 1.60 (0.65–3.93) 0.98 (0.43–2.27) *p*=0.93 1.0 3.02 (1.14–8.02) 2.02 (0.85–4.82) *p*=0.19	Age, sex, race, education, pack–years of smoking, body mass index, total dietary intake of calories	Frequency of self-reported alcohol use multiplied by 0.5 if patient's portion size was small; by 1 if the portion size was medium; and by 1.5 if the portion size was large.
Gammon *et al*. (1997), Connecticut, USA, 1993–95	Gastric cardia adenocarcinomas (223 men, 38 women), other gastric adenocarcinomas (254 men, 114 women); aged 30–79 years; histologically confirmed, newly diagnosed; all identified by use of established rapid-reporting systems	695 (555 men, 140 women) identified by Waksberg's random-digit dialling, aged 30–64 years; frequency-matched by age, sex; overall response rate, 70.2%	Structured questionnaire administered by trained interviewers		*Any intake* Never Ever <5 drinks/week 5–11 drinks/week 12–30 drinks/week >30 drinks/week	 125 238 74 68 55 41	*Gastric adenocarcinoma* 1.0 0.8 (0.6–1.1) 0.7 (0.5–1.1) 0.9 (0.6–1.3) 0.7 (0.4–1.0) 0.6 (0.4–1.0)	Age, sex, geographical centre, race, body mass index, income, cigarette smoking, all other types of alcohol use	Interviews administered directly to the study subject, rather than to the closest next of kin (usually the spouse) for more than 67% of cases and 96% of controls

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Muñoz *et al*. (1997), northern Italy, 1985–92	88, aged <75 years (median age, 62 years) reported a family history of stomach cancer in first degree relatives; refusal rate <3%	103 hospital controls (median age, 57 years) reported a family history of stomach cancer in first degree relatives; 80% of cases and controls resided in the same region and >90% in northern Italy.	Structured interview		<1 day/week 1–3 days/week ≥4 days/week	26 31 31	1.0 0.61 (0.34–1.42) 0.73 (0.27–1.98)	Sex, age, residence, education	88 cases and 103 controls reported a family history of stomach cancer in first degree relatives.
DeStefani *et al*. (1998a), Montevideo, Uruguay, 1992–96	331 men, aged 25–84 years; admitted to any of four major hospitals in Montevideo; 311 microscopically confirmed adenocarcinoma of stomach; 77.2% located in the antrum and pylorus; response rate, 92.8%	622 hospitalized men; frequency-matched by age, residence; response rate, 92.6%	Interviewer-administered standardized questionnaire		*Total alcohol consumption* Non–drinkers 1–60 g 61–120 g >120	 64 70 65 112	 1.0 1.0 (0.7–1.5) 1.5 (0.9–2.3) 2.4 (1.6–3.7) p<0.001	Age, residence, smoking, vegetable intake	Pure alcohol content was calculated according to concentrations specific to Uruguay: 6% for beer; 12% for wine and 46% for spirits.

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
López-Carrillo *et al*. (1998), Mexico (no study dates given)	220 (44.5% women 55.4% men), aged 24–88 years; histologically confirmed adenocarcinoma of the stomach from 15 large hospitals	752 (60.6% women, 39.4% men) population-based, aged 20–98 years; surrogate responders, 7%	Structured interview		*Ethanol (g/day)* Abstainers <1.5 1.5–4.9 ≥5.0	 91 23 59 47	 1.0 1.01 (0.52–1.96) 1.27 (0.76–2.11) 1.93 (1.00–3.71) *p*=0.068	Age, sex, total calorie intake, chili pepper, history of peptic ulcer, socioeconomic status, cigarette smoking, fruit, vegetables, salt, processed meats	One drink (1 oz or 30 mL) of tequila = 14.03 g ethanol; one drink (200 mL can/bottle) of beer = 12.96 g; one drink (60 mL) of wine = 9.58 g; and one drink of rum or brandy (30 mL) = 14.03 g ethanol; cases represented 80% of stomach cancer cases reported to the Mexican National Cancer Registry

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Chow *et al*. (1999), Warsaw, Poland, 1994–97	464 (302 men, 162 women) from 22 hospitals in Warsaw, aged 21–79 years; confirmed histologically mainly as intestinal (67%) or diffuse (14%); participation rate, 90%	480 (314 men, 166 women) Warsaw residents randomly selected from a computerized registry of all legal residents in Poland; frequency-matched by age, sex; participation rate, 82%	Interviewer-administered standardized questionnaire; a 30-mL blood sample collected	(ICD-0; 151 ICD-0-2 C16)	Current non–drinker	170	1.0	Age, education, years lived on a farm, pack–years of cigarette smoking, history of cancer	Current drinking of beer, wine or liquor was inversely related to risk for stomach cancer among men but not women.
					<1 drink/week	41	0.7 (0.4–1.2)		
					1–<3 drinks/week	42	0.5 (0.3–0.9)		
					3–<7 drinks/week	32	0.4 (0.2–0.7)		
					≥7 drinks/week	79	1.2 (0.7–2.0)		
					Age started (years)				
					<20	81	0.5 (0.3–0.8)		
					20–24	66	0.5 (0.3–0.9)		
					≥25	44	1.0 (0.6–1.7)		
					Drink–years				
					<10	72	0.6 (0.4–0.9)		
					10–19	29	0.5 (0.3–0.9)		
					20–29	20	0.6 (0.3–1.3)		
					30–39	12	0.5 (0.2–1.3)		
					40–79	32	1.3 (0.6–2.6)		
					≥80	27	1.0 (0.5–2.0)		
Ye *et al*. (1999), northern and central Sweden, 1989–95	90 (71 men, 19 women) gastric cardia cancer, 260 (190 men, 70 women) and 164 (87 men, 77 women) distal gastric cancer of intestinal and diffuse types, aged 40–79 years; histologically confirmed; participation rate, 62%	1164 (779 men, 385 women) randomly selected from population registers, aged 40–79 years; frequency-matched by age, sex; participation rate, 76%	Interviewer-administered structured questionnaire		*Total alcohol consumption (mL 100% alcohol/ month)*			Age, gender, residence area, body mass index, socioeconomic status, smoking, use of smokeless tobacco, use of different kinds of alcoholic beverages	Interviewed about lifetime smoking, use of smokeless tobacco and use of alcohol 20 years ago
							Intestinal type		
					Non-drinkers	52	1.0		
					1–35	64	1.2 (0.8–1.9)		
					36–160	73	1.2 (0.8–1.9)		
					>160	66	1.2 (0.7–1.9)		
							p=0.56		
							Diffuse type		
					Non-drinkers	36	1.0		
					1–35	50	1.3 (0.8–2.1)		
					36–160	42	1.0 (0.6–1.7)		
					>160	34	1.0 (0.5–1.8)		
							p=0.73		

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Zaridze *et al*. (2000), Moscow, Russia, 1996–97	448 (248 men, 200 women), aged <75 years; confirmed histologically as cancer of cardia (92) or non-cardia (356); lived in Moscow city; participation rate, 98%	610 (292 men, 318 women) patients restricted to Moscow city residents; conditions included respiratory (10%) and heart (10%) diseases, diseases of the nervous system (10%) and hypertension and stroke (9%); cancer and/or gastrointestinal diseases excluded; participation rate, 97%	Self-administered questionnaire; blood samples		*Gastric cardia* Never Ever Never Ever *Non-gastric* Never Ever Never Ever	 4 56 14 18 20 168	*Men* 1.0 2.7 (0.9–8.3) *Women* 1.0 0.8 (0.4–1.9) *Men* 1.0 1.7 (1.1–3.2) *Women* 1.0 1.3 (0.8–1.9)	Age, education, smoking	There was an effect of interaction between smoking and vodka consumption on the risk for cardia cancer.

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Muñoz *et al*. (2001), Venezuela, 1991–97	292, aged >35 years; histologically confirmed; non-epithelial tumours of the stomach excluded	485 (119 hospital, 366 neighbourhood); 1:2 matched by age (±5 years), sex	Structured interview				*Men*	Age, socioeconomic status	Only 1/143 female controls reported being an ever drinker; analysis of alcoholic beverage consumption therefore confined to men; most common forms of alcohol consumed were beer and aguardiente (sugar cane spirit): 69% of men who were current or former drinkers drank beer, 52% drank aguardiente and 28% drank other alcoholic drinks.
					Never/occasional	89	1.0		
					Current	76	2.9 (1.9–4.3)		
					Former	42	3.5 (2.0–6.0)		

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Wu *et al.* (2001), Los Angeles, USA, 1992–97	277 cancer of cardia (231 men, 46 women), 443 distal stomach (261 men, 182 women), aged 30–74 years; histologically confirmed; participation rate, 56%	1356 whites, latinos, African-Americans and Asian Americans (999 men, 357 women); matched by sex, race, date of birth, ethnicity; neighbourhood control subject was sought by use of a systematic algorithm based on the address of the case patient; diagnosis of stomach or oesophageal cancer excluded	Interviewer-administered structured questionnaire, completed by 55% of those identified and 77% of those approached		*Gastric cardia* Never Former Current *Distal* Never Former Current	 48 118 109 148 150 194	 1.0 0.91 (0.6–1.4) 0.98 (0.7–1.5) 1.0 0.85 (0.6–1.2) 0.96 (0.7–1.3)	Age, sex, smoking, race, birth place, education	Race: whites, African-Americans, latinos and Asian Americans

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Hamada *et al.* (2002), Sao Paulo, Brazil, Japanese ancestry, 1991–94	96 (60 men, 36 women) of Japanese ancestry; aged 38–89 years; histologically confirmed; among 87 cases with known location, 80 tumours (92%) were in the lower portion (body or antrum); no patients refused the interview	192 (120 men, 72 women) patients; 80 of 192 patients recruited voluntarily from the Japanese community in Sao Paulo; matched by age (± 5 years), sex	Interviewer-administered standardized questionnaire; 15-mL blood sample		*Consumption frequency* <1/month 1 day/month–4 days/week Daily *Lifetime alcohol consumption* <1000 g 1000–2000 g >2000 g	 68 17 11 84 2 8	 1.0 1.7 (0.8–3.9) 1.8 (0.7–4.7) $p = 0.16$ 1.0 0.5 (0.1–2.7) 2.0 (0.6–2.5) $p = 0.38$	Country of birth	Alcohol consumption not associated with risk for stomach cancer
Kikuchi *et al.* (2002), Tokyo, Japan, 1993–95	718 (494 men, 224 women), aged <70 years; histologically confirmed; classified by type (intestinal or diffuse), stage (early or advanced) and subsite of the lesions (proximal, middle or distal)	883 (448 men, 435 women) recruited from several health check programmes in a hospital in the same area between June 1993 and November 1994	Self-administered questionnaire; sera provided		*Alcohol–years*[a] 0 (never drinker) Occasional (1–134.9) 135–1349.9 ≥1350 0 (never drinker) Occasional (0.1–134.9) ≥135.0	 34 31 90 138 57 29 15	*Men* 1.89 (0.97– 3.69) 1.0 2.82 (1.63– 4.86) 2.84 (1.97–4.83) *Women* 1.54 (0.90–2.63) 1.0 1.39 (0.66–2.93)	Age, smoking, *Helicobacter pylori* status	Alcohol–years (mL intake of pure alcohol per day multiplied by years of drinking); a J- or U-shaped effect on risk for stomach cancer; models designated ‘occasional’ drinker as reference or ‘never’ drinker as reference

Table 2.38 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Nishimoto *et al*. (2002), Sao Paulo, non-Japanese Brazilians, 1991–94	236 (170 men, 66 women) with no Asian background, aged 40–79 years; 78% white; no refusal to be interviewed	236 (170 men, 66 women) hospital-based; matched by age (±5 years), sex; 86.4% white; refusal rate, 8.4%	Interviewer-administered standardized questionnaire; 15-mL blood sample		*Consumption frequency* <1/month 1 day/month–4 days/week Daily *Lifetime alcohol consumption* <1000 g 1000–2000 g >2000 g	 158 29 49 173 10 41	 1.0 0.4 (0.2–0.8) 1.1 (0.7–1.9) p=0.93 1.0 1.9 (0.6–5.9) 1.0 (0.6–1.6) p=0.88	Race (white or non-white), education, fruit and vegetable intake	Alcohol consumption not associated with risk for stomach cancer; the association did not change when analysis restricted to men.
Shen *et al*. (2004), China, 1997–98	165 (110 men, 55 women), aged 34–81 years; 108 intestinal-type gastric cancer, 57 gastric cardia cancer; identified by endoscopic and pathological diagnosis	295 (190 men, 105 women) healthy cancer-free subjects living in the same community, either siblings of cases or non-blood relatives (spouses and spouses' siblings of same gender as cases), aged 30–78 years	Interviewer-administered structured questionnaire; blood sample		Never Current Past	97 18 50	1.00 0.18 (0.10–0.35) 1.80 (1.06–3.08) p<0.01	Age, gender	Possible recruitment bias in the selection of controls including cases' siblings

ACDS, adenocarcinoma of distal stomach; ACOGC, adenocarcinoma of oesophagus and gastric cardia; CI, confidence intreval; ICD, International Clasification of Diseases Odds ratio when risk of the second category is defined as 1.0

Table 2.39 Case–control studies of stomach cancer and alcoholic beverage consumption in China (published in the Chinese literature)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Hu *et al*. (1989), Heilungjiang, Harbin, 1985–86	241; age and sex distribution not given; 100% histologically confirmed; response rate not given	Hospital patients from surgery department (non-cancer); matched to cases on age, sex, residence; response rate not given	Interviewer-administered questionnaire	Salty food intake + alcoholic beverage drinking Alcoholic beverage drinking + years of having chronic gastritis	*Odds ratios* 1.80 5.53	Hardness of food, average vegetable intake, smoking index, salty food intake, years of having chronic gastritis	95% CI not provided [*p*-value <0.05]
Wu & Yao (1994), Shanshi, 1990	200 incident (178 men, 22 women), aged 30–79 years; 100% histologically confirmed; response rate not given	200 population; matched to cases on residence, sex, race, occupation, age	Interviewer-administered questionnaire	*Intake* >1 time/week	*Odds ratio* 2.87	Logistic models	

Table 2.39 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Ye *et al.* (1998), Changle and Fuqing cities of Fujian Province, 1994–95	272 (233 men, 39 women), aged 30–78 years; lived in that area for more than 20 years; histologically or surgically confirmed; response rate not given	1:2 population; matched to cases by age, race, residence; not diagnosed with stomach diseases for past 3 years	Interviewer-administered questionnaire	Hard liquor Liquor Wine Beer	*Odds ratios* 1.41 (0.63–3.1) 1.12 (0.86–1.47) 1.09 (0.89–1.33) 1.33 (0.93–1.88)		
Qiu *et al.* (1999), Guangxi, 1992–97	319 hospitalized (226 men, 93 women), aged 18–76 years; 100% histologically confirmed; response rate not given	1:1 population, aged 17–78 years; matched to cases by sex, age, residence; not diagnosed with any malignancy; response rate not given	Interviewer-administered questionnaire	Alcohol drinking	*Odds ratio* 6.22 (3.08–10.92)	Multivariate logistic regression modeling	

Table 2.39 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Sun *et al.* (1999), Harbin, 1995–96	361 hospitalized (264 men, 97 women); aged 30–74 years; mean age: men (58.3), women (57.4); 100% histologically confirmed; response rate not given	1525 randomly selected healthy population; age similar to cases; mean age: men (48.5); women (48.6)	Interviewer-administered questionnaire	Intake No Yes	 1.0 1.82 (1.37–2.41)	Age, sex, education, occupation, smoking	Odds ratio for smoking + drinking white wine + having chronic stomach diseases, 62.55 (18.44–212.18)
Sun *et al.* (2000), Harbin, 1996–99	201 (146 men, 55 women); mean age, 60.14 years; diagnosed by city hospitals; response rate not given	1818 (1560 men, 558 women) randomly selected from Harbin; mean age, 59.53 years; matched on sex, age; response rate not given	Interviewer-administered questionnaire	Alcohol drinking Smoking and drinking	1.29 (0.89–1.86) 2.34 (1.52–2.60)	Not listed	Categorization of each variable not listed

Table 2.39 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Ding *et al.* (2001a,b) Taixing, Jiungsu, 1998–99	591 oesophageal cancer, 360 liver cancer, 430 stomach cancer (921 men, 460 women), aged 21–89 years; not histologically confirmed; response rate not given	1:1 population; matched on age, sex, residential area; response rate not given	Interviewer-administered questionnaire	Drinking white wine	*Odds ratio* 2.76	Results from multivariate logistic regression models	95% CIs not provided; categorization of variable not clear
Shen *et al.* (2001), Yangzhong, Jiangsu, 1997–98	265 with endoscopy and pathology diagnosis (117 from higher incidence area; 148 from lower incidence area); sex and age distribution not described, but percentage of men and mean age significantly higher in cases than in controls	2066 (850 from higher incidence area; 1216 from lower incidence area) selected from the spouse and siblings of cases or the sibling-in-law	Interviewer-administered questionnaire	Men ever drinking alcohol in higher incidence area Men ever drinking alcohol in lower incidence area	*Odds ratio* 3.6 3.7 (1.3–10.8)	Results from multivariate logistic regression model	CI not clear

Table 2.39 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Tong *et al.* (2001), Tongliao, Inner Mongolia, 1999	76 oesophageal cancer (71 men, 5 women), aged 39–80 years; mean age, 58.5 years; 44 stomach cancer (35 men, 9 women), aged 35–78 years; mean age, 58.6 years; 100% histologically confirmed; response rate not given	1:3 hospital patients, aged 33–82 years; mean age, 58.2 years; matched on age, sex, residence area, time of diagnosis; response rate not given	Interviewer-administered questionnaire	Oesophagus and stomach combined Alcohol drinking (Yes/No)	*Odds ratio* 4.15 (1.71–15.92)	Results from multiple logistic regression model	

Table 2.39 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Zheng *et al.* (2001), Fujian, 2000	251 (93 cardia, 85 non-cardia gastric cancer, 73 non-digestive tract cancer), aged 30–79 years; sex ratio (men/women), 6; lived in Fujian for more than 20 years; answered questions clearly; diagnosis confirmed by pathology, surgery, or endoscopy; response rate, 98.1%	97 hospital patients selected from orthopaedics and urinary departments, aged 30–79 years; lived in Fujian for more than 20 years; answered questions clearly; response rate, 98.1%	Interviewer-administered questionnaire	Hard liquor (Yes/No)	Cardia 3.25 (0.90–8.41) Non-cardia 2.08 (0.88–4.96)		
Chen *et al.* (2002b), Changle, Fujian, 1999	310, mean age, 60.8 years; sex ratio (male/female), 5; 95% histologically confirmed	1:1 selected from neighbours or colleagues of cases; matched to cases by age	Interviewer-administered questionnaire				No significant association between alcohol drinking and the use of refrigerator and the risk for stomach cancer.

Table 2.39 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Gao *et al*. (2002a,b), Huaian, Jiangsu, 1997–2000	153 stomach cancer (118 men, 35 women); mean age, 61.1 years for men, 59.8 years for women; 141 oesophageal cancer (78 men, 63 women); mean age, 60.9 years for men, 60.7 years for women; 100% histologically confirmed; response rate not given	223 randomly selected population (149 men, 74 women); mean age, 58.9 years for men, 57.6 years for women; matched to cases on age; response rate not given	Questionnaire; blood samples	Alcohol drinking (frequently versus not)	1.76 (1.01–3.07)	Sex, age, vegetable intake, fruit intake, pickled vegetables, meat intake, soya product intake	Alcohol drinking increased the risk for stomach cancer among GSTM1 non-null people.

Table 2.39 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Mu *et al.* (2003), Taixing, Jiangsu, 2000	206 stomach cancer, 204 liver cancer, 218 oesophageal cancer; sex ratio (male/female), 2 for stomach, 3.5 for liver, 2 for oesophageal cancer; aged >50 years, 88.1% for stomach cancer, 59.8% for liver cancer, 85.8% for oesophageal cancer	415 healthy population from Taixing; selected according to age and sex distributions of three case series; lived in Taixing for more than 10 years; sex ratio (male/female), 2.15; aged ≥50 years, 75.8%	Interviewer-administered questionnaire; blood samples	*Green tea drinkers* Alcohol drinking Not frequent Frequent *Green tea non-drinkers* Alcohol drinking Not frequent Frequent	 1.0 0.44 (0.23–0.86) 1.0 2.32 (1.23–4.38)	Age, sex, education level	

Table 2.39 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Fei & Xiao (2004), Shanghai	189 hospitalized, aged 29–91 years; mean age, 63.6 years; sex ratio (male/female), 1.4; 100% histologically confirmed; response rate not given	567 selected from the same hospital (medical check-up patients, non-digestive tract disease, non-cancer patients) as cases or from neighbours of cases; no difference between case and control groups on age, sex, ethnic group, residential area; response rate not given	Interviewer-administered questionnaire	Alcohol drinking (yes vs no)	*Odds ratio* 2.38 (1.48–3.82)		Univariate logistic regression analysis

Table 2.39 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Yang *et al.* (2004), Jintan, Huaian, Jiangsu, 1998–2003	285 (212 men, 73 women), aged 31–84 years; mean age, 61.4 years; % of histologically confirmed not given; response rate not given	265 (191 men, 74 women) aged 30–87 years; mean age, 61.5 years; selected and matched 1:1 to cases on residency, ethnic group, sex, age; residents with cancer and digestive tract diseases and those who did not answer questions clearly excluded; response rate not given	Questionnaire; blood sample	Alcohol drinking (yes/no)	*p*-value, 0.84	Crude analysis	

Table 2.39 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Luo (2005), Luoyang, Henan, 2003–2004	153 (117 men, 36 women), aged 38–74 years; lived in Luoyang for at least 15 years	153 healthy selected randomly from Luoyang; matched to cases on age, sex, ethnicity; lived in Luoyang for more than 15 years	Interviewer-administered questionnaire	Alcohol drinking (yes versus no)	2.14 (1.42–3.21)	Not described	Variables not well defined

CI, confidence interval; GSTM1, gluthathione *S*-transferase M1

Table 2.40 Selected cohort and case–control studies of cancer in subsites of the stomach and intake of alcoholic beverage

Reference, study location, period	Alcoholic beverage consumption	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)
Cohort studies									
Sasazuki *et al*. (2002), Japan, Japan Public Health Cohort Study		**Cardia and upper third gastric**		**Distal gastric cancer**					
		All histological types		*Differentiated type*		*Undifferentiated type*			
	0–3 times/month	3	1.0	32	1.0	17	1.0		
	0–161.0 g/week	8	2.5 (0.7–9.5)	27	0.9 (0.5–1.5)	11	0.7 (0.3–1.4)		
	162.0–322.0 g/week	13	3.3 (0.9–11.6)	38	1.1 (0.7–1.8)	15	0.9 (0.5–1.9)		
	≥322.5 g/week	11	3.0 (0.8–11.1)	27	0.9 (0.5–1.5)	20	1.3 (0.7–2.6)		
			p=0.66		p=1.00		p=0.07		
Lindblad *et al* (2005), United Kingdom, General Practitioner Research Database (nested case–control study)		*Gastric cardia*		*Non–cardia gastric*		*Unknown subsite of gastric adenocarcinoma*			
			Odds ratio		**Odds ratio**				
	Units/day								
	0–2	55	1.00	124	1.00	172	1.00		
	3–15	33	1.08 (0.70–1.69)	61	0.99 (0.72–1.36)	72	0.82 (0.61–1.09)		
	16–34	14	1.22 (0.67–2.24)	19	0.91 (0.55–1.51)	25	0.79 (0.51–1.22)		
	>34	4	1.04 (0.37–2.93)	2	0.29 (0.07–1.18)	10	0.96 (0.49–1.87)		
	Unknown use	89	1.38 (0.84–2.26)	121	0.57 (0.38–0.87)	222	1.20 (0.89–1.62)		

Table 2.40 (continued)

Reference, study location, period	Alcoholic beverage consumption	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)
Case–control studies									
Jedrychowski *et al*. (1993), Poland, 1986–90	Average vodka per occasion	**Cardia**				**Non-cardia**			
		Intestinalis		*Diffusum*		*Intestinalis*		*Diffusum*	
	Non-drinker	6	1.0	6	1.0	26	1.0	20	1.0
	100 g	13	2.12 (0.69–6.50)	5	1.22 (0.28–5.35)	38	2.48 (1.28–4.82)	17	1.10 (0.48–2.50)
	250 g	36	2.28 (0.83–6.31)	9	1.16 (0.31–4.40)	77	2.06 (1.14–3.71)	57	1.70 (0.87–3.34)
	>250 g	24	3.04 (1.11–8.28) p=0.03	8	1.64 (0.46–5.83) p=0.47	58	2.47 (1.35–4.51)	44	1.81 (0.91–3.58)
Kabat *et al*. (1993), USA, 1981–90		*Distal oesophagus/ cardia adenocarcinoma*		*Distal stomach adenocarcinoma*					
	Men	NR							
	Non-drinker		1.0		1.0				
	Occasional		2.0 (1.1–3.5)		1.0 (0.6–1.7)				
	1–3.9 oz WE/ day		2.1 (1.2–3.6)		0.5 (0.3–0.9)				
	≥4 oz WE/ day		2.3 (1.3–4.3)		0.7 (0.4–1.3)				
	Women	NR							
	Non-drinker		1.0		1.0				
	Occasional		0.6 (0.2–1.9)		0.6 (0.3–1.4)				
	1–3.9 oz WE/ day		0.9 (0.2–3.5)		0.6 (0.2–1.8)				
	≥4 oz WE/ day		3.8 (0.9–16.6)		0.9 (0.3–3.1)				

Table 2.40 (continued)

Reference, study location, period	Alcoholic beverage consumption	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)
Inoue *et al*. (1994), Nagoya, Japan, 1988–91		*Cardia*		*Middle*		*Antrum*			
	Drinker (versus non-drinker)	NR	1.60 (0.92–2.78)	NR	1.47 (0.94–2.28)	NR	1.00 (0.69–1.46)		
	Current drinker		1.45 (0.82–2.57		1.38 (0.88–2.16)		0.96 (0.65–1.41)		
	Former drinker		2.81 (1.21–6.54)		2.29 (1.12–4.68)		1.36 (0.69–2.70)		
	<1 year after quitting		3.71 (1.02–13.5)		3.63 (1.23–10.7)		2.16 (0.75–6.25)		
	≥1 year after quitting		2.47 (0.93–6.59		1.78 (0.75-4.23)		1.06 (0.46–2.45)		
Ji *et al*. (1996), Shanghai, China, 1988–89	**Men** *Ethanol (g/ week)*	*Cardia*		*Distal*					
	<175	8	0.55 (0.25–1.21)	51	1.14 (0.76–1.71)				
	175–349	14	0.75 (0.40–1.43)	54	1.08 (0.73–1.61)				
	350–524	23	1.37 (0.78–2.41)	57	1.07 (0.72–1.58)				
	≥525	16	0.81 (0.44–1.50) p=0.93	80	1.36 (0.93–1.97) p=0.17				
	Non-drinker	80	1.0	272	1.0				
	Former drinker	6	1.03 (0.40–2.67)	43	2.16 (1.27–3.69)				
	Current drinker	57	0.86 (0.58–1.28)	218	1.11 (0.87–1.38)				

Table 2.40 (continued)

Reference, study location, period	Alcoholic beverage consumption	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)
Ji *et al*. (1996), (contd)	*Duration (years)*								
	<15	10	0.52 (0.26–1.06	54	0.92 (0.63–1.34)				
	15–<24	27	1.19 (0.72–1.98)	89	1.23 (0.88–1.72)				
	≥35	26	0.88 (0.52–1.48)	115	1.40 (1.01–1.94)				
			p=0.88		*p*=0.03				
	Lifetime ethanol (g/week × years)								
	<2450	6	0.37 (0.15–0.88)	37	0.83 (0.54–1.28)				
	2450–7462	20	1.27 (0.71–2.26)	71	1.45 (1.00–2.11)				
	7463–15 399	18	1.01 (0.55–1.83)	46	0.83 (0.55–1.26)				
	≥15 400	17	0.84 (0.45–1.56)	88	1.55 (1.07–2.26)				
			p=0.91		*p*=0.06				
Zhang *et al*. (1996), USA, 1992–94		*Oesophagus and gastric cardia adenocarcinoma*		*Distal stomach adenocarcinoma*					
	No	14	1.00	20	1.00				
	≤1/week	26	3.02 (1.14–8.02)	20	1.60 (0.65–3.93)				
	>1/week	55	2.02 (0.85–4.82)	27	0.98 (0.43–2.27)				
			p=0.19		*p*=0.93				

Table 2.40 (continued)

Reference, study location, period	Alcoholic beverage consumption	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)
Gammon *et al*. (1997), USA, 1993–95	*Any*	*Gastric cardia adenocarcinoma*		*Other gastric adenocarcinomna*					
	Never	63	1.0	125	1.0				
	Ever	196	0.7 (0.5–1.1)	238	0.8 (0.6–1.1)				
	<5 drinks/ week	46	0.6 (0.4–1.0)	74	0.7 (0.5–1.1)				
	5–11 drinks/ week	59	0.8 (0.5–1.3)	68	0.9 (0.6–1.3)				
	12–30 drinks/week	52	0.7 (0.4–1.1)	55	0.7 (0.4–1.0)				
	>30 drinks/ week	39	0.7 (0.4–1.2)	41	0.6 (0.4–1.0)				
DeStefani *et al*. (1998a), Montevideo, Uruguay, 1992–96	*Total*	*Cardia*		*Fundus*		*Antrum*			
	1–60 g	8	1.0	7	1.0	49	1.0		
	61–120 g	6	0.6 (0.2–1.9)	7	1.1 (0.4–3.2)	78	1.5 (1.0–2.3)		
	>120 g	10	1.0 (0.4–2.7)	11	1.8 (0.6–5.1)	113	2.6 (1.7–3.9)		
			p=0.93		p=0.25		p<0.001		
Ye *et al*. (1999), Sweden, 1989–95	*Total (mL 100% alcohol/ month)*	**Cardia cancer** *All histological types*		**Distal stomach cancer** *Intestinal type*		*Diffuse type*			
	Non-drinker	18	1.0	52	1.0	36	1.0		
	1–35	20	0.9 (0.4–1.9)	64	1.2 (0.8–1.9)	50	1.3 (0.8–2.1)		
	36–160	27	0.8 (0.4–1.7)	73	1.2 (0.8–1.9)	42	1.0 (0.6–1.7)		
	>160	22	0.7 (0.3–1.5)	66	1.2 (0.7–1.9)	34	1.0 (0.5–1.8)		
			p=0.30		p=0.56		p=0.73		

Table 2.40 (continued)

Reference, study location, period	Alcoholic beverage consumption	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)
Lagergren *et al*. (2000), Sweden	*Any*	*Gastric cardia adenocarcinoma*							
	Never	34	1.0						
	Ever	228	0.8 (0.5–1.2)						
	Ethanol (g)/ week								
	1–15	73	0.9 (0.5–1.5)						
	16–70	79	0.6 (0.4–1.1)						
	>70	76	0.9 (0.5–1.5)						
Zaridze *et al*. (2000), Moscow, Russia, 1996–97	*Vodka (L/ year)*	*Cardia (men)*		*Other subsites (men)*					
	Never	4	1.0	24	1.0				
	Low <2.6	16	2.8 (0.9–9.2)	62	2.0 (1.0–3.8)				
	Medium 2.6–10.4	19	3.6 (1.1–11.8)	62	2.2 (1.1–4.1)				
	High >10.4	21	3.9 (1.2–12.3)	40	1.3 (0.7–2.5)				
			p=0.03		p=0.77				
Wu *et al*. (2001), Los Angeles, USA, 1992–97		*Gastric cardia adenocarcinoma*		*Distal gastric adenocarcinoma*					
	1–7 drinks/ week		1.00 (0.7–1.5)		0.83 (0.6–1.2)				
	8–21 drinks/ week		0.70 (0.4–1.1)		0.68 (0.5–1.0)				
	22–35 drinks/week		1.09 (0.7–1.8)		1.10 (0.7–1.7)				
	≥36 drinks/ week		1.35 (0.8–2.3)		1.35 (0.8–2.2)				
			p=0.42		p=0.29				

Table 2.40 (continued)

Reference, study location, period	Alcoholic beverage consumption	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)
Kikuchi *et al*. (2002), Tokyo, Japan, 1993–95	*Alcohol–years*	*Proximal*		*Distal*					
	Men	NR							
	0		2.72 (1.13–6.53)		1.28 (0.60–2.76)				
	0.1–134.9		1.0		1.0				
	135–1349.9		2.24 (1.01–4.96)		1.85 (1.00–3.41)				
	≥1350		2.46 (1.17–5.17)		1.56 (0.86–2.84)				
			p=0.06		*p*=0.25				
	Women	NR							
	0 (never drinker)		1.50 (0.70–3.21)		1.69 (0.85–3.35)				
	0.1–134.9		1.0		1.0				
	≥135.0		0.43 (0.10–2.05)		1.78 (0.67–4.71)				
			p=0.21		*p*=0.28				

CI, confidence interval; NR, not reported

cancer. In two studies of histological types, the intestinal type seemed to be more strongly associated with alcoholic beverage consumption (Jedrychowski *et al*., 1993).

(a) Gastric cardia cancer

Prospective cohort studies have reported an association between alcoholic beverage consumption and the risk for adenocarcinoma of the gastric cardia and distal stomach (Sasazuki *et al*., 2002; Lindblad *et al*., 2005; Tran *et al*., 2005). Sasazuki *et al*. (2002) reported an elevated risk for cardia cancer of all histological types with alcoholic beverage consumption, although the relationship failed to reach significance. Tran *et al*. (2005) reported inverse associations for cardia and non-cardia cancer with alcoholic beverage consumption. The relative risks were 0.84 (95% CI, 0.72–0.97) for cardia cancer and 0.79 (95% CI, 0.61–1.02) for non-cardia cancer.

Among 12 case–control studies that reported an association between alcoholic beverage consumption and cardia cancer, five studies reported a statistically significant association (Jedrychowski *et al*., 1993; Kabat *et al*., 1993; Inoue *et al*., 1994; Zaridze *et al*., 2000; Kikuchi *et al*., 2002). The adjusted odds ratios were between 2.3 and 3.9 for heavy drinkers and a strong dose–response relationship was demonstrated in four of the five studies.

Zaridze *et al*. (2000) reported that the effect of hard liquor (vodka) consumption was stronger for cancer of the cardia in men. Compared with non-drinkers, the adjusted odds ratios in men were 2.8 (95% CI, 0.9–9.2) for light drinkers, 3.6 (95% CI, 1.1–11.8) for medium drinkers and 3.9 (95% CI, 1.2–10.2) for heavy drinkers.

An elevated risk for cardia cancer was observed among heavy drinkers in two case–control studies, but the results were not statistically significant (Zhang *et al*., 1996; Wu *et al*., 2001). Five studies observed no association between alcoholic beverage consumption and cardia cancer (Ji *et al*., 1996; Gammon *et al*., 1997; De Stefani *et al*., 1998a; Ye *et al*., 1999; Lagergren *et al*., 2000). In a population-based case–control study of 90 cases of gastric cardia cancer, 260 and 164 cases of intestinal and diffuse types of distal gastric cancer, respectively, results from Ye *et al*., (1999) showed that intake of alcoholic beverages was not associated with an increased risk for any type of cardia or gastric cancer. In a case–control study in Shanghai, China, Ji *et al*. (1996) examined the role of alcoholic beverage drinking as a risk factor for carcinoma by anatomic subsite of the stomach. Alcoholic beverage consumption was associated with a moderately excess risk for distal stomach cancer (odds ratio, 1.55; 95% CI, 1.07–2.26), but was not related to the risk for cardia cancer.

(b) Distal stomach cancer

Among 11 studies of distal stomach cancer, six observed a positive association (Jedrychowski *et al*., 1993; Inoue *et al*., 1994; Ji *et al*., 1996; De Stefani *et al*., 1998a; Zaridze *et al*., 2000; Kikuchi *et al*., 2002). The relationship was not as strong as that for cardia cancer, but the dose–response relationship was just as clear.

2.7.4 *Type of alcoholic beverage (Table 2.41)*

Some investigators considered the role of different types of alcoholic beverage and reported that the consumption of beer, spirits or wine did not affect the incidence of stomach cancer (Hansson *et al*., 1994; Zhang *et al*., 1996; Ye *et al*., 1999; Wu *et al*., 2001). In northern Italy, where wine was the most frequently consumed alcoholic beverage and accounted for approximately 90% of all alcoholic beverage consumption in the population, D'Avanzo *et al*. (1994) reported that the risk estimates adjusted for age and sex were 1.1 for light-to-moderate wine drinkers, 1.3 for intermediate drinkers, 1.6 for heavy drinkers and 1.4 for very heavy drinkers (≥8 drinks per day). López-Carrillo *et al*. (1998) reported an assessment of alcoholic beverage consumption in Mexico, including the popular Mexican liquor tequila, in relation to the incidence of stomach cancer. After adjustment for known risk factors, wine consumption was positively associated with the risk for developing stomach cancer (odds ratio, 2.93; 95% CI, 1.27–6.75) in the highest category of wine consumption, which corresponded to at least 10 glasses of wine per month, with a significant trend (P=0.005).

In a multicentric hospital-based case–control study carried out in Poland, the relative risk for stomach cancer increased as the frequency and amount of vodka drunk increased. People who drank vodka at least once a week had an threefold higher risk compared with non-drinkers (relative risk, 3.06; 95% CI, 1.90–4.95) (Jedrychowski *et al*., 1993). Alcoholic beverage consumption, particularly that of vodka, was found to increase the risk for gastric cancer in a Russian study (Zaridze *et al*., 2000). A case–control study that included 331 cases and 622 controls conducted in Montevideo, Uruguay, found that alcoholic beverage consumption (particularly that of hard liquor and beer) was associated with an odds ratio of 2.4 (95% CI, 1.5–3.9), after controlling for the effect of tobacco, vegetables and other types of beverage (De Stefani *et al*., 1998a). In another multicentric, hospital-based case–control study conducted in Germany, increased consumption of beer showed a positive association with risk whereas increased consumption of wine and liquor showed a significantly negative association (Boeing *et al*., 1991).

2.7.5 *Effect modification (Table 2.42)*

Several studies reported on the joint effects of alcoholic beverage consumption and tobacco smoking (Kabat *et al*., 1993; Hansson *et al*., 1994; Inoue *et al*., 1994; Ji *et al*., 1996; De Stefani *et al*., 1998a; Zaridze *et al*., 2000). The results of a case–control study in Nagoya, Japan, showed that the joint effect of drinking and smoking may play an important role in the development of stomach cancer, especially that of cardia cancer (odds ratio, 4.7; 95% CI, 1.1–20.2) (Inoue *et al*., 1994). However, most studies did not evaluate potential effect modification between alcoholic beverage consumption and tobacco smoking.

Table 2.41 Selected cohort and case–control studies of stomach cancer and different types of alcoholic beverage

Reference, location, period	Cohort/cases and controls	Beer			Wine			Hard liquor		
		Exposure	Cases	Relative risk (95% CI)	Exposure	Cases	Relative risk (95% CI)	Exposure	Cases	Relative risk (95% CI)
Cohort study										
Nomura *et al.* (1990), USA, Hawaii, American Men of Japanese Ancestry Study	7990 American men of Japanese ancestry, born 1990–19, residing on the Hawaiian island of Oahu; follow-up, 19 years	Non-drinker	64	1.0	Non-drinker	124	1.0	Non-drinker	86	1.0
		<10 oz/month	10	0.7 (0.4–1.4)	1 oz/month	13	1.1 (0.6–1.9)	<5 oz/month	29	0.9 (0.6–1.4)
		10–99 oz/month	17	1.2 (0.7–2.1)	≥2 oz/month	11	0.7 (0.4–1.3)	5–49 oz/month	26	1.5 (1.0–2.2)
		100–499 oz/month	28	1.1 (0.7–1.8)				≥50 oz/month	8	1.0 (0.5–2.1)
		≥500 oz/month	28	1.1 (0.7–1.7)						
Case–control studies										
D'Avanzo *et al.* (1994), Milan, Italy, 1985–93	746 cases of histologically confirmed stomach cancer; 2053 hospital controls	Non-drinker	672	1.0	Non-drinker	197	1.0	Non-drinker	650	1.0
		< 1 drink/day	35	0.9 (0.6–1.4)	<2 drinks/day	108	1.1 (0.8–1.4)	<1 drink/day	45	0.7 (0.5–0.9)
		1–2 drinks/day	15	1.6 (0.9–3.1)	2–<4 drinks/day	201	1.1 (0.9–1.4)	1–<2 drinks/day	31	1.0 (0.7–1.6)
		≥ 2 drinks/day	24	1.1 (0.7–1.9)	4–6 drinks/day	121	1.3 (1.0–1.7)	≥2 drinks/day	20	0.9 (0.5–1.5)
					6–<8 drinks/day	56	1.6 (1.1–2.4)			
					≥8 drinks/day	63	1.4 (1.0–2.0)			

Table 2.41 (continued)

Reference, location, period	Cohort/cases and controls	Beer			Wine			Hard liquor		
		Exposure	Cases	Relative risk (95% CI)	Exposure	Cases	Relative risk (95% CI)	Exposure	Cases	Relative risk (95% CI)
Hansson *et al.* (1994), Sweden, 1989–92	338 histologically confirmed cases of gastric cancer; 679 controls	Non-drinker	278	1.0	Non-drinker	154	1.0	Non-drinker	123	1.0
		Drinkers	60	0.95 (0.68–1.37)	1–59 mL/ month	86	1.35 (0.97–1.88)	1–79 mL/ month	98	1.23 (0.87–1.76)
					60–199 mL/ month	31	0.70 (0.44–1.13)	80–319 mL/ month	57	0.91 (0.61–1.38)
					200–599 mL/ month	51	0.21 (0.80-1.83)	≥320 mL/ month	60	1.27 (0.83–1.96)
					≥600 mL/ month	16	0.57 (0.31–1.04)			p=0.61
							p≥0.33			
Zhang *et al.* (1996), USA, 1992–94	95 adenocarcinomas of oesophagus and gastric cardia, 67 adenocarcinomas of the distal stomach; 132 cancer-free controls	No	20	1.00	No	20	1.00	No	20	1.00
		≤1/week	17	1.13 (0.46–2.76)	≤1/week	21	1.21 (0.51–2.83)	≤1/week	19	1.91 (0.76–4.79)
		>1/week	11	1.43 (0.45–4.58) p=0.55	>1/week	12	0.97 (0.36–2.58) p=0.99	>1/week	12	0.66 (0.22–1.99) p=0.73
Gammon *et al.* (1997), USA, 1993–95	368 gastric adenocarcinoma and 695 other gastric	Never	200	1.0	Never	258	1.0	Never	188	1.0
		Ever	166	0.8 (0.6–1.1)	Ever	108	0.7 (0.5–0.9)	Ever	177	1.0 (0.8–1.4)

Table 2.41 (continued)

Reference, location, period	Cohort/cases and controls	Beer			Wine			Hard liquor		
		Exposure	Cases	Relative risk (95% CI)	Exposure	Cases	Relative risk (95% CI)	Exposure	Cases	Relative risk (95% CI)
DeStefani et al. (1998a), Montevideo, Uruguay, 1992–96	331 cases; 622 controls (men only)	Non-drinker	265	1.0	Non-drinker	97	1.0	Non-drinker	166	1.0
		1–60 g/day	18	1.1 (0.6–2.1)	1–60 g/day	106	1.1 (0.7–1.5)	1–60 g/day	62	1.0 (0.7–1.5)
			20	1.9 (0.9–3.7)						
		61–120 g/day	0	–	61–120 g/day	72	1.4 (0.9–2.2)	61–120 g/day	30	1.7 (0.9–2.9)
				p=0.06						
		>120 g/day			>120 g/day	36	0.9 (0.4–1.8)	>120 g/day	53	2.1 (1.1–3.9)
							p=0.47			p=0.01
López-Carrillo *et al.* (1998), Mexico	220 newly diagnosed adenocarcinoma of the stomach; 757 population-based controls	Non-beer consumer	105	1.0	Non-wine consumer	133	1.0	Non-liquor consumer	114	1.0
		<1 drink/day	60	1.06 (0.64–1.73)	<1 drink	54	2.08 (1.26–3.44)			
		≥1 drink/day	54	1.04 (0.55–1.94)	≥1 drink	32	2.93 (1.27–6.75)	<1 drink/day	17	0.78 (0.38–1.61)
				p=0.115			p=0.005	≥1 drink/day	89	1.83 (1.07–3.10) p=0.175
Ye *et al.* (1999), Sweden, 1989–95	90 gastric cardia, 260 and 164 distal gastric cancer of intestinal and diffuse types; 1164 frequency-matched controls	Light beer			Non-drinker	65	1.0	Non-drinker	58	1.0
		<400 mL/month	118	1.0	1–59 mL/month	43	1.6 (1.0–2.6)	1–79 mL/month	41	0.9 (0.5–1.5)
		400–2399 mL/month	24	0.9 (0.5–1.4)	60–199 mL/month	15	0.6 (0.3–1.2)	80–319 mL/month	32	0.8 (0.5–1.5)
		≥2400 mL/month	22	0.9 (0.5–1.5) p=0.60	200–599 mL/month	25	1.3 (0.7–2.4)	≥320 mL/month	32	1.4 (0.7–2.8) p=0.42
					≥600 mL/month	15	1.1 (0.6–2.3) p=0.90			

Table 2.41 (continued)

Reference, location, period	Cohort/cases and controls	Beer			Wine			Hard liquor		
		Exposure	Cases	Relative risk (95% CI)	Exposure	Cases	Relative risk (95% CI)	Exposure	Cases	Relative risk (95% CI)
Wu *et al.* (2001), Los Angeles; USA, 1992–97	277 cardia, 443 non-cardia; 1356 controls	None		1.0	None		1.0	None		1.0
		<7 drinks/ week		0.90 (0.7–1.3)	<7 drinks/ week		0.90 (0.7–1.2)	<7 drinks/ week		0.63 (0.5–0.9)
		7–14 drinks/ week		1.01 (0.7–1.6)	7–14 drinks/ week		0.77 (0.5–1.3)	7–14 drinks/ week		0.61 (0.4–1.0)
		≥15 drinks/ week		1.67 (1.1–2.6)	≥15 drinks/ week		0.44 (0.2–1.2)	≥15 drinks/ week		0.70 (0.4–1.1)
				p=0.09			p=0.04			p=0.02

CI, confidence interval

Table 2.42 Cohort and case–control studies of stomach cancer and alcoholic beverage consumption in men and women

Study reference	Description	Drinking level	Men		Women	
			No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)
Cohort study						
Kato *et al*. (1992a), Japan	9753 Japanese men and women; age: men, ≥ 40 years; women, ≥ 30 years; response rate, 85.9%; follow–up 1986–91	None	8	1.00	18	1.00
		Occasional	9	2.31 (0.88–6.07)	3	1.12 (0.32–3.90)
		Daily <50mL	6	1.31 (0.45–3.81)	1	1.29 (0.17–9.69)
		Daily ≥50 mL	12	3.63 (1.44–9.11)		
Case–control studies						
Kabat *et al*. (1993), USA, 1981–90	152 (122 men, 31 women) cases; 4162 men, 2222 women controls; matched by age, sex, race, hospital	Non-drinker		1.0		1.0
		Occasional		1.0 (0.6–1.7)		0.6 (0.3–1.4)
		1–3.9 oz/day		0.5 (0.3–0.9)		0.6 (0.2–1.8)
		≥4 oz/day		0.7 (0.4–1.3)		0.9 (0.3–3.1)

Table 2.42 (continued)

Study reference	Description	Drinking level	Men		Women	
			No. of cases	Relative risk (95% CI)	No. of cases	Relative risk (95% CI)
Zaridze *et al*. (2000), Moscow, Russia, 1996–97	489 (248 men, 200 women), histologically confirmed; 610 (292 men, 318 women) hospital-based controls	*Vodka (L/year)*				
		Never	28	1.0	95	1.0
		Low <2.6	78	2.0 (1.1–3.7)	62	1.5 (1.0–2.4)
		Medium 2.6–10.4	81	2.3 (1.3–4.2)		
		High >10.4	61	1.7 (0.9–3.1) *p*=0.20	45	1.3 (0.8–2.2) *p*=0.17

CI, confidence interval

When stratified by gender, the results for men were statistically significant while those for women showed similar point estimates but insignificant trends. Kato *et al*. (1992a) examined the risk for men and women separately in a clinical epidemiological study and observed an increased risk for stomach cancer in daily consumers of alcoholic beverages compared with non-drinkers, but this association was not statistically significant. In a case–control study conducted in Japan, light drinkers showed the lowest risk among both men and women, and heavy drinkers showed the highest risk among men. In other words, the association was J-shaped among men and U-shaped among women (Kikuchi *et al*., 2002).

2.8 Cancers of the colon and/or rectum

Most of the studies of alcoholic beverage consumption and colorectal cancer included in the previous Monograph (IARC, 1988) were based on information about heavy alcoholic beverage drinkers or alcoholics and persons employed in the brewery industry, or were case–control studies; only five cohort studies were reviewed. Since that time, several additional cohort studies, case–control studies, as well as meta-analyses and a pooling project, representing research from Asia, Australia, Europe, North and South America, have been published. In total, these provide important information on associations of alcoholic beverage consumption and the risk for colorectal cancer overall, risk for specific anatomical sites within the large bowel and relationships with specific alcoholic beverages. In addition, several studies carefully considered potential confounding factors such as sex, age, level of obesity and smoking status, and others also included diet and physical activity. Finally, this large body of evidence allows for international comparisons of the strength and consistency of associations between alcoholic beverage intake and risk for colorectal cancer.

2.8.1 *Cohort studies*

(a) Special populations (Table 2.43)

Nine studies examined the risk for colon cancer and eight studies examined the risk for rectal cancer among heavy alcoholic beverage drinkers, alcoholics or brewery workers (Sundby, 1967; Hakulinen *et al*., 1974; Monson & Lyon, 1975; Adelstein & White, 1976; Dean *et al*., 1979; Jensen, 1979; Robinette *et al*., 1979; Schmidt & Popham, 1981; Carstensen *et al*., 1990).

Among the nine studies on colon cancer, the number of observed deaths or incident cases ranged from three to 82. Six studies showed no evidence of an association. In two studies, there were non-statistically significant elevated risks (relative risk, 1.2–1.3) among brewery workers (Dean *et al*., 1979, Carstensen *et al*., 1990).

Among the eight studies of rectal cancer, the number of observed deaths or incident cases ranged from none to 85. While five reported no excess risk for rectal cancer, two

Table 2.43 Cohort studies of colon and rectal cancers and alcoholic beverage consumption in special populations

Reference, location	Study subjects	Organ site (ICD code)	No. of cases	No. of deaths expected	Relative risk (95% CI)	Adjustment factors	Comments
Sundby (1967), Norway	Alcoholics from Oslo psychiatric departments, 1722 men, 1925–62; aged 15–70 years	Colon Rectum	9 12	9.4 6.4			Local reference
Hakulinen *et al*. (1974), Helsinki, Finland	Approximately 205 000 male alcohol misusers and mean of 4370 male chronic alcoholics aged >30 years, registered as chronic alcoholics between 1967 and 1970, morbidity during same period determined from Finnish Cancer Registry	Colon	*Misusers* 82 *Alcoholics* 3	 86.6 (p>0.1) 1.63 (p>0.5)		Age	Local reference
Monson & Lyon (1975), Massachusetts, USA	1139 men and 243 women admitted in 1930, 1935 or 1940 to a mental hospital with a diagnosis of chronic alcoholism; followed until January 1971; 66% had complete follow-up.	Colon (ICD 153) Rectum (ICD 154)	7 4	11.2 5.7	*PCMR* 0.6 (0.3–1.3) 0.7 (0.2–1.8)	Age	Compared with US population; proportion
Adelstein & White (1976), England and Wales	1595 male and 475 female alcoholics followed up to 21 years; two sources: Mental Health Enquiry admission form; patient records from patients diagnosed with alcoholism; 15–90 years old	Intestine (ICD 152, 153) Rectum (ICD 154)	6 men 3 women 4 men 0 woman	4.92 1.90 3.32 0.92	NC/NG NC/NG	Age	Reference death rates are the sex-specific rates of England and Wales for 1972.

Table 2.43 (continued)

Reference, location	Study subjects	Organ site (ICD code)	No. of cases	No. of deaths expected	Relative risk (95% CI)	Adjustment factors	Comments
Dean *et al.*, (1979), Dublin, Ireland	Deaths between 1954 and 1973 among male blue-collar brewery workers	Colon (ICD 153)	32	24.1	1.3 (0.9–1.9)	Age	Compared with Dublin skilled and unskilled manual workers
		Rectum (ICD 154)	32	19.7	1.6 (1.1–2.3)		
Jensen (1979), Denmark	14 313 Danish brewery workers employed at least 6 months in 1939–63; followed for cancer incidence and mortality in 1943–73; age not given; workers are allowed 2.1 L of free beer/day (77.7 g pure alcohol).	Colon	*Incidence*			Age, sex	Local male population
			50	48	1.0 (0.8–1.4)		
			85	84	1.0 (0.8–1.3)		
		Rectum	*Mortality*				
			63	58	1.1 (0.8–1.4)		
			62	54	1.1 (0.9–1.5)		
Robinette *et al.* (1979), USA	4401 chronic alcoholic male veterans, hospitalized in 1944–45 and followed in 1946–74 for mortality; 29 years follow-up, age not given	Large intestine (ICD 153)	7	NC/NG	0.8 (0.3–1.9)	Age	Compared with age-matched male veterans hospitalized for nasopharyngitis
		Rectum (ICD 154)	6	NC/NG	3.3 (0.7–22.4)		
Schmidt & Popham (1981), Ontario, Canada	9889 alcoholic men aged ≥15 years admitted to the clinical service of the Addiction Research Foundation of Ontario between 1951 and 1970; maximum 21 years of follow-up	Large intestine (ICD 153)	19	18.2	1.0[a]	Age	Local reference population; CI not reported
		Rectum (ICD 154)	10	9.9	1.0[a]		

Table 2.43 (continued)

Reference, location	Study subjects	Organ site (ICD code)	No. of cases	No. of deaths expected	Relative risk (95% CI)	Adjustment factors	Comments
Carstensen *et al*. (1990), Sweden	6230 men occupied in the Swedish brewery industry at the time of the 1960 census and followed between 1961 and 1979; 20–69 years of age	Colon (ICD 153)	48	41	1.2 (0.9–1.5)	Age	Local male population
		Rectum (ICD 154)	49	29	1.7 (1.3–2.2) $p<0.001$		

CI, confidence interval; ICD, International Classification of Diseases; NC/NG, not calculated/not given; PCMR, proportionate cancer mortality ratio

[a] Confidence interval not given

found statistically significant 1.6–1.7-fold higher risks for men who had been employed in the brewery industry (Dean *et al*., 1979; Carstensen *et al*., 1990). Another study, based on six deaths, reported a non-significant 3.4-fold higher risk for rectal cancer mortality for chronic alcoholic male US veterans compared with US veterans hospitalized for nasopharyngitis (Robinette *et al*., 1979).

(b) General population (Table 2.44)

Seven studies provided results for colon and rectum combined, and four of these observed no association of alcoholic beverage consumption with mortality from (Garland *et al*., 1985; Kono *et al*., 1986) or incidence of (Flood *et al*., 2002; Sanjoaquin *et al*., 2004) colorectal cancer. Based on data from the large US Cancer Prevention Study, Thun *et al*. (1997) reported a non-significant (P=0.06) inverse trend for the relationship between alcoholic beverage intake and the risk for mortality from colorectal cancer in women and no association in men. In a study of residents of a US retirement community, Wu *et al*. (1987) found a significant 2.4-fold higher risk for colorectal cancer among men, but not among women, who consumed 30 mL alcohol per day. Similarly, in a study of Seventh Day Adventists, the relative risk for colorectal cancer was 2.0 (95% CI, 1.0–4.2) for those who consumed alcoholic beverages at least once a week compared with those who drank alcoholic beverages less than once a week (Singh & Fraser, 1998).

At least 16 prospective cohort studies reported on the relationship between alcoholic beverage intake and the risk for colon cancer in China, Japan, northern Europe, the United Kingdom and the USA. Six studies reported no association (Gordon & Kannel, 1984; Goldbohm *et al*., 1994; Harnack *et al*., 2002; Pedersen *et al*., 2003; Wei *et al*., 2004; Chen *et al*., 2005a). In the study of Klatsky *et al*. (1988), a significant association was observed in women but not in men. Of the nine studies that reported statistically significant positive associations between alcoholic beverage intake and risk for colon cancer, six were conducted in Japanese populations or in American men of Japanese descent (Hirayama, 1989; Chyou *et al*., 1996; Murata *et al*., 1996; Otani *et al*., 2003; Shimizu *et al*., 2003; Wakai *et al*., 2005). In these studies, the magnitude of association ranged from 1.4 to 5.4 for the highest compared with the lowest (i.e. none) level of alcoholic beverage intake. In studies in the USA (Su & Arab, 2004; Wei *et al*., 2004), the magnitude of risk was 1.6–1.7 for intake of approximately 1–2 drinks per day compared with non-drinkers. In the Finnish study of smokers, there was a 3.6-fold higher risk for colon cancer among those who consumed at least two drinks per day compared with those who consumed less than 0.5 drinks per day (Glynn *et al.,* 1996). None of the prospective cohort studies reported significantly lower risks for colon cancer associated with alcoholic beverage intake. Most studies adjusted for the potential confounding effects of age, body-mass index, smoking status and socioeconomic status or education; some also adjusted for physical activity and/or specific dietary factors (as described in detail below).

Table 2.44 Cohort studies of colon and rectal cancer and alcoholic beverage consumption

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Gordon & Kannel (1984), Framingham, MA, USA, Framingham Study	4747 men and women, aged 29–62 years at initial examination in 1948, and queried on alcoholic beverage intake biannually beginning in 1950–54; followed for 22 years for mortality	Interview by physician for average number of drinks per 30-day period	Colon	~10 oz ethanol/ month	17 men 19 women	1.22 0.80	Adjusted for age, cigarettes/ day, systolic blood pressure, relative weight, lipoproteins; no significant relationship between alcohol consumption and colon cancer
Garland *et al.* (1985), Chicago, IL, USA, Western Electric Cohort Study	1954 men, aged 40–55 years employed for at least 2 years at the Western Electric Company; no personal history of cancer; queried on total diet at baseline and at 1 year; followed for 19 years for mortality; cause of death from death certificates; vital status known for 99.9%	In-person 28-day diet history interviews by trained nutritionists	Colorectal	Ethanol (mL/day)	49		Compared alcoholic beverage intake reported at initial examination; no difference in mean alcoholic beverage intake between men who died of colorectal cancer and all others (alive and dead); no information regarding the exposure or relative risks given
Kono *et al.* (1986), Japan, Japanese Physicians Cohort Study	5135 male Japanese doctors surveyed on smoking and drinking habits in 1965; followed 19 years through to 1983 for mortality; cause of death determined from death certificate; vital status known for 99%; ages not given	Self-administered standardized questionnaire to assess current daily alcoholic beverage intake	Colorectal (ICD-8 153–154)	Non-drinker Former drinker Occasional drinker <2 go/day ≥2 go/day	8 4 12 8 7	1.0 1.2 (0.4–4.0) 1.3 (0.5–3.2) 1.1 (0.4–3.0) 1.4 (0.5–4.0)	Adjusted for age, smoking habits; 1 go of sake ≈ 27 mL alcohol

Table 2.44 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Wu *et al.* (1987), Los Angeles, CA, USA	11 644 (4163 men, 7456 women) residents of a retirement community with no personal history of colorectal cancer, surveyed in 1981–82; vital status or cancer incidence determined by biennial questionnaire, hospital pathology reports, health department; vital status known for 95%; age not given	Mailed, self-administered standardized questionnaire to assess average weekly alcohol intake	Colorectal		58 men		Adjusted for age; results similar for men after adjustment for physical activity, body mass index, smoking; for men, results similar for right and left colon, but with lower statistical significance for left colon; for women, an association was apparent (not significant) for the left colon.
				Non-daily		1.0	
				1–30 mL ethanol/ day		2.2 (1.1–4.4)	
				≥30 mL ethanol/ day		2.4 (1.3–4.5)	
					68 women		
				Non-daily		1.0	
				1–30 mL ethanol/ day		1.1 (0.6–2.1)	
				≥30 mL ethanol/ day		1.4 (0.8–2.6)	
Klatsky *et al.* (1988), Oakland, CA, Kaiser-Permanente Multiphasic Health Examination Cohort	106 203 white and black men and women who underwent multiphasic examination in 1978–84; followed for cancer incidence until 1984; age not given; vital status not given	Standardized questionnaire to assess usual daily intake over the previous year	Colon (ICD-8153)	Never drinker	30	1.0	Adjusted for sex, age, race, body mass index, coffee use, total serum cholesterol, education, smoking; associations stronger after excluding cases diagnosed within 6 months after examination; associations for colon cancer showed a significant association in women but not men; no differences in associations by beverage type
				Former drinker	6	0.8 (0.3–2.1)	
				<1 drink/day	98	1.2 (0.7–1.8)	
				1–2 drinks/day	49	1.6 (0.9–2.6)	
				≥3 drinks/day	20	1.7 (0.9–3.2)	
						p-trend=0.11	
			Rectum (ICD-8154)	Never drinker	6	1.0	
				Former drinker	4	2.2 (0.6–8.2)	
				<1 drink/day	29	1.4 (0.6–3.6)	
				1–2 drinks/day	17	2.3 (0.8–6.3)	
				≥3 drinks/day	10	3.2 (1.1–9.6)	
						p-trend=0.03	

Table 2.44 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Hirayama (1989), Japan, Six Prefecture Study	122 261 male and 142 857 female Japanese adults, aged 40 years and older surveyed in 1965; followed for 17 years; all residents from 6 prefectures	Interviewer-administered standardized questionnaire to assess usual alcoholic beverage intake	Sigmoid colon	Non-drinker Infrequent (1–2 times/month) Occasional (1–2 times/week) Daily Non-drinker Drinker	43 men 48 women	1.0 2.03 3.83 (p<0.05) 5.42 (p<0.01) p-trend<0.001 1.0 1.92 (p<0.05)	Adjusted for age; smoking, diet, sex; highest risk observed for daily beer drinkers, although sake and shochu also associated with a significantly increased risk for sigmoid colon cancer; information regarding women's consumption of alcohol was limited.
Goldbohm *et al.* (1994)[a], Netherlands, Netherlands Cohort Study	58 279 men and 62 573 women, aged 55–69 years with no history of non-skin cancer, surveyed in 1986; follow-up for cancer incidence through the cancer registries through to 1989, or 3.3. years with 100% follow-up; estimated complete case ascertainment for 95% of cases; case–cohort design with 3346 total cohort members in analysis; 204 municipal population registries throughout the country used	Mailed self-administered standardized questionnaire to assess habitual intake	Colon	Abstainers 1–4.9 g ethanol/day 5–14.9 g ethanol/day 15–29.9 g ethanol/day ≥30 g ethanol/day	63 51 34 36 21	1.0 0.7 (0.5–1.0) 0.6 (0.4–0.9) 0.9 (0.5–1.6) 1.1 (0.3–3.6) p-trend=0.79	Adjusted for sex, age, family history, smoking, body-mass index, education, history of gall bladder surgery, intake of energy, energy-adjusted fat, meat protein, fibre; cases that occurred in first year of follow-up were excluded; for colon cancer, no difference in risk between men and women; associations did not differ according to any specific beverage type.
			Rectum	Abstainers 1–4.9 g ethanol/day 5–14.9 g ethanol/day 15–29.9 ethanol/day ≥30 g ethanol/day	19 26 17 25 19	1.0 1.2 (0.6–2.4) 0.8 (0.4–1.6) 1.5 (0.7–3.2) 2.0 (0.4–9.6) p-trend=0.09	

Table 2.44 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Chyou *et al.,* (1996)[a], Oahu, Hawaii, USA, Honolulu Heart Study	7945 American men of Japanese descent, born 1900–19, residents of Oahu, identified by the Selective Service draft file of 1942; no personal history of colorectal cancer; interviewed between 1965 and 1968 and followed through to 1995 for cancer incidence using Hawaii Tumor Registry; vital status, 98.2%	24-h diet recall including usual monthly intake of beer, spirits and wine (including sake)	Colon	0 oz/month <4 oz/month 4–<24 oz/month ≥24 oz/month	120 44 76 88	1.0 0.7 (0.5–9.0) 1.1 (0.8–1.4) 1.4 (1.0–1.8) *p*-trend=0.005	Adjusted for age, body-mass index, smoking, serum cholesterol, heart rate, monounsaturated fatty acids, calories from alcohol; in multivariate analysis, calories from alcohol significantly associated with colon cancer; amount of alcoholic beverages consumed associated with rectal cancer
			Rectum	0 oz/month < oz/month 4–<24 oz/month ≥24	32 19 35 37	1.0 1.1 (0.6–2.0) 2.0 (1.2–3.2) 2.3 (1.4–3.7) *p*-trend=0.0001	
Glynn *et al.* (1996)[a], Southwest Finland, α-Tocopherol β-Carotene Cancer Prevention Study	27 109 Finnish men, aged 50–69 years, who smoked five or more cigarettes per day; included those with a personal history of non-melanoma skin cancer and in-situ cancer; men randomized to a supplement that contained α-tochopherol, β-carotene, both, or placebo; complete diet and smoking data; followed up to 8 years for cancer incidence using the Finish Cancer Registry; 100% complete	Self-administered diet history standardized questionnaire to assess usual consumption over the previous 12 months	Colon (ICD-9153)	Q1 ≤5.3 g ethanol/ day Q2 >5.3–≤13.4 g ethanol/day Q3 >13.4–≤27.7 g ethanol/day Q4 >27.7 g ethanol/ day	5 7 8 15	1.0 1.5 (0.5–4.8) 1.8 (0.6–5.6) 3.6 (1.3–10.4) *p*-trend=0.01	Adjusted for age, physical activity during work, intake of total energy, starch, sweets, sugar, coffee, calcium; results for men in the no β-carotene arm; for colorectal cancer combined, associations strongest for beer and wine intake; in the β-carotene arms, no associations with total alcoholic beverage intake or any beverage
			Rectum (ICD-9154)	Q1 ≤5.3 g ethanol/ day Q2 >5.3–≤13.4 g ethanol/day Q3 >13.4–≤27.7 g ethanol/day Q4 >27.7 g ethanol/ day	3 3 7 5	1.0 1.0 (0.2–5.1) 2.3 (0.6–9.0) 1.5 (0.3–6.7) *p*-trend=0.37	

Table 2.44 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Murata *et al.* (1996), Chiba, Japan	Nested case–control study; 17 200 men who underwent gastric screening in 1984; cancer cases identified through the Chiba Cancer Registry over the 9-year follow-up; 153 colon cancers and 154 rectal cancers identified and matched to two controls on birth year (±2 years), first digit of address code	Self-administered standardized questionnaire at time of screening to assess current drinking	Colon (ICD-9153)	0 cup/day 0.1–1.0 cup/day 1.1–2.0 cups/day ≥2.1 cups/day	13 31 10 7	1.0 3.5 (p<0.01) 1.9 3.2 (p<0.05) p-trend <0.05	Matched on birth year, address code; exposure is sake-equivalents (1 cup = 27 mL ethanol); associations not modified by cigarette smoking; associations strongest for proximal colon compared with sigmoid colon; CI not reported
			Rectum (ICD-9154)	0 cup/day 0.1–1.0 cup/day 1.1–2.0 cups/day ≥2.1 cups/day	21 11 9 2	1.0 0.8 1.9 1.4 p-trend >0.05	
Thun *et al.* (1997), USA, Cancer Prevention Study II	251 420 women and 238 206 men, aged 30–104 years enrolled beginning in 1982; followed through to 1991 for cancer mortality; excludes people with cirrhosis or non-skin cancer at baseline; complete follow-up on nearly 98% of the cohort	Mailed, self-administered standardized questionnaire to assess current alcoholic beverage intake	Colon (ICD-9153), Rectum (ICD-9154)	*Men* None Less than daily 1 drink/day 2–3 drinks/day ≥4 drinks/day	 211 216 111 182 131	*Men* 1.0 1.0 (0.9–1.3) 1.0 (0.8–1.3) 1.1 (0.9–1.4) 1.2 (1.0–1.5) p-trend=0.1	Adjusted for age, race, education, body-mass index, smoking, crude index of fat intake, vegetable consumption; other cancers not colorectal; in women use of hormone therapy; values based on men and women who reported no heart disease or hypertension; use of medication for reported conditions, stroke or diabetes at baseline.
				Women None Less than daily 1 drink/day 2–3 drinks/day ≥4 drinks/day	 305 131 40 76 24	*Women* 1.0 0.8 (0.7–1.0) 0.6 (0.4–0.8) 0.9 (0.7–1.2) 0.7 (0.5–1.1) p-trend=0.06	

Table 2.44 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Singh & Fraser (1998)[a], California, USA, Adventist Health Study	32 051 non-hispanic white women, aged ≥25 years, with no history of cancer completed a questionnaire in 1976; incidence of cancer over 6 years of follow-up determined from annual mailings and review of medical records (97% complete follow-up), or by linking to two California tumour registries	Mailed, self-administered standardized questionnaire	Colon (135 cases) (ICD-9153), Rectum (22 cases) (ICD-9154)	<1 time/week ≥1 time/week	138 8	1.0 2.0 (1.0–4.2)	Adjusted for sex, age, parental history of colon cancer; study population had a low prevalence of alcohol consumption; no data specific to rectal cancer given
Flood *et al.* (2002), USA, Breast Cancer Detection and Demonstration Project	45 264 women, aged 40–93 years participated in a breast cancer screening programme and completed a dietary questionnaire in 1987–89 and follow-up questionnaire in 1995–98 to report incident cancer; 1993–1995 follow-up; no personal history of colorectal cancer or implausible high or low levels of energy intake; 125 women reported consuming more than 6 drinks per day; 90% complete follow-up	Mailed, self-administered standardized questionnaire for usual intake	Colon or rectum (ICD-O 153.0–153.4, 153.6–153.9, 154.0–154.1)	0 serving/day 0.01–0.50 servings/day 0.51–1.00 servings/day 1.01–2.00 servings/day >2.00 servings/day	301 101 52 25 11	1.0 0.9 (0.7–1.2) 1.0 (0.7–1.3) 0.9 (0.6–1.4) 1.2 (0.6–2.1) *p*-trend=0.84	Adjusted for energy, dietary folate, methionine, smoking; no confounding by NSAID use, smoking, education, body mass index, height, physical activity, vitamin D calcium, red meat, grain, total fat or fibre intake; no interaction of alcoholic beverages with folate intake or NSAID use; interaction with smoking when association of alcoholic beverages with colorectal cancer observed only in nonsmokers

Table 2.44 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Harnack *et al.* (2002)[a], Iowa, USA, Iowa Women's Health Study	35 216 postmenopausal women aged 55–69 years, with no personal history of non-skin cancer completed a mailed questionnaire in 1986; followed through to 1998 for cancer incidence using Iowa Health Registry and national death index for vital status; 99% complete vital status	Mailed, self-administered standardized questionnaire assessed usual intake over the last year.	Colon (ICD-O18.0–18.9)	<20 g ethanol/day	572	1.0	Adjusted for age, pack–years cigarettes, body-mass index, estrogen use, intake of calcium, vitamin E, energy; for total colon, distal colon and rectal cancer, no interaction with folate intake; for proximal colon, lower risk for those with high folate and low alcoholic beverage intake; there also appeared to be an interaction of alcohol with haeme and zinc intake (Lee *et al*., 2004)
				≥20 g ethanol/day	26	1.1 (0.7–1.6)	
			Rectum (ICD-O20.0)	<20 g ethanol/day	116	1.0	
				≥20 g ethanol/day	7	0.9 (0.4–2.1)	
Otani *et al.* (2003), multicentre, Japan, Japan Public Health Center Study	42 540 male and 47 464 female Japanese, aged 40–69 years; no personal history of cancer; followed from 1990 or 1993 through to 1999; cancer incidence determined from population-based tumour registries, hospital records or death certificates; 99.6% complete follow-up.	Self-administered standardized questionnaire to assess current and past alcoholic beverage intake; former and never-drinkers combined				*Men*	Adjusted for age, family history of colorectal cancer, body-mass index, smoking status, physical activity, centre location; in men, no interaction of smoking with alcoholic beverage consumption for colon, rectal or colorectal cancer; no associations for colorectal cancer in women
			Colon (ICD-O 180–189)	Non-drinker	62	1.0	
				Occasional	16	0.8 (0.4–1.3)	
				1–149 g ethanol/ week	51	1.0 (0.7–1.4)	
				150–229 g ethanol/ week	71	1.3 (0.9–1.8)	
				≥300 g ethanol/ week	99	1.9 (1.4–2.7) *p*-trend=0.001	
			Rectum (ICD-O 199–209)	Non-drinker	25	1.0	
				Occasional	8	1.0 (0.5–2.3)	
				1–149 g ethanol/ week	32	1.6 (0.9–2.6)	
				150–229 g ethanol/ week	36	1.7 (1.0–1.4)	
				≥300 g ethanol/ week	47	2.4 (1.5–4.0) *p*-trend=0.005	

Table 2.44 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Pedersen *et al.* (2003), Copenhagen, Denmark, Copenhagen Centre for Prospective Population Studies	15 491 men and 13 641 women, aged 23–95 years; no history of non-skin cancer; participated in one of three prospective studies initiated in 1964, 1970 or 1976; followed for a mean of 14.7 years through to 1998; follow-up 99.3% complete; a nationwide cancer register used	Self-administered standardized questionnaire to assess average daily intake of alcoholic beverages on weekend days and on weekdays	Colon (ICD-7 153 or ICD-10 18.0–18.9)	<1 drink/week	96	1.0	Adjusted for sex, age, smoking, body-mass index, study of origin No differences in association between men and women; no interactions with smoking; no significant associations with any specific type of beverage although positive trends of rectal cancer with beer and liquor intake
				1–6 drinks/week	129	1.0 (0.8–1.3)	
				7–13 drinks/week	77	0.9 (0.7–1.2)	
				14–27 drinks/week	68	0.9 (0.6–1.2)	
				28–40 drinks/week	27	1.1 (0.7–1.7)	
				≥41 drinks/week	14	0.8 (0.5–1.5)	
						p-trend=0.58	
			Rectum (ICD-7 154 or ICD-10 20.0)	<1 drink/week	28	1.0	
				1–6 drinks/week	60	1.5 (0.9–2.3)	
				7–13 drinks/week	43	1.5 (0.9–2.5)	
				14–27 drinks/week	43	1.7 (1.0–2.8)	
				28–40 drinks/week	17	2.1 (1.1–4.0)	
				≥41 drinks/week	11	2.2 (1.0–4.6)	
						p-trend=0.03	
Shimizu *et al.* (2003), Takayama, Japan	13 392 men and 15 659 women, aged ≥35 years; no personal history of non-melanoma skin cancer, surveyed in 1992; cancer incidence determined from hospital records; followed through to 2000	Self-administered standardized questionnaire to assess usual alcoholic beverage intake	Colon			*Men*	Adjusted for age, height, body-mass index, smoking, years of education; significant dose–response relationship between alcohol consumption and colon cancer in both sexes
				No alcohol	5	1.0	
				≤36.7 g ethanol/day	45	1.8 (0.7–4.5)	
				>36.7 g ethanol/day	58	2.7 (1.1–6.8)	
						p-trend=0.01	
						Women	
				No alcohol	34	1.0	
				≤3.75 g ethanol/day	28	1.1 (0.6–2.0)	
				>3.75 g ethanol/day	32	1.8 (1.0–3.2)	
						p-trend=0.03	
			Rectum			*Men*	
				No alcohol	8	1.0	
				≤36.7 g ethanol/day	20	0.6 (0.2–1.4)	
				>36.7 g ethanol/day	31	1.2 (0.5–2.7)	
						p-trend=0.06	
						Women	
				No alcohol	7	1.0	
				≤3.75 g ethanol/day	15	1.2 (0.4–3.3)	
				>3.75 g ethanol/day	19	1.8 (0.7–4.6)	
						p-trend=0.17	

Table 2.44 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Sanjoaquin *et al.* (2004), United Kingdom, Oxford Vegetarian Study	10 998 vegetarians and non-vegetarians (4162 men, 6836 women), aged 16–89 years; no personal history of cancer; surveyed in 1980–84, followed for an average of 17 years; cancer incidence determined from the National Health Service cancer registry	Self-administered standardized questionnaire	Colorectal	<1 unit/week 1–7 units/week >7 units/week	30 39 26	1.0 1.5 (0.9–2.5) 1.5 (0.9–2.7) *p*-trend=0.12	Adjusted for sex, age, smoking status; association with alcohol partially confounded by smoking
Su & Arab (2004), USA, NHANES I Epidemiologic Follow-up Study	3887 men and 6531 women, aged 25–74 years; no personal history of non-skin cancer; screened in 1982–84; cancer incidence from self-report and cancer mortality from proxy and national death index; followed through to July 1993; follow-up 92.2% complete	Interviewer-administered standardized questionnaire to assess usual consumption over the previous year, as well as intake at younger ages	Colon (ICD-O 153)	Non-drinker <1 drink/day ≥1 drink/day *Years drinking* 0 0–17 17–34 >34	63 22 26 52 3 17 39	1.0 1.1 (0.6–1.8) 1.7 (1.0–2.8) *p*-trend=0.04 1.0 0.7 (0.2–2.3) 1.3 (0.7–2.4) 1.7 (1.1–2.8) *p*-trend=0.02	Adjusted for sex, age, race, body-mass index, education, intake of poultry, non-poultry meat, seafood, multivitamin use, history of colonic polyps, smoking status; no difference in associations by sex; no association with beer or wine; stronger positive associations with liquor intake, greater number of years drinking, younger age at start drinking; consistent drinking positively associated with risk for colon cancer but no association for quitters

Table 2.44 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Wei *et al.* (2004), USA (two cohorts), Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)	87 733 women, aged 30–55 years from the Nurses' Health Study and 46 632 men, aged 40–75 years from the Health Professionals Follow-up Study; no personal history of non-skin cancer; follow-up for cancer incidence through biennial questionnaire with confirmation from medical records, and for vital status through proxy report or national death index; women followed up from 1980 through to May 2001; men followed up from 1986 through to January 2000	Self-administered standardized questionnaire to assess average intake over the previous year	Colon			*Men* - HPFS	Adjusted for age, family history of cancer, body-mass index, physical activity, intake of beef, pork, lamb, processed meat, calcium, folate, height, pack–years smoking before age 30, history of endoscopy; associations of alcohol with colon and rectal cancer were not statistically significantly different. In the combined analysis of NHS and HPFS, there were statistically significant positive associations with colon cancer (p-trend=0.001) but not rectal cancer (p-trend=0.11). In an earlier analysis of the HPFS, there was a statistically significant interaction of alcohol with folate intake (Giovannucci *et al.*, 1995)
				0 g ethanol/day	37	1.0	
				<10 g ethanol/day	149	1.1 (0.8–1.5)	
				10–19 g ethanol/day	98	1.3 (0.9–1.9)	
				≥20 g ethanol/day	111	1.5 (1.0–2.3)	
				Past	72	1.3 (0.9–2.0)	
						p-trend=0.003	
						Women - NHS	
				0 g ethanol/day	200	1.0	
				<10 g ethanol/day	281	1.0 (0.8–1.2)	
				10–19 g ethanol/day	106	1.0 (0.8–1.3)	
				≥20 g ethanol/day	69	1.1 (0.9–1.5)	
				Past	16	0.6 (0.4–1.1)	
						p-trend=0.27	
	HPFS: 46 632 men, aged 40–75 years; followed 1986–2000		Rectum	0 g ethanol/day	11	1.0	
				<10 g ethanol/day	43	0.9 (0.5–1.8)	
				10–19 g ethanol/day	35	1.3 (0.7–2.6)	
				≥20 g ethanol/day	28	1.1 (0.5–2.3)	
				Past	18	1.1 (0.5–2.3)	
						p-trend=0.6	
	NHS: 87 733 women, aged 30–55 years; followed 1980–2000			0 g ethanol/day	56	1.0	
				<10 g ethanol/day	91	1.1 (0.8–1.6)	
				10–19 g ethanol/day	28	1.0 (0.6–1.5)	
				≥20 g ethanol/day	24	1.5 (0.9–2.4)	
				Past	5	0.7 (0.3–1.8)	
						p-trend=0.23	

Table 2.44 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Chen *et al.* (2005a), Zhejiang, China	30 952 men and 33 148 women screened for colorectal cancer in 1989–90, aged ≥ 30 years; no history of cancer; followed for 10.6 years through to 2001; follow-up 99.9% complete	Interviewer-administered standardized questionnaire to assess drinking status and usual intake over the previous year	Colon (ICD-O 153.0–153.7)	Non-drinker	61	1.0	Adjusted for sex, age, smoking status, occupation, education, marital status; no differences in risk for men and women; only one case among former drinkers
				Former drinker	1	0.4 (0.1–2.8)	
				Occasional	22	1.1 (0.6–1.8)	
				Daily	23	1.0 (0.5–1.8)	
			Rectum (ICD-O 154–154.1)	Non-drinker	73	1.0	
				Former drinker	0	NS	
				Occasional	28	1.2 (0.7–2.0)	
				Daily	34	1.2 (0.7–2.1)	
Wakai *et al.* (2005), Japan, Japan Collaborative Cohort Study	23 708 men and 34 028 women, aged 40–79 years; no history of colorectal cancer; underwent municipal health check-up in 1988–90 through to 1997; followed for cancer incidence and vital status with linkage to cancer registry and review of death certificates; follow-up 96.7% complete	Standardized questionnaire to assess drinking status and usual intake	Colon	*Men*			Adjusted for age, area, education, family history of colorectal cancer, body-mass index, smoking habits, walking time, sedentary work, intake of green leafy vegetables, beef; 1 go ≈ 22 g ethanol; association between drinking habits and risk of colon cancer in men; 'J' shaped association was found between alcohol intake and risk of rectal cancer; lowest not among light drinkers.
				Non-drinker	24	1.0	
				Former drinker	19	2.0 (1.1–3.7)	
				0–0.9 go/day	43	2.0 (1.2–3.3)	
				1.0–1.9 go/day	63	2.2 (1.4–3.6)	
				2.0–2.9 go/day	36	1.8 (1.0–3.0)	
				≥3.0 go/day	20	2.4 (1.3–4.4)	
						p-trend=0.85	
				Women			
				Non-drinker	149	1.0	
				Former drinker	6	1.6 (0.7–3.6)	
				0–0.9 go/day	22	1.1 (0.7–1.7)	
				≥1 go/day	5	1.2 (0.5–3.0)	
						p-trend=0.96	

Table 2.44 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Wakai *et al.* (2005) (contd)			Rectum			*Men*	
				Non-drinker	30	1.0	
				Former drinker	14	1.3 (0.7–2.4)	
				0–0.9 go/day	16	0.6 (0.3–1.1)	
				1.0–1.9 go/day	35	1.0 (0.6–1.7)	
				2.0–2.9 go/day	29	1.2 (0.7–2.0)	
				≥3.0 go/day	12	1.3 (0.7–2.6)	
						p-trend=0.027	
						Women	
				Non-drinker	50	1.0	
				Former drinker	1	0.8 (0.1–5.8)	
				0–0.9 go/day	5	0.7 (0.3–1.7)	
				≥1 go/day	2	1.5 (0.4–6.5)	
						p-trend=0.36	

CI, confidence interval; ICD, International Classification of Diseases; NS, not significant; NSAID, non-steroidal anti-inflammatory drugs

[a]Studies included in the meta-analysis of Moskal *et al.* (2007)

Fourteen prospective cohort studies assessed associations of alcoholic beverage intake with the risk for rectal cancer. Eight of these found no association (Goldbohm *et al*., 1994; Glynn *et al*., 1996, Murata *et al*., 1996; Harnack *et al*., 2002; Wei *et al*., 2004; Chen *et al*., 2005a; Wakai *et al*., 2005). Similarly to colon cancer, most of the six studies that showed a positive association between alcoholic beverage consumption and rectal cancer were conducted in Japanese populations or men of Japanese descent (Hirayama, 1989; Chyou *et al*., 1996; Otani *et al*., 2003; Shimizu *et al*., 2003), although one study from the USA (Klatsky *et al*., 1988) and one from Denmark (Pedersen *et al*., 2003) also found significantly positive associations. In general, the magnitude of association for rectal cancer was similar to, although slightly lower than, that for colon cancer in most studies.

(c) Meta-analyses (Table 2.45)

Despite the large number of cohort studies that assessed associations of alcoholic beverage consumption with risk for colon and/or rectal cancer and the large sample sizes included in many of them, the available evidence from these studies is limited for several reasons. First, most studies had very few cases (<50) in the highest category of alcoholic beverage intake, which limits the power to obtain precise estimates of modest risks. Second, it is not clear whether associations might differ according to anatomical site within the colon (i.e. proximal versus distal colon) or by type of alcoholic beverage. Third, associations in some studies might be confounded or modified by gender, level of obesity, diet or other lifestyle factors. To address these issues, Cho *et al*. (2004) conducted a detailed analysis of the relationship between alcoholic beverage consumption and the risk for colorectal cancer using pooled data from eight large cohort studies conducted in Europe or North America. The criteria for study inclusion in the pooling project were: (*a*) prospective cohort; (*b*) inclusion of at least 50 cases of colorectal cancer; (*c*) assessment of long-term dietary intake; (*d*) a validation study of dietary assessment; and (*e*) measurement of alcoholic beverage intake. As described in Table 2.45, this analysis included more than 4600 cases among approximately 490 000 men and women, aged 15–107 years at baseline, and reported follow-up rates were between 94 and 100%. In multivariate analyses that adjusted for age, tobacco smoking, body-mass index, education, height, physical activity, family history of colorectal cancer, use of non-steroidal anti-inflammatory drugs, use of multivitamins, energy intake and intake of other dietary factors, the relative risks for colorectal cancer across the five increasing levels of intake were 0.94, 0.97, 1.01, 1.16 and 1.41 (p for trend=0.001) compared with non-drinkers. The strength of the associations did not differ between men and women (relative risks for the highest versus the lowest categories of intake were 1.41 for both). While the risk for colorectal cancer was slightly stronger for wine intake (relative risk, 1.82 for ≥30 g alcohol per day compared with 0 g of alcohol per day) than for beer (relative risk, 1.37) or liquor (relative risk, 1.21), the differences among types of alcoholic beverage were not statistically significant. In addition, associations were not

Table 2.45 Meta-analyses of colon, rectal and colorectal cancer and alcoholic beverage consumption

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Longnecker *et al*. (1990), meta-analysis of 5 prospective cohort studies and 22 case–control studies	Eligibility for inclusion: (a) alcoholic beverage intake had to be determined quantitatively by personal history; (b) study results had to be able to be translated into a numerical measure of association.		Colon or rectum	All relative risks for an intake of 24 g ethanol/day	*Subgroups (no. of studies)* All (27) Men (13) Women (13) *Colon* (14) *Rectum* (14) Cohort (5) Case–control (22)	 1.10 (1.05–1.14) 1.1 (1.0–1.2) 1.1 (1.0–1.2) 1.1 (1.0–1.2 1.1 (1.0–1.2) 1.3 (1.2–1.5) 1.1 (1.0–1.1)	Weak association between alcohol consumption and risk for colorectal cancer

Table 2.45 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Cho *et al.* (2004), pooling project of 8 cohort studies: ATBC Cancer Prevention Study; Canadian National Breast Screening Study; Health Professionals Follow-up Study; Iowa Women's Health Study; Netherlands Cohort Study; New York State Cohort; Nurses' Health Study; Sweden Mammography Study	489 979 men and women, aged 15–107 years at baseline; follow-up of 6–16 years; follow-up conducted through cancer and death registries, or self-report and medical record review; estimated follow-up rates ranged from 94 to 100% (one study had no information on follow-up rate); total of 4687 cases identified	Most questionnaires assessed usual consumption	Colorectal	*Total alcohol*			Adjusted for age, smoking, body-mass index, education, height, physical activity, family history of colorectal cancer, NSAID use, multivitamin use, energy intake, red meat intake, total milk intake, folate intake from food, alcohol intake from other beverages; for women also adjusted for use of oral contraceptives and postmenopausal hormone therapy
				0 g ethanol/day	1466	1.0	
				>0–<5g ethanol/day	1475	0.94 (0.86–1.03)	
				5–<15 g ethanol/day	849	0.97 (0.88–1.06)	
				15–<30 g ethanol/ day	485	1.01 (0.86–1.18)	
				30–<45 g ethanol/ day	244	1.16 (0.99–1.36)	
				≥45 g ethanol/day	168	1.41 (1.16–1.72) *p*-trend<0.001	
				Beer			
				0 g ethanol/day	2612	1.0	
				>0–<30 g ethanol/ day	1219	1.01 (0.89-1.13)	
				≥30 g ethanol/day	67	1.37 (1.00–1.87) *p*-trend=0.2	
				Wine			
				0 g ethanol/day	2078	1.0	
				>0–<30 g ethanol/ day	1768	0.97 (0.89–1.05)	
				≥30 g ethanol/day	52	1.82 (1.28–2.59) *p*-trend=0.001	
				Liquor			
				0 g ethanol/day	2392	1.0	
				>0–<30 g ethanol/ day	1347	0.98 (0.88–1.09)	
				≥30 g ethanol/day	159	1.21 (0.99–1.47) *p*-trend=0.1	

Table 2.45 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Cho *et al*. (2004) (contd)			Colon	*Total alcohol*			
				0 g ethanol/day	Not reported	1.0	
				>0–<5 g ethanol/ day		0.92 (0.84–1.01)	
				5–<15 g ethanol/day		0.94 (0.84–1.05)	
				15–<30 g ethanol/ day		1.01 (0.82–1.24)	
				30–<45 g ethanol/ day		1.08 (0.89–1.31)	
				≥45 g ethanol/day		1.45 (1.14–1.83) *p*-trend<0.001	
			Rectum	*Total alcohol*			
				0 g ethanol/day	Not reported	1.0	
				> 0–<5 g ethanol/ day		1.01 (0.83–1.22)	
				5–<15 g ethanol/day		0.99 (0.82–1.19)	
				15–<30 g ethanol/ day		1.05 (0.83–1.32)	
				30–<45 g ethanol/ day		1.42 (1.07–1.88)	
				≥45 g ethanol/day		1.49 (1.49–2.12) *p*-trend=0.006	

Table 2.45 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors/ comments
Moskal *et al*. (2007), meta-analysis of 16 prospective cohort studies from Asia, Europe and USA (cohorts included are noted in Table 2.44)	Criteria for inclusion were: (a) prospective cohort that evaluated the association of alcoholic beverage intake with risk for colorectal cancer; (b) published in English between 1990 and June 2005; (c) references in MEDLINE; (d) colorectal cancer incidence as the end-point; (e) provide relative risks and 95% CIs; (f) for dose–response analysis, had to report at least three categories of exposure, number of cases and comparison subjects for each category; five cohort studies for colorectal, 14 studies for colon and 12 studies for rectal cancer included 6300 cases.	All studies collected self-reported alcoholic beverage intake	Colorectal, colon or rectum	All relative risks for an increase of 100 g ethanol/week	*Subgroup (no. of studies)* All (7) Men (3) Women (3) Asia (4) Europe (2) USA (1) All (14) Men (7) Women (3) Asia (7) Europe (3) USA (4) All (12) Men (6) Women (3) Asia (7) Europe (3) USA (2)	*Colorectal* 1.19 (1.14–1.27) 1.21 (1.02–1.43) 1.05 (0.92–1.20) 1.21 (1.14–1.27) 1.44 (1.10–1.87) 1.02 (0.87–1.20) *Colon* 1.15 (1.07–1.23) 1.18 (1.13–1.24) 1.14 (1.00–1.30) 1.15 (1.10–1.21) 1.14 (0.85–1.52) 1.23 (1.12–1.35) *Rectum* 1.15 (1.10–1.21) 1.19 (1.12–1.26) 1.16 (0.94–1.44) 1.16 (1.09–1.23) 1.10 (1.02–1.20) 1.43 (1.18–1.72)	Adjustment factors not reported; results also showed dose–response relationships for colon and for rectum ($p<0.05$); relative risks for colon: 25 g/week, 1.02; 50 g/week, 1.07; 100 g/week, 1.15; relative risks for rectum: 25 g/week, 1.04; 50 g/week, 1.07; 100 g/week, 1.15

ATBC, α-Tocopherol β-Carotene; CI, confidence interval; ICD, international Classification of Diseases; NSAID, non-steroidal anti-inflammatory drugs

significantly different among anatomical sites (i.e. total colon versus rectum, proximal versus distal colon), and associations of specific beverage types also did not differ by anatomical site. Finally, as described in detail below, only body-mass index appeared to modify significantly the relationship between alcoholic beverage consumption and risk for colorectal cancer in the cohort-pooling project. The interactions of alcoholic beverages with multivitamin use, total folate intake, methionine intake, tobacco smoking and, in postmenopausal women, use of hormone therapy were not statistically significant ($P>0.2$).

Moskal *et al*. (2007) conducted a large meta-analysis that included 16 prospective cohort studies published between 1990 and 2005. Inclusion criteria for that analysis are shown in Table 2.45. In the meta-analysis, the average relative risk associated with an increase in consumption of 100 g ethanol per week was 1.19 for colorectal cancer, 1.15 for colon cancer and 1.15 for rectal cancer. In general, associations were only slightly stronger for men than for women. There was no consistent pattern of differences in magnitude of associations among Asian, European, or US studies; however, there was evidence of geographical heterogeneity for colon cancer ($P=0.003$).

2.8.2 *Case–control studies (Table 2.46)*

Thirty-eight case–control studies have investigated alcoholic beverage consumption and the risk for colon, rectal or colorectal cancer. The total number of cases included ranged from as few as 25 to as many as 1225.

Nine of the 38 studies provided results for colon and rectum combined. Among these, there was no evidence of a statistically significant association in four studies (Higginson, 1966; Wynder *et al*., 1969; Manousos *et al*., 1983; Boutron *et al*., 1995) and a non-significant positive association in three others (Stocks, 1957; Pernu, 1960; Yamada *et al*., 1997). A strong positive association was found in the study of Muñoz *et al*. (1998) in Argentina where there was a threefold higher risk for colorectal cancer associated with intake of ≥24 g alcohol per day compared with <24 g alcohol per day. Conversely, Olsen and Kronborg (1993) reported a lower risk for colorectal cancer associated with four or more Kcal of total energy from alcoholic beverage intake compared with 0 Kcal per day (relative risk, 0.4; 95% CI, 0.3–1.0).

Twenty-six case–control studies examined the relationship between alcoholic beverage consumption and the risk for colon cancer specifically. There was no evidence of a significant association in 15 of these (Wynder & Shigematsu, 1967; Graham *et al*., 1978; Tuyns *et al*., 1982; Miller *et al*., 1983; Tajima & Tominaga, 1985; Kune *et al*., 1987; Ferraroni *et al*., 1989; Peters *et al*., 1989; Slattery *et al*., 1990; Choi & Kahyo, 1991b; Riboli *et al*., 1991; Gerhardsson de Verdier *et al*., 1993; Newcomb *et al*., 1993; Tavani *et al*., 1998; Ji *et al*., 2002). One study reported a significant inverse relationship between alcoholic beverage consumption and the risk for colon cancer (Hoshiyama *et al*., 1993). In one study, a twofold higher risk for colon cancer was observed for >12.9 g alcohol per day in women (95% CI, 0.9–4.5) and no association in men (Potter

Table 2.46 Case–control studies of colon and rectal cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Stocks (1957), United Kingdom, 1929–32	166 colorectal; from hospital with a special interviewer appointed	1750 hospital-based; aged 45–74 years	Interview	*Beer drinking* <Daily ≥Daily *Men* Abstainer Moderate drinker Heavy drinker *Women* Abstainer Moderate drinker Heavy drinker	 74 92 24 141 	Obs/Exp *Men* 1.0 1.4 (0.9–2.1) *Women* No association *Men* 1.0 1.1 2.1 *Women* 1.0 1.1 –	Adjusted for age and sex; heavy cigarette smoking occurred with frequent beer drinking in women.
Pernu (1960), Helsinki, Finland, 1944–58	666 intestines (317 men, 349 women); all ages; prevalent cases treated at several Finnish Hospitals between 1944 and 1958; 53% histologically confirmed; response rate, 30%	1773 population; aged ≥ 30 years; selected by a group of Parish Sisters; response rate, 39.7%	Mailed self-administered standardized questionnaires				No adjustment factors; cases were over-represented on early stage disease [calculated relative risks based on the data presented]; CI not reported.

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Higginson (1966), Kansas, USA, 1959	340 colorectal (196 men, 144 women); selected from seven Kansas hospitals and interviewed before surgery; 100% histologically confirmed; response rate not given	1020 (588 men, 432 women) hospital-based; matched (3:1) for sex, age (±10 years), race; response rate not given	Interviewer-administered standardized questionnaire	Non-drinker Light drinker Moderate drinker Heavy drinker		1.0 0.9 0.8 1.0	No adjustment factors; assessed exposure 2 years before diagnosis; no differences in associations according to alcoholic beverage type [calculated relative risks presented]; CI not reported; number of cases not reported.

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Wynder & Shigematsu (1967), New York, USA, 1959–61, 1963–64	288 colon (174 men, 114 women) and 204 rectal (140 men, 64 women) identified from hospital; histological confirmation not given; response rate not given	273 (206 men, 67 women); matched on age, hospital; response rate not given	Interview	*Colon*	*Men*		No adjustment for social or other behavioural factors; no association in men or women; for men, there was a higher proportion of heavy drinkers among cases versus controls; no association for women; rectal cancer associated with heavy drinking; more male beer drinkers than controls.
				Never	28		
				1 per month to < 1 per day	70		
				1–2 per day	31		
				3–4 per day	28		
				≥7 per day	14		
				Sporadic heavy	3		
				Rectal			
				Never	24		
				1 per month to < 1 per day	34		
				1–2 per day	38		
				3–4 per day	21		
				≥7 per day	22		
				Sporadic heavy	3		

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Wynder & Shigematsu (1967) (contd)				*Colon*	*Women*		
				Never	60		
				1 per month to < 1 per day	34		
				1–2 per day	17		
				3–4 per day	2		
				≥7 per day	0		
				Sporadic heavy	0		
				Rectal			
				Never	40		
				1 per month to < 1 per day	17		
				1–2 per day	4		
				3–4 per day	1		
				≥7 per day	1		
				Sporadic heavy	0		

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Wynder *et al*. (1969), Japan	69 colon (38 men, 31 women) and 88 rectal (42 men, 46 women) from the Japan Cancer Hospital and the National Cancer Institute Hospital; histological confirmation not given; response rate not given	307 (160 men, 147 women) representing two different groups: (1) with cancer other than gastrointestinal; (2) patients with non-malignant disease; matched on age, hospital; response rate not given	Interviewer-administered standardized questionnaire	*Colon* Men Women *Rectal* Men Women	 38 31 42 46		Authors state there were no meaningful differences in alcoholic beverage consumption between cases and controls; relative risks not reported.

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Williams & Horm (1977), USA, 1969–71 (Third National Cancer Survey)	Colon (294 men, 359 women) age ≥35 years; participants in Third National Cancer Survey Rectal (165 males, 138 females) age ≥35 years; participants in Third National Cancer Survey	1494 men, 2829 women with other cancers. 1623 male, 3050 female with other cancer	Interviewer-administered standardized questionnaire	*Colon* None <50 oz/year ≥50 oz/year None <50 oz/year ≥50 oz/year *Rectal* None <50 oz/year ≥50 oz/year None <50 oz/year ≥50 oz/year	 NG 52 96 NG 47 29 NG 27 42 NG 11 14	*Men* 1.0 1.4 1.5 (p<0.05) *Women* 1.0 1.2 1.4 *Men* 1.0 0.8 0.7 *Women* 1.0 0.8 2.0 (p<0.05)	Adjusted for age, race, smoking; controls excluded cancers of the lung, larynx, mouth, oesophagus, and bladder; for men, statistically significant associations were observed for high levels of wine, beer and spirit intake with risk for colon cancer.
Graham *et al.* (1978), New York, USA, 1959–65	256 colon and 330 rectal; white men admitted to Roswell Park Institute; 100% histologically confirmed; response rate not given	783 (colon) and 628 (rectal) hospital-based white men; frequency matched on age; response rate not given	Interviews			No association with colon or rectum for total alcohol, beer, wine or whiskey	No adjustments; the authors noted that data were also collected for women but did not present those results; they stated that results were similar.

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Tuyns *et al.* (1982), France, 1975–80	142 colon (80 men, 82 women) and 198 rectal (104 men, 94 women) identified in Calvados	Population-based; random sample from the same area; response rate, 75%	Interviewer-administered standardized questionnaire	*Colon* Non-consumer Consumer *Rectal* Non-consumer Consumer	 21 121 26 172	 1.0 1.4 (0.3–5.7) 1.0 1.6 (0.5–5.5)	Adjusted for sex, age
Manousos *et al.* (1983), Athens, Greece, 1979–80	100 colon or rectal (of which 35 were rectal) admitted to one of two large teaching hospitals in Athens; 100% histologically confirmed; response rate, 100%	100 hospital-based admitted to the orthopaedic department; matched for sex, age (±5 years), hospital; response rate, 100%	Interview	*Colorectal* 0 glasses of beer/ week 1–10 glasses of beer/week ≥11 glasses of beer/ week *Rectal* 0 glasses of beer/ week 1–10 glasses of beer/week ≥11 glasses of beer/ week	 68 24 8 27 5 3	 *p*-trend >0.25 *p*-trend >0.5	Matched on sex and age; futher adjustment for meat and vegetable consumption attenuated the association; no associations for wine, ouzo, brandy or other hard liquor; relative risk and CI not reported

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Miller *et al.* (1983), Canada, 1976–78	348 colon (171 men, 177 women) and 194 rectal (114 men, 80 women) newly diagnosed in Ontario or Calgary; histological confirmation not given; response rate not given	Two series: (1) 542 neighbourhood; individually matched on age (±5 years), sex, area of residence; (2) 535 hospital-based who underwent abdominal surgery in same hospital as the case; frequency-matched on sex, age; response rate not given	Interviewer-administered standardized questionnaire	*Colon* 0 g ethanol/day 0.1–47.6 g ethanol/day >47.6 g ethanol/day 0 g ethanol/day 0.1–17.7 g ethanol/day >17.7 g ethanol/day *Rectal* 0 g ethanol/day 0.1–47.6 g ethanol/day >47.6 g ethanol/day 0 g ethanol/day 0.1–17.7 g ethanol/day >17.7 g ethanol/day		*Men* 1.0 1.2 1.4 *p*-trend=0.1 *Women* 1.0 1.0 1.0 *p*-trend=0.41 *Men* 1.0 0.5 ($p<0.05$) 1.3 *p*-trend=0.43 *Women* 1.0 1.3 0.8 *p*-trend=0.34	Adjusted for age, saturated fat food group; the two control groups were combined for all analyses; for the association of beer intake with rectal cancer, a marginally significant trend for women ($p=0.09$) but not for men ($p=0.22$); wine and spirit intake not examined

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Pickle *et al.* (1984), Nebraska, USA, 1970–77	58 colon (ICD 153; 11 living and 15 deceased men, 13 living and 19 deceased women) and 28 rectal (ICD 154; 5 living and 9 deceased men, 5 living, 9 deceased women) identified through search of medical records in two counties in Nebraska; 100% histologically confirmed; response rate not given	176 hospital-based (44 living and 45 deceased men, 43 living and 44 deceased women) selected from admission lists; matched to the case (2:1) by hospital, sex, race, age (±5 years); response rate not given	Interviewer-administered standardized questionnaire	**Commercial beer** *Colon* Non-drinker >0 drink/week *Rectal* Non-drinker >0 drink/week		 1.0 2.7 (1.3–5.5) 1.0 1.4 (0.5–3.7)	Adjusted for sex, ever smoked cigarettes, ever smoked pipe; additional analyses for commercial beer consumption and colon cancer examined dose (p-trend=0.05); analyses were also conducted for home-made beer and for commercial and home-made wine consumption; no significant associations for either colon or rectal cancer.

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Tajima & Tominaga (1985), Japan, 1981–84	Colon (27 men, 15 women) and rectal (25 men, 26 women), aged 40–70 years; seen at the Aichi Cancer Center; 100% histologically confirmed; response rate not given	182 hospital-based men; matched on age (±5 years), time of interview (±6 months); response rate not given	Interviewer-administered standardized questionnaire	*Colon* Non-drinker Drinker *Rectal* Non-drinker Drinker		*Men* 1.0 0.68 (p>0.5) *Men* 1.0 0.60 (p>0.5)	Adjusted for age; data also collected for women but only the results for men were presented; some evidence of an inverse association with sake intake
Kabat *et al.* (1986), New York, USA, 1976–81	218 rectal (130 men, 88 women), aged 20–80 years; diagnosed at Memorial Sloane Cancer Center in New York; 100% histologically confirmed; response rate not given	585 (336 men, 249 women) hospital-based with diseases not associated with smoking; matched to cases (1–3:1) on sex, age (±8 years), calendar year of hospital interview (±2 years); response rate not given	Interviewer-administered standardized questionnaire	Never <1 oz/day 1–7.9 oz/day 8–31.9 oz/day ≥32 oz/day Never <1 oz/day 1–7.9 oz/day 8–31.9 oz/day ≥32 oz/day	30 31 26 21 22 67 12 7 2 0	*Men* 1.0 1.6 (0.9–2.8) 1.3 (0.7–2.4) 1.8 (0.9–3.5) 3.5 (1.8–7.0) *Women* 1.0 0.5 (0.3–1.0) 0.5 (0.2–1.2) 0.7 (0.1–3.2) –	Matched on sex, age, calendar year of hospital interview, religion, education; in men, heavy beer consumption associated with an increased risk for rectal cancer

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Potter & McMichael (1986), Adelaide, Australia, 1979–80 (colon), 1979–81 (rectal)	220 colon (121 men, 99 women) and 199 rectal (124 men, 75 women), aged 30–74 years; identified from the South Australian Cancer Registry; histological confirmation not given; response rate, 82.8%	438 colon (241 men, 197 women) and 396 rectal (248 men, 148 women) selected from the electoral rolls of Adelaide; matched 2:1 to cases on sex, age; response rate, 69%	Self-administered dietary questionnaire	*Colon* ≤0.1 g ethanol/day 0.1–4.0 g ethanol/day 4.1–12.8 g ethanol/day 12.9–31.8 g ethanol/day >31.8 g ethanol/day ≤0.1 g ethanol/day 0.1–0.95 g ethanol/day 0.96–3.9 g ethanol/day 4.0–12.9 g ethanol/day >12.9 g ethanol/day		*Men* 1.0 0.6 (0.3–1.3) 0.4 (0.2–1.0) 0.8 (0.4–1.7) 1.0 (0.5–2.1) *Women* 1.0 1.4 (0.7–2.7) 1.2 (0.5–2.6) 2.0 (0.9–4.4) 2.0 (0.9–4.5)	Matched on sex, age; in analysis for specific beverage types, colon cancer significantly associated with spirit intake but not beer or wine in men and women; in multivariate analysis adjusted for occupation, protein and fibre intake, spirit intake remained significantly associated with colon cancer in men.

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Potter & McMichael (1986) (contd)				*Rectal*		*Men*	For women, the association was attenuated after adjustment for oral contraceptive use, parity and fibre and protein intake; rectal cancer significantly associated with spirit intake in men and wine intake in women; *p*-trend not reported
				≤0.1 g ethanol/day		1.0	
				0.1–4.0 g ethanol/ day		0.7 (0.3–1.3)	
				4.1–12.8 g ethanol/ day		0.8 (0.4–1.5)	
				12.9–31.8 g ethanol/ day		0.6 (0.3–1.2)	
				>31.8 g ethanol/day		0.7 (0.4–1.5)	
						Women	
				≤0.1 g ethanol/day		1.0	
				0.1–0.95 g ethanol/ day		0.6 (0.2–1.3)	
				0.96–3.9 g ethanol/ day		1.7 (0.7–3.9)	
				4.0–12.9 g ethanol/ day		1.1 (0.5–2.5)	
				>12.9 g ethanol/day		1.5 (0.6–3.7)	

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Kune *et al.* (1987), Melbourne, Australia	715 colorectal (383 men, 325 women), aged 35–75 years; histological confirmation not given; response rate not given	727 (396 men, 328 women) population-based; matched on sex, age; response rate not given	Interviewer-administered standardized questionnaire	*Colon* 0 g ethanol/day 1–112 g ethanol/day 113–280 g ethanol/day ≥281 g ethanol/day 0 g ethanol/day 1–112 g ethanol/day 113–280 g ethanol/day ≥281 g ethanol/day *Rectal* 0 g ethanol/day 1–112 g ethanol/day 113–280 g ethanol/day ≥281 g ethanol/day 0 g ethanol/day 1–112 g ethanol/day 113–280 g ethanol/day ≥281 g ethanol/day		*Men* 1.0 1.4 1.0 1.0 *Women* 1.0 1.1 1.2 1.4 *Men* 1.0 1.5 1.1 1.5 *Women* 1.0 1.3 1.5 0.9	Adjusted for sex, age, beef, fat, milk, fibre, vegetable, vitamin C, pork, fish, vitamin supplement intake; for colon cancer, no associations with any beverage type; for men and women, beer consumption associated with a higher risk for rectal cancer; spirit intake associated with a lower risk for rectal cancer in men; *p*-values and CI not reported

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Ferraroni *et al.* (1989), Milan, Italy, 1983–88	455 colon (221 men, 234 women) and 295 rectal (170 men, 125 women); aged 75 years; identified from the four largest teaching and general hospitals in Milan; 100% histologically confirmed; response rate not given	1944 (1334 men, 610 women) hospital-based; admitted to one of several Milan area hospitals; response rate not given	Interviewer-administered standardized questionnaire	*Colon* <3 drinks/day 3–6 drinks/day >6 drinks/day *Rectal* <3 drinks/day 3–6 drinks/day >6 drinks/day	 290 107 58 187 62 46	 1.0 1.1 1.2 p=0.67 1.0 0.8 0.9 p=0.46	Adjusted for sex, age, social class, education, marital status, smoking, coffee; no associations with any specific beverage type; in a subsequent analysis of 828 colon and 498 rectal cancer cases and 2024 controls, there was an inverse trend for risk for colon cancer associated with beer intake and no association with rectal cancer (La Vecchia *et al.*, 1993); CI not reported.

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Peters *et al.* (1989), Los Angeles, USA, 1974–82	106 colon and 41 rectal white men, aged 24–44 years; residents of California identified through the Los Angeles County Cancer Surveillance Program; 100% histologically confirmed; response rate, 65%	147 population-based; identified by an algorithm that used the house of the index case as a reference point; matched (1:1) on race, sex, date of birth (±5 years), neighbourhood; response rate not given	Interviewer-administered standardized questionnaire	*Colon* 0–9 g ethanol/day 10–39 g ethanol/day 40–69 g ethanol/day ≥70 g ethanol/day *Rectal* 0–9 g ethanol/day 10–39 g ethanol/day 40–69 g ethanol/day ≥70 g ethanol/day	 61 39 25 20 61 39 25 20	 1.0 1.0 (0.5–1.9) 0.8 (0.4–1.5) 1.6 (0.6–3.7) 1.0 1.2 (0.5–2.7) 0.6 (0.2–1.8) 1.4 (0.4–4.5)	Adjusted for age and education; no associations with any specific beverage type

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Freudenheim *et al*. (1990), New York, USA, 1978–86	422 rectal (277 men, 145 women), aged ≥ 40 years; identified from hospital pathology and surgical records; 100% histologically confirmed; response rate not given	277 men and 145 women; population-based; matched (1:1) on sex, age, neighbourhood; response rate, 57%	Interviewer-administered standardized questionnaire	*Drink–years (drinks/year × years drinking)* Quartile 1 Quartile 2 Quartile 3 Quartile 4 Tertile 1 Tertile 2 Tertile 3		*Men* 1.0 1.1 (0.7–1.8) 1.0 (0.6–1.7) 1.8 (1.1–2.9) *p*-trend=0.06 *Women* 1.0 0.9 (0.5–1.7) 1.9 (1.0–3.6) *p*-trend >0.05	Matched on sex, age, neighbourhood; associations for lifetime alcohol intake; in men, significant associations of rectal cancer with total alcohol and beer which persisted after adjustment for total calories, fat, dietary fibre, vitamin C or carotene. In a subsequent analysis, some evidence of an interaction of folate with alcoholic beverage intake on risk for rectal cancer in men (Freudenheim *et al*., 1991).

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Longnecker (1990), USA multi-site, 1986–88	251 right colon and 383 rectal (men only), aged 31 years; only identified from records departments at 49 New England hospitals and through the Massachusetts Cancer Registry in an additional 19 hospitals; histological confirmation not given; response rate, 66%	992, aged ≥ 31 years; selected from in-law relatives, friends of cases and population lists or Health Care Financing Administration for those aged ≥ 65 years and older; matched on age (±5 years), state; response rate, 65%	Telephone interviewer-administered questionnaire followed by a mailed self-administered standardized questionnaire	*Right colon*			Adjusted for age, income, tobacco smoking; results for consumption 5 years prior to diagnosis; similar for associations of alcohol intake 20 years prior to diagnosis for both right colon and rectal cancer; associations for colon and rectal strongest for beer intake with no significant associations for wine or liquor; significant association of alcoholic beverage consumption with right colon and with rectal cancer for those with low calcium or low vitamin D intake, but not for those with high calcium or high vitamin D intake
				0 drink/day	71	1.0	
				0.5 drink/day	59	0.9 (0.6–1.3)	
				1 drink/day	31	1.0 (0.6–1.5)	
				2 drinks/day	27	1.0 (0.6–1.7)	
				3–4 drinks/day	40	1.7 (1.1–2.7)	
				≥5.0 drinks/day	21	1.8 (1.0–3.2)	
						p-trend=0.007	
				Rectal			
				0 drink/day	97	1.0	
				0.5 drink/day	107	1.1 (0.8–1.5)	
				1 drink/day	46	0.9 (0.6–1.4)	
				2 drinks/day	48	1.2 (0.8–1.9)	
				3–4 drinks/day	64	1.7 (1.1–2.5)	
				≥5.0 drinks/day	30	1.5 (0.9–2.5)	
						p-trend=0.007	

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Slattery *et al.* (1990), Utah, USA, 1979–83	231 colon (ICD-0 153.0–154.0; 112 men, 119 women), aged 40–79 years; identified through the Utah Cancer Registry; 100% histologically confirmed; response rate, 71%	391 (185 men, 206 women) population-based; selected using random-digit dialling; response rate, 74%	Interviewer-administered standardized questionnaire	*Men* Never 1–15 g ethanol/ week >15 g ethanol/week *Women* Never 1–15 g ethanol/ week >15 g ethanol/week	 60 26 26 100 15 4	*Men* 1.0 1.4 (0.7–3.0) 1.1 (0.5–2.4) *Women* 1.0 1.1 (0.5–2.1) 0.6 (0.2–1.9)	Men: adjusted for age, religion, body-mass index, calories, crude fibre intake, pipe use, caffeine intake for multiple logistic models; women: unadjusted; associations did not differ by colon subsite (ascending versus descending).
Choi & Kahyo (1991b), Seoul, Republic of Korea, 1986–90	114 colon (ICD-9 153; 63 men, 51 women) and 133 rectal (ICD-9 154;67 men, 66 women) identified from the Korea Cancer Hospital of Seoul; 100% histologically confirmed; response rate not given	189 male colon, 153 female colon, 201 male rectal, 198 female rectal selected from patients without cancer at the same hospital; matched 3:1 on sex, birth year (±5 years), admission date; response rate not given	Interviewer-administered standardized questionnaire	*Colon* Non-drinker Light Moderate Medium–heavy Heavy *Rectal* Non-drinker Light Moderate Medium–heavy Heavy	 19 14 18 10 2 11 22 16 14 4	 1.0 0.6 (0.3–1.4) 1.1 (0.5–2.5) 1.0 (0.4–2.3) 0.7 (0.1–3.6) 1.0 2.2 (1.0–7.5) 2.0 (0.8–4.9) 2.5 (1.1–5.6) 4.7 (1.3–2.8)	Adjusted for age, marital status, education, cigarette smoking, diet; too few female drinkers so results limited to men

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Hu *et al.* (1991), Harbin, China, 1985–88	111 colon and 225 rectal, aged 30–75 years; from local hospitals; 100% histologically confirmed; response rate not given	335 hospital-based, aged 30–74 years; selected from the same hospitals as cases; matched on sex, age (±5 years), residential area; response rate not given.	Interviewer-administered standardized questionnaire	*Colon* <1.0 kg/year ≥1.0 kg/year *Rectal* <1.0 kg/year ≥1.0 kg/year		*Men and women* 1.0 6.42 ($p<0.01$) *Men* 1.0 2.1 ($p<0.05$)	Adjusted for green vegetable, chives and celery intake Adjusted for grain, chives and celery intake Results for current consumption; in multivariate analysis, no association with alcoholic beverage in women; CI not reported

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Riboli *et al.* (1991), Marseilles, France, 1979–85	196 colon (92 men, 104 women) and 193 rectal (95 men, 98 women) identified from 11 major hospitals; 100% histologically confirmed; response rate, 100%; age not given	389 selected from specialized medical centres for treatment of injury or trauma; matched 1:1 on sex, age (±2 years); response rate, 90%	Interviewer-administered standardized questionnaire	*Colon* 0 mL ethanol/day 1–30.1 mL ethanol/day 30.2–53.9 mL ethanol/day 54–90.7 mL ethanol/day >90.7 mL ethanol/day 0 mL ethanol/day 1–9.9 mL ethanol/day 10–15.5 mL ethanol/day 15.6–25.8 mL ethanol/day >90.7 mL ethanol/day	 5 22 22 19 24 29 22 14 19 20	*Men* 1.0 0.9 0.9 0.8 1.0 *p*-trend=0.99 *Women* 1.0 1.4 0.9 1.3 1.4 *p*-trend=0.43	Adjusted for age, calories, fibre from fruit and vegetables; for colon cancer, no significant associations with any specific beverage type; rectal cancer includes those with multiple locations (i.e. colon and rectum); for rectal cancer, only significant association was with beer intake and no association with wine or distilled beverages.

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Riboli *et al.* (1991) (contd)				*Rectal*		*Men*	
				0 mL ethanol/day	3	1.0	
				1–30.1 mL ethanol/day	20	1.1	
				30.2–53.9 mL ethanol/day	20	1.0	
				54–90.7 mL ethanol/day	28	1.5	
				>90.7 mL ethanol/day	24	1.3 *p*-trend=0.42	
						Women	
				0 mL ethanol/day	21	1.0	
				1–9.9 mL ethanol/day	23	2.0	
				10–15.5 mL ethanol/day	15	1.2	
				15.6–25.8 mL ethanol/day	21	1.7	
				>90.7 mL ethanol/day	18	1.5 *p*-trend=0.33	

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Gerhardsson de Verdier *et al*. (1993), Stockholm, Sweden, 1986–88	352 colon (163 men, 189 women) and 217 rectal (107 men, 110 women), aged 40–80 years; identified through local hospital and the regional cancer registry; 100% histologically confirmed; response rate, 79%	512 (236 men, 276 women) population-based; selected from complete register of the population; frequency-matched on sex, year of birth (10-year categories); response rate, 82%	Self-administered standardized questionnaire	*Colon* 0–9.9 g ethanol/day 10.0–19.9 g ethanol/day 20.0–29.9 g ethanol/day ≥30 g ethanol/day *Rectal* 0–9.9 g ethanol/day 10.0–19.9 g ethanol/day 20.0–29.9 g ethanol/day ≥30 g ethanol/day	 282 37 18 15 166 30 11 10	 1.0 0.7 (0.5–1.2) 1.2 (0.6–2.3) 0.9 (0.4–1.8) 1.0 1.0 (0.6–1.6) 1.2 (0.6–2.7) 1.1 (0.5–2.4)	Adjusted for sex, year of birth, total energy, protein, dietary fibre, body mass, physical activity, smoking; no differences in associations between men and women; no associations with any specific beverage type

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Hoshiyama *et al*. (1993), Saitama, Japan, 1984–90	79 colon (37 men, 42 women) and 102 rectal (61 men, 41 women), aged 40–69 years; admitted to a single cancer centre hospital; 100% histologically confirmed; response rate not given	653 (343 men, 310 women) population-based; identified from electoral rolls; frequency-matched on sex, age, class; response rate, 27.5%	Interviewer-administered standardized questionnaires	*Colon* Never Past Occasional <50 mL ethanol/day ≥50 mL ethanol/day *Rectal* Never Past Occasional <50 mL ethanol/day ≥50 mL ethanol/day	 42 2 18 9 9 41 2 19 19 21	 1.0 0.4 (0.0–2.0) 0.6 (0.3–1.1) 0.3 (0.1–0.8) 0.3 (0.1–0.9) 1.0 0.3 (0.0–1.7) 0.5 (0.2–1.0) 0.5 (0.2–1.1) 0.6 (0.3–1.3)	Adjusted for sex and age; heavier drinking not associated with increased risk for colon or rectal cancer
Meyer & White (1993), Washington, USA, 1985–89	424 colon, men and women aged 30–62 years; identified through the Seattle-Pugent Sound SEER Registry; histological confirmation not given; response rate, 74.7%	414 population-based; identified by random-digit dialling; frequency-matched on sex, age, residence; response rate, 79.1%	Mailed self-administered questionnaire	 0 g ethanol/day 0.1–9.9 g ethanol/day 10–29 g ethanol/day ≥30 g ethanol/day Total consumption 0 g ethanol/day 0.1–9.9 g ethanol/day 10–29 g ethanol/day ≥30 g ethanol/day Total consumption	 	*Men* 1.0 1.9 1.7 2.6 (1.04–1.54) *p*-trend <0.05 *Women* 1.0 1.3 1.8 2.5 (1.03–1.72) *p*-trend <0.05	Adjusted for age, interviewer; no CI provided; the test for trend is that for analysis associated with one-category increment; wine and liquor, but not beer, were associated with colon cancer in men, but no clear associations with beverage type in women.

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Newcomb *et al.* (1993), Wisconsin, USA, 1990–91	779 women (536 colon and 243 rectal), aged < 75 years; identified by Wisconsin Cancer Reporting System; histological confirmation not given; response rate, 70%	2315 women; population-based; those aged <65 years selected from the driver's licence lists; those aged 65–74 years identified from the Health Care Financing Administration; response rate, 90%	Telephone interviewer-administered standardized questionnaire	*Colon* None 1–2 drinks/week 3–5 drinks/week 6–10 drinks/week ≥11 drinks/week *Rectum* None 1–2 drinks/week 3–5 drinks/week 6–10 drinks/week ≥11 drinks/week	 122 239 77 46 33 47 93 48 26 19	 1.0 1.0 (0.8–1.3) 0.9 (0.6–1.3) 0.9 (0.6–1.4) 1.3 (0.8–2.2) *p*-trend=0.61 1.0 0.9 (0.6–1.4) 1.5 (0.9–2.3) 1.3 (0.8–2.2) 1.9 (1.0–3.5) *p*-trend=0.01	Adjusted for age, body-mass index, screening sigmoidoscopy history, family history of colorectal cancer; colon cancer positively associated with liquor intake, inversely associated with wine intake and not associated with beer intake; rectal cancer positively associated with beer intake and not associated with wine or liquor intake

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Olsen & Kronborg (1993), Funen, Denmark, 1986–90	49 colorectal (21 men, 28 women), aged 45–74 years; selected in two steps from a screening clinical trial, first those with a positive Haemoccult II-test, and then those with a cancer on colonoscopy; histologically confirmed; response rate not given	362 (157 men, 205 women); identified as those with a negative Haemoccult II-test; matched on date of test, sex, age from first step of selection; response rate not given	Interviewer-administered standardized questionnaire	0% of kcal 1–3% of kcal ≥4% of kcal	17 10 18	1.0 1.4 (0.8–2.3) 0.6 (0.3–1.0)	Adjusted for sex, age, dietary fibre; cases and controls selected from screenees of a Haemoccult clinical trial; no statistically significant associations were found between alcohol consumption and cancer.

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Boutron *et al.* (1995), Côte d'Or, France, 1985–90	171 colorectal (109 men, 62 women), aged 30–79 years; identified from all gastroenterology practices of the region; 100% histologically confirmed; response rate, 79.9%	309 (159 men, 150 women) population-based; selected from the census lists; frequency-matched on age, sex; response rate, 53.5%	Interviewer-administered standardized questionnaire	*Men* <10 g ethanol/day 10–19 g ethanol/day 20–39 g ethanol/day 40–59 g ethanol/day ≥60 g ethanol/day *Women* <5 g ethanol/day 5–9 g ethanol/day ≥10 g ethanol/day	 16 12 26 24 31 41 4 17	*Men* 1.0 1.5 (0.6–4.4) 1.2 (0.6–2.6) 1.9 (0.9–4.5) 1.3 (0.6–2.9) p >0.1 *Women* 1.0 0.6 (0.2–1.8) 0.9 (0.5–1.9) p>0.1	Adjusted for age; for men, a 2.5-fold higher risk associated with cider intake but not with beer or liquors; for women, a 3.4-fold higher risk for colorectal cancer associated with beer intake and no association with cider or liquor intake
Le Marchand *et al*. (1997), Hawaii, USA, 1987–91	825 colon (467 men, 358 women) and 350 rectal (221 men, 129 women); identified through the Hawaii Tumor Registry; 100% histologically confirmed; response rate, 66%; age <84 years	1175 (825 men, 350 women); identified from list of Oahu residents who had participated in a Department of Health survey; matched 1:1 on sex, age (±2.4 years); response rate, 71%	Interviewer-administered standardized questionnaire	*Right colon* Never Past Current Never Past Current	 	*Men* 1.0 2.6 (1.4–5.2) 2.0 (1.0–3.4) *Women* 1.0 3.1 (1.0–9.4) 2.5 (0.9–7.0)	Adjusted for age, family history of colorectal cancer, pack–years, lifetime physical activity, body-mass index 5 years ago, intake of egg, dietary fibre, calcium, total calories; caloric intake, physical activity and obesity were independently associated with colorectal cancer.

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Le Marchand *et al*. (1997) (contd)				*Left colon*		*Men*	
				Never		1.0	
				Past		1.7 (0.8–3.3)	
				Current		1.1 (0.7–2.0)	
						Women	
				Never		1.0	
				Past		1.3 (0.5–3.4)	
				Current		1.0 (0.5–2.3)	
				Rectal		*Men*	
				Never		1.0	
				Past		1.4 (0.8–2.4)	
				Current		1.1 (0.6–2.0)	
						Women	
				Never		1.0	
				Past		1.5 (0.6–4.1)	
				Current		1.0 (0.3–3.0)	
Yamada *et al*. (1997), Tokyo, Japan, 1991–93	66 colorectal (55 men, 11 women) (excluded *in situ*), aged 34–80 years; examinees of a multiphasic health check-up; 100% histologically confirmed; response rate not given	132 (110 men, 22 women); identified from the same multi-phasic examination; matched 2:1 on sex, age, number of prior health check-ups; response rate not given	Self-administered standardized questionnaire	0 g ethanol/day	23	1.0	Adjusted for sex, age, body-mass index, cigarettes smoked per day
				1–20 g ethanol/day	24	1.1 (0.4–3.1)	
				21–40 g ethanol/day	55	0.7 (0.3–1.9)	
				≥41 g ethanol/day	30	2.0 (0.7–5.4)	
						p-trend=0.09	

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Muñoz *et al.* (1998), Córdoba, Argentina, 1993–97	146 colon and 44 rectal (89 men, 101 women), aged 23–79 years; admitted to several hospitals in area; 100% histologically confirmed; response rate not given	393 (201 men, 192 women) hospital-based, aged 23–79 years; response rate not given	Interviewer-administered standardized questionnaire	Non-drinker <24 g ethanol/day ≥24 g ethanol/day	40 59 91	1.0 2.2 (1.4–3.7) 3.1 (1.8–5.2) *p*-trend=0.001	Adjusted for sex, age, social class, body-mass index; no differences in associations between men and women

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Tavani *et al.* (1998), Italy multi-site, 1991–96	1225 colon (ICD-10 C18.0–18.7; 688 men, 537 women) and 728 rectal (ICD-10 C19 and C20; 437 men, 291 women), aged 24–74 years; identified from area major teaching hospitals; 100% histologically confirmed; response rate, ~96%	4154 (2073 men, 2081 women) hospital-based, aged 20–74 years; admitted to the same network of hospitals; response rate, ~96%	Interviewer-administered standardized questionnaire	*Colon* Never drinker Ex-drinker 1–11.8 g ethanol/day 11.8–22.7 g ethanol/day 22.7–34.4 g ethanol/day 34.4–51.8 g ethanol/day ≥51.8 g ethanol/day	 248 89 169 190 188 172 169	 1.0 1.2 (0.9–1.6) 1.2 (0.9–1.5) 1.3 (1.0–1.6) 1.2 (0.9–1.5) 1.1 (0.8–1.4) 1.0 (0.8–1.3) *p*-trend=0.001	Adjusted for sex, age, education, physical activity, smoking status, family history, intake of β-carotene, vitamin C, total energy; no evidence of interaction with sex or cigarette smoking; strongest associations with spirit, grappa or amari consumption but no association with wine or beer; no differences in associations according to site within the colon

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Tavani *et al.* (1998) (contd)				*Rectum*			
				Never drinker	147	1.0	
				Ex-drinker	51	1.1 (0.7–1.5)	
				1–11.8 g ethanol/ day	87	1.1 (0.8–1.5)	
				11.8–22.7 g ethanol/ day	132	1.5 (1.1–1.9)	
				22.7–34.4 g ethanol/ day	114	1.2 (0.9–1.6)	
				34.4–51.8 g ethanol/ day	97	0.9 (0.7–1.3)	
				≥51.8 g ethanol/day	100	0.9 (0.7–1.2) *p*-trend=0.657	

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Ji *et al.* (2002), Shanghai, China, 1990–92	931 colon (ICD-9 153.0–153.9; 462 men, 469 women) and 874 rectal (ICD-9 154.0–154.9; 463 men, 411 women), aged 30–74 years; identified through the Shanghai Cancer Registry; 95% colon, 98% rectal histologically confirmed; response rate, 92% colon, 91% rectal	1552 (851 men, 701 women) population-based; randomly selected from among Shanghai residents based on personal identification cards; frequency-matched on sex, age (±5 years); response rate not given	Interviewer-administered standardized questionnaire	*Colon* Non-drinker Former drinker Current drinker Non-drinker Former drinker Current drinker *Rectum* Non-drinker Former drinker Current drinker Non-drinker Former drinker Current drinker	 248 41 173 448 6 15 255 34 174 390 4 17	*Men* 1.0 2.3 (1.4–3.7) 1.0 (0.8–1.3) *Women* 1.0 1.4 (0.4–4.3) 0.7 (0.4–1.3) *Men* 1.0 1.1 (0.9–1.4) 0.6 (0.4–1.0) *Women* 1.0 1.2 (0.7–2.3) 1.1 (0.3–4.1)	Adjusted for age, income, cigarette smoking; body-mass index, years of education, diet, history of colorectal polyps and proxy interview status did not confound associations; no differences in risk between proximal and distal colon; for men, associations appeared to be restricted to hard liquor; interaction of alcoholic beverage consumption and cigarette smoking not statistically significant.

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Sharpe *et al.* (2002), Montréal, Canada, multisite, 1979–85	355 colon and 230 rectal (ICD-9 153–154; all men), aged 35–70 years; diagnosed at all large hospitals in the region; 100% histologically confirmed; response rate, 85.6%	500 population-based; identified from random-digit dialling or from electoral lists; frequency-matched on age, area of residence; response rate, 72%	Interviewer-administered standardized questionnaire	*Proximal colon* Never drank weekly Drank weekly Drank daily *Distal colon* Never drank weekly Drank weekly Drank daily *Rectum* Never drank weekly Drank weekly Drank daily	 41 55 80 28 51 100 37 74 119	 1.0 1.1 (0.6–1.7) 1.0 (0.6–1.7) *p*-trend=0.9 1.0 1.4 (0.9–2.5) 2.3 (1.4–3.7) *p*-trend=0.001 1.0 1.5 (0.9–2.4) 1.6 (1.0–2.6) *p*-trend=0.06	Adjusted for age, respondent status, ethnicity, family income, years of education, marital status, cigarette smoking; no meaningful associations with wine or spirit intake; heavy beer intake associated with proximal colon, distal colon and rectal cancer

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Ho *et al.* (2004), Hong Kong, 1998–2000	452 colon (251 men, 201 women) and 357 rectal (213 men, 144 women), aged 20–85 years; identified from three public hospitals; 100% histologically confirmed; response rate, 82.2%	926 (530 men, 396 women) hospital-based; inpatients identified from the same departments as the cases admitted for acute, non-malignant surgical conditions; matched on sex, age (±5 years); response rate, 95.5%	Interviewer-administered standardized questionnaire	*Colon* Never Former drinker Current drinker *Rectal* Never Former drinker Current drinker	 219 97 133 164 84 111	 1.0 1.0 (0.7–1.3) 1.5 (1.1–2.0) *p*-trend=0.02 1.0 1.1 (0.7–1.5) 1.3 (1.0–1.9) *p*-trend=0.1	Adjusted for sex, age, geographical distribution, marital status, education, physical activity, analgesia intake, family history of colorectal cancer, smoking habit, diet; showed an inverse relationship with time since stopping drinking.

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Kim *et al.* (2004), Seoul, Republic of Korea 1998–2000	111 colon and 132 rectal (127 men, 107 women), aged 30–79 years; selected from two university hospitals; 100% histologically confirmed; response rate not given	225 (108 men, 117 women) hospital-based; aged 30–79 years; response rate not given	Interviewer-administered standardized questionnaire	*Colon* <5 g ethanol/day 5–29 g ethanol/day ≥30 g ethanol/day *Rectal* <5 g ethanol/day 5–29 g ethanol/day ≥30 g ethanol/day	 58 23 30 81 24 27	 1.0 1.2 (0.6–2.7) 2.7 (1.2–6.1) 1.0 0.7 (0.4–1.5) 1.4 (0.7–3.0)	Adjusted for sex, age, total energy intake, family history of colorectal cancer, body mass index, smoking, vigorous physical activity, red meat intake, *MTHFR* genotype; no evidence of an interaction of alcoholic beverages with *MTHFR* genotype on risk for colon, rectal or colorectal cancer

Table 2.46 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors/ comments
Murtaugh *et al*. (2004), northern California and Utah, USA, 1997–2001	952 incident rectal, aged 30–79 years, English speaking; in California, cases were members of the Kaiser Permanente Medical Care Program and identified by the Kaiser and Northern California Tumor Registry, in Utah cases were identified by the Utah SEER registry; response rate, 65%	1205; frequency-matched on sex, age (±5 years); in California, controls selected from the membership lists of Kaiser; in Utah, controls ≥65 years randomly selected from social security lists and those aged <65 years selected from driver's licence lists; response rate, 65.2%	Interviewer-administered diet history			*Men*	Adjusted for age, energy, fibre, calcium intake, physical activity; results for alcohol intake in the last 20 years; similar results observed for intake in the previous 10 years; cases with a previous colorectal tumour, familial adenomatous polyposis, ulcerative colitis and Crohn disease were ineligible; not clear if similar exclusion was made for controls; no associations with specific beverage type; results from 10-year use reported when 20-year use data were missing
				None	251	1.0	
				Low	183	0.9 (0.7–1.2)	
				High	172	1.3 (0.9–1.7)	
						Women	
				None	227	1.0	
				Low	116	1.1 (0.8–1.4)	
				High	72	1.2 (0.8–1.7)	

CI, confidence interval; MTHFR, methylenetetrahydrofolate reductase; SEER, Surveillance, Epidemiology and End Result

& McMichael, 1986). In the nine studies that showed a significant positive association, the relative risks ranged from approximately 1.5 to 6.4 for the highest versus the lowest level of alcoholic beverage intake (Williams & Horm, 1977; Pickle *et al*., 1984; Longnecker, 1990; Hu *et al*., 1991; Meyer & White, 1993; Le Marchand *et al*., 1997; Sharpe *et al*., 2002; Ho *et al*., 2004; Kim *et al*., 2004). Overall, there were no consistent differences in associations between the proximal and distal colon among the case–control studies.

At least 28 case–control studies have investigated rectal cancer, 18 of which showed no statistically significant association with alcoholic beverage consumption (Wynder & Shigematsu, 1967; Graham *et al*., 1978; Tuyns *et al*., 1982; Manousos *et al*., 1983; Miller *et al*., 1983; Pickle *et al*., 1984; Tajima & Tominaga, 1985; Potter & McMichael, 1986; Kune *et al*., 1987; Ferraroni *et al*., 1989; Peters *et al*., 1989; Riboli *et al*., 1991; Gerhardsson de Verdier *et al*., 1993; Hoshiyama *et al*., 1993; Le Marchand *et al*., 1997; Tavani *et al*., 1998; Ji *et al*., 2002; Kim *et al*., 2004). In two other studies, the relative risk for heavy versus light drinkers was 1.3 (95% CI, 0.9–1.7) (Murtaugh *et al*., 2004) and that for current versus never drinkers was 1.5 (95% CI, 0.9–1.9) (Ho *et al*., 2004). Eight studies showed a positive association (Williams & Horm, 1977; Kabat *et al*., 1986; Freudenheim *et al*., 1990; Longnecker, 1990; Choi & Kahyo, 1991b; Hu *et al*., 1991; Newcomb *et al*., 1993; Sharpe *et al*., 2002).

The meta-analysis of Longnecker *et al*. (1990) included data from 22 case–control studies (Table 2.45). In that analysis, the relative risk for colorectal cancer associated with an intake of 24 g alcohol per day was 1.07 (95% CI, 1.02–1.12). It should be noted that the results for the five cohort studies were stronger (relative risk, 1.3) than those for case–control studies.

2.8.3 *Potential confounding*

Several studies assessed whether an association between alcoholic beverage consumption and risk for colorectal cancer might be confounded by obesity and/or other lifestyle factors. For heavy alcoholic beverage drinkers and alcoholics, it is reasonable to assume that poor diet in particular could contribute to an apparent association. However, based on studies of alcoholics or men who worked in the brewery industry, there is only limited evidence of an elevated risk for colon or rectal cancer. As noted in the Tables, nearly all of the cohort studies adjusted for sex, age and smoking status, and some included covariates for body-mass index, dietary factors and physical activity. In addition, as described previously, one of the criteria for inclusion of data into the cohort pooling project was available information on diet. This allowed for a detailed assessment of potential confounding by specific dietary factors including total energy, fat, meat, fibre and specific micronutrients. Even after adjustment for all of the dietary factors considered, the association of alcoholic beverage intake with colorectal cancer persisted.

2.8.4 *Effect modification*

Whether the association between alcoholic beverage consumption and the risk for colorectal cancer is modified by gender or lifestyle factors has been examined in some studies (see Tables 2.44–2.46 for details). Some data suggest that associations are stronger for men than for women; levels of alcoholic beverage intake are on average higher among men but, in some studies, the number of cases among women with a high alcoholic beverage intake was insufficient to conduct a detailed analysis. Overall, there is little evidence of a meaningful difference in the association of alcoholic beverage intake with risk for colorectal cancer between men and women.

A few studies examined effect modification by cigarette smoking. In one cohort study, the association of alcoholic beverage consumption with the risk for colorectal cancer was observed only among nonsmokers (Flood *et al*., 2002). However, at least three other cohort studies (Murata *et al*., 1996; Otani *et al*., 2003; Pedersen *et al*., 2003) and two case–control studies (Tavani *et al*., 1998; Ji *et al*., 2002) failed to demonstrate any significant effect modification by smoking.

There is growing interest in the potential effect modification of folate intake. Freudenheim *et al*. (1991) found a nearly fivefold higher risk for rectal cancer among men with a high alcoholic beverage/low folate intake compared with men with a low alcoholic beverage/high folate intake. Subsequently, these findings were supported by those of Giovannucci *et al*. (1995) who found no elevated risk for colon cancer associated with high alcoholic beverage intake among men with high folate intake. However, data from at least two other cohort studies (Flood *et al*., 2002; Harnack *et al*., 2002) failed to support a significant interaction between alcoholic beverage and folate intake. In many studies, the power to detect significant interactions might have been limited. Therefore, the modifying effects of folate on alcoholic beverages were also examined in the large cohort pooling project. While not statistically significant ($P>0.2$), the results indicated a slightly stronger association of alcoholic beverage consumption with colorectal cancer for those with low folate intake and essentially no association for those with high folate intake.

Whether the degree of obesity modifies the relationship between alcoholic beverage consumption and risk for colorectal cancer remains unclear since few studies to date have had adequate power to consider this interaction carefully. In the cohort pooling project, the positive association with alcohol consumption was slightly stronger in leaner individuals than in heavier individuals; the relative risk associated with ≥30 g ethanol per day compared with 0 g ethanol per day was 1.84 for persons whose body-mass index was <22 kg/m^2 but 1.08 for persons with a body-mass index of ≥25 kg/m^2 (p for interaction=0.03).

2.8.5 *Conclusion*

In summary, there is little evidence of a higher than expected risk for colon or rectal cancer among heavy alcoholic beverage drinkers, alcoholics or brewery workers. However, a large body of evidence from prospective cohort studies reported a statistically significant positive association between alcoholic beverage intake and the risk for colon, rectal or colorectal cancer, and no study reported a significant inverse association. These findings are supported by those of a large cohort pooling project and a recent meta-analysis of cohort studies. Although the evidence from individual case–control studies is less consistent, a meta-analysis of 22 case–control studies also supported a positive association. In contrast, two individual case–control studies found an inverse association. The positive association of alcoholic beverage consumption with risk for colorectal cancer does not appear to be confounded by other lifestyle or sociodemographic factors, since most large cohort and case–control studies adjusted for the potential confounding effects of gender, race/ethnicity, age, body-mass index, smoking status and socioeconomic status or education; some of these also adjusted for physical activity and/or specific dietary factors.

Based on data from the pooling project and the most recent meta-analysis of prospective cohort studies, the strength of association appears to be modest with a relative risk of 1.4 for an intake of ≥45 g alcohol per day compared with 0 g per day. However, there is uncertainty regarding the dose–response relationship.

The association between alcoholic beverage consumption and the risk for colorectal cancer does not appear to vary according to anatomical site within the large bowel or type of alcoholic beverage. Similarly, based on the available information, there is no consistent evidence of effect modification by gender or smoking status. Whether degree of obesity or dietary factors such as folate intake modify the relationship is unclear, since only a few studies have examined these interactions.

2.9 Cancer of the pancreas

2.9.1 *Cohort studies*

(a) Special populations (Table 2.47)

Ten cohort studies of men and women with a high alcoholic beverage intake (i.e. among alcoholics or brewery workers) have reported on the risk for pancreatic cancer. Four studies (Carstensen *et al*., 1990; Tønnesen *et al*., 1994; Sigvardsson *et al*., 1996; Karlson *et al*., 1997) found a significant excess risk among heavy alcoholic beverage drinkers compared with the national population, although all of these studies were based on small numbers of cases (i.e. <50). One study of men employed in a brewery in Sweden (and who were allowed a ration of 1 L of beer per day) and who were followed-up for nearly 20 years reported a significant excess rate of pancreatic cancer. The authors noted that a large reduction in the number of breweries occurred during the

Table 2.47 Cohort studies of pancreatic cancer in special populations

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Hakulinen *et al.* (1974), Finland, Alcohol Misuse Records and Alcoholics	205 000 male 'alcohol misusers' registered for convictions for drunkenness, 1944–59; 4370 alcoholic men on Social Welfare Register, aged ≥30 years, 1967–70; follow-up until 1970	Incidence rates compared with national population rates	Population rate (Exp) Alcoholics (Obs)	2.2 4	NS		Results not stated for cohort of alcoholics on Social Register; no individual exposure data; no information on potential confounders
Monson & Lyon (1975), Massachusetts, USA	1382 men and women hospitalized with alcoholism in 1930, 1935, 1940; mortality follow-up until 1971	Mortality rates compared with US whites	Population rate (Exp) Alcoholics (Obs)	5.1 3	1.0 0.6	Age, sex, calendar time	Half lost to follow-up; no individual exposure data; no information on potential confounders
Dean *et al.* (1979), Ireland, Dublin Brewers	1628 deaths recorded 1954–73 in male brewery workers (average intake, 58 g/day)	Mortality rates compared with local population rates	Population rate (Exp) Brewers (Obs)	14 17	1.0 1.09 (NS)		Predominantly beer intake; no individual exposure data; no information on potential confounders

Table 2.47 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Jensen (1979), Denmark, Danish Brewery Workers Union	14 313 brewers (free 2-L daily ration of beer) and 1063 mineral water factory workers, recruited from 1943; follow-up until 1973; 44 cases identified through registry/death certificates	Incidence and mortality rates compared with national rates			*Incidence*	Age, sex, area, time	No individual exposure data; no information on potential confounders
			Population rate (Exp)	40	1.0		
			Brewers (Obs)	44	1.09 (0.80–1.47)		
					Mortality		
			Population rate (Exp)	41	1.0		
			Brewers (Obs)	44	1.08 (0.78–1.44)		
Robinette *et al.* (1979), US Army Veterans	4401 men hospitalized with alcoholism and 4401 with nasopharyngitis recruited 1944–45; matched by age; follow-up of mortality until 1975	None	Nasopharyngitis	5	1.0	Age	Mortality only; ~50% aged <30 years at entry; no individual exposure data; no information on potential confounders
			Alcoholism	4	0.87 (0.22–3.25)[a]		
Schmidt & Popham (1981), Ontario, Canada	9889 men hospitalized for alcoholism, 1951–70; follow-up until 1971	Mortality rates compared with regional rates	Population rate (Exp)	9.24	1.0		No individual exposure data; no information on potential confounders
			Alcoholics (Obs)	11	1.19 (NS)		

Table 2.47 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Carstensen *et al.* (1990), Sweden, Cancer Environment Register	6230 male brewers listed in 1960 census, aged 20–69 years (ration of 1 L/day); follow-up until 1979; 38 cases identified through registry	Incidence rates compared with national rates	Population rate (Exp) Brewers (Obs)	23 38	1.0 1.66 (1.18–2.28) p-value <0.01	Age, follow-up period, region	Reduction in breweries in 1960–80 so potential misclassification of jobs probable, no individual exposure data; no information on potential confounders
Tønnesen *et al.* (1994), Denmark, Copenhagen Alcoholics	18 307 male and female alcoholics, recruited 1954–87 from outpatient clinics (~200 g ethanol/day); follow-up until 1987	Incidence rates compared with national rates	Population rate (Exp) Alcoholics (Obs)	31 41	1.0 1.3 (1.0–1.8) p-value ≤0.05	Age, sex, calendar time	Most drank beer; not adjusted for smoking; no individual exposure data; no information on potential confounders
Sigvardsson *et al.* (1996), Sweden	15 508 alcoholic women (Temperance Board records/ convictions) in 1947–77 and comparison group of 15 508 women, matched by age and region (population register); follow-up not stated; 48 cases identified by registry	Incidence rates in alcoholics compared with rates in matched comparison group	Comparison group Alcoholics	18 48	1.0 2.7 (1.6–4.6)	Matching factors	Excluded ~6000 older women with no identity number; large changes in alcoholic beverage availability and attitudes during follow-up; no individual exposure data; no information on potential confounders

Table 2.47 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Karlson *et al.* (1997); Ye *et al.* (2002), Sweden, Inpatient Hospital Register (retrospective cohort)	Karlson *et al.* (1997): Analytical cohort of 4043 patients discharged with pancreatitis associated with alcoholism, 1965–83; mean age, 46 years; follow-up until 1989; 15 cases (13 men, 2 women) (excluding 1 year of follow-up) Ye *et al.* (2002): 178 688 male and female patients with hospital discharge of alcoholism, 1964–95; 305 cases identified through cancer registry (excluding 1 year of follow-up)	Incidence rates compared with national rates	Population (Exp) Alcoholics (Obs) Population (Exp) Alcoholics (Obs)	Not stated 15 222 305	1.0 2.9 (1.6–4.8) 1.0 1.4 (1.2–1.5)	Age, sex, calendar year	No individual exposure data; no information on potential confounders Increased risk in men and women separately, but not adjusted for smoking; increased risk among younger patients

CI, confidence interval; Exp, expected; NS, not significant; Obs, observed; SIR, standardized incidence ratio; SMR, standardized mortality ratio

[a] 90% confidence interval

follow-up period (1960–80), and that potential misclassification of exposure is probable (Carstensen *et al*., 1990). Three cohort studies of alcoholics in Sweden and Denmark also reported significant excess rates of pancreatic cancer compared with national incidence rates (Tønnesen *et al*., 1994; Sigvardsson *et al*., 1996; Ye *et al*., 2002), matched by age, sex and calendar time.

None of these studies provided individual exposure data and thus dose–response relationships could not be examined and potential confounding factors such as cigarette smoking could not be taken into account. Finally, it must be noted that high alcoholic beverage consumption may induce chronic pancreatitis, a known risk factor for pancreatic cancer. One study based on hospital discharge records in Sweden found that the rate of pancreatic cancer among patients with pancreatitis associated with alcoholism was higher than that among the national population, but similar to the rates found among patients with chronic or recurrent pancreatitis as a whole (Karlson *et al*., 1997).

(b) General population (Table 2.48)

Twelve cohort studies examined alcoholic beverage consumption and the subsequent risk for pancreatic cancer in the general population. Three studies reported a significant excess risk with increased alcoholic beverage intake (Klatsky *et al*., 1981; Heuch *et al*., 1983; Zheng *et al*., 1993). An early report from the Kaiser-Permanente study found a significantly increased risk for men and women who drank ≥6 drinks per day compared with non-drinkers (Klatsky *et al*., 1981), although this was not confirmed in a subsequent follow-up (Hiatt *et al*., 1988; Friedman & van den Eeden, 1993). Another study reported an excess risk among those with a frequent intake (i.e. ≥14 times per month) compared with none or very limited use (Heuch *et al*., 1983). [Data on smoking history were only available for a sub-sample of the cohort (~5000 men) and this relative risk estimate was therefore based on small numbers. Further, the excess risk appeared to be weaker among cases without histological confirmation, which suggests that some selection bias may have occurred.] A cohort study conducted among the Lutheran Brotherhood in the USA also reported a significant threefold excess risk for death from pancreatic cancer among men who drank 10 or more times per month compared with never drinkers after adjustment for age and smoking, based on 57 deaths (Zheng *et al*., 1993).

The majority of the studies, most of which were conducted in the USA and Japan among populations with low to moderate alcoholic beverage intake, have not found a significant association between alcoholic beverage intake and pancreatic cancer. One cohort study in Japan reported a significant excess risk among former drinkers compared with never drinkers (Inoue *et al*., 2003), which was seen in both men and women. [Former drinkers may have ceased drinking because they are ill, causing a spuriously high relative risk in this category.]

All of these cohort studies adjusted for cigarette smoking, and some incorporated adjustments for other potential confounders such as diet, diabetes and family history.

Table 2.48 Cohort/nested case–control studies of pancreatic cancer and alcoholic beverage consumption in the general population

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Klatsky *et al.* (1981); Hiatt *et al.* (1988); Friedman & van den Eeden (1993), USA, Kaiser-Permanente Medical Care Program	Klatsky *et al.* (1981): Nested case–control study of 8060 men and women in health plan; recruited 1964–68; high-intake group (2084) matched to 3 controls with varying intake (age, date, race, sex, smoking, location); follow-up till 1976; 16 deaths identified from death certificates	Self-administered questionnaire	*Usual drinks/day* 0 ≤2 3–5 ≥6	16 deaths 2 5 3 6	 Not stated ≥6 versus ≤2, *p*=<0.01	Matching factors	

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
(contd)	Hiatt *et al.* (1988)/ Analytical cohort of 122 984 men and women receiving health check-ups; baseline at 1978; follow-up until 1984; 48 cases identified through hospital discharge data and cancer registry. histologically confirmed, 76%		*Drinks/day* None Past <1 >1	48	 1.0 2.6 (0.8–8.6) 1.3 (0.5–3.1) 0.9 (0.3–2.7)	Age, sex, race, blood glucose level, smoking, coffee	

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
(contd)	Friedman & van den Eeden (1993): Nested case–control study from original recruitment date of 1964; aged 15–94 years; follow-up until 1988; 450 cancers identified through hospital discharge data and cancer registry verified through medical records; 2687 controls matched on age, sex, site, date of recruitment		*Use in last year (drinks/day)* None <3 ≥3	450	 1.0 1.12 (0.85–1.48) 1.35 (0.90–2.03)	Age, race, smoking	35% of cases diagnosed within 1 year of entry; no association with getting drunk on workdays, drinking in the morning, heavy alcohol user (yes versus no) or spouse having a drinking problem

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Heuch *et al.* (1983), Norway, 1960–67	Analytical cohort of 16 713 men and women, aged 45–74 years (4995 had information on alcohol intake and smoking); based on 3 groups: men from 1960 census (48%); brothers of migrants (20%); relatives of gastrointestinal cases from a previous case–control study (32%); follow-up until 1973; 63 cases identified via cancer registry; histologically confirmed, 29%	Self-administered questionnaire (1964 to groups 1 and 2, and 1967 to group 3); frequent use equivalent to beer or spirits 14 times/ month	*Alcohol use* None or very limited use Frequent use *p* for trend	18 *p* for trend	 1.0 10.82 0.001	Age, sex, region, urban/rural, smoking	Results presented for 18 histologically confirmed cases (men) with smoking data; weaker (but still significant) association in cases with no histological confirmation

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Kono *et al.* (1986), Japan, Japanese Physicians	Analytical cohort of 5135 men recruited in 1965; follow-up until 1983; 14 deaths identified from death certificates; response rate, 51%	Self-administered questionnaire	*Intake in last 20 years* None Former Occasional <2 go (sake)/day ≥2 go (sake)/day	 3 2 5 1 3	 1.0 1.9 (0.3–11.7) 1.4 (0.3–5.9) 0.4 (0.0–4.0) 1.5 (0.3–7.9)	Age, smoking	No association for daily versus none; low response rate
Zheng *et al.* (1993), USA, Lutheran Brotherhood Insurance Society	Analytical cohort of 17 633 men, aged ≥35 years, recruited 1966; follow-up until 1986; 57 deaths identified from death certificates	Self-administered questionnaire	*Total intake (times/month)* Never <3 3–9 ≥10	 7 13 13 18	 1.0 2.0 (0.5–5.2) 3.6 (1.4–9.3) 3.1 (1.2–8.0)	Age, smoking	Low alcohol intake (26% ≤2.5 drinks/week); significant increased risk for beer and spirits
Shibata *et al.* (1994), USA, Laguna Hills Residents, Los Angeles	Analytical cohort of 13 976 men and women recruited 1982; 80% aged 65–80 years; follow-up until 1990; 65 cases identified from pathology reports from participating hospitals	Self-administered questionnaire	*Drinks/day* <1 1–2 >2	 24 27 12	 1.0 1.01 (0.58–1.77) 0.91 (0.44–1.88)	Age, sex, smoking	

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Harnack *et al.* (1997), USA, Iowa Women's Health Study	Analytical cohort of 33 976 women, aged 55–69 years, recruited 1986; follow-up for incidence and mortality through registry until 1994; 66 cases (verification not stated)	Self-administered questionnaire	*Drinks/week* None 0.5–2 >2 *p* for trend	 29 18 19	 1.0 1.46 (0.81–2.63) 1.65 (0.90–3.03) 0.11	Age, smoking	Increased risk for spirits (>1 unit/ week, 2.1) and also seen in never smokers, but small numbers
Coughlin *et al.* (2000), USA, Columbia, Puerto Rico, American Cancer Society, Cancer Prevention Study-II	Analytical cohort of 1.2 million men and women, recruited 1982, aged ≥30 years; mortality follow-up until 1996; 3751 deaths (1967 men, 1784 women) identified from death certificates	Self-administered questionnaire	*Drinks/day* None Some 1 >1 None Some 1 >1	 329 198 226 564 390 194 151 244	*Men* 1.0 0.9 (0.8–1.1) 0.9 (0.8–1.1) 0.9 (0.8–1.1) *Women* 1.0 0.9 (0.8-1.1) 0.8 (0.7-1.0) 0.9 (0.8-1.1)	Age, race, education, family history, gallstones, diabetes, body-mass index, smoking, red meat, citrus fruit and juices, vegetable intake	Cases not verified; no interaction with smoking

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Michaud *et al.* (2001), USA, HPFS and NHS	Analytical cohort of 136 593 men and women, using data from 1980 and 1986; follow-up until 1996 (women, aged >30 years); and 1998 (men, aged 40–75 years); self-reported cases verified by pathology and medical records	Self-administered questionnaire	*Intake (g/day)* 0 0.1–1.4 1.5–4.9 5–29.9 ≥30 *p* for trend	288	 1.0 0.78 (0.47–1.30) 1.15 (0.78–1.69) 1.0 (0.69–1.44) 1.0 (0.57–1.76) 0.94	Age, smoking, body-mass index, diabetes, cholecystecomy, energy intake, time period	No association for type of beverage or with past heavy drinking; no association by body mass index, age or smoking
Stolzenberg-Solomon *et al.* (2001), Finland, ATBC Cancer Prevention Study	Analytical cohort of 27 101 male smokers, aged 50–69 years, recruited 1985; follow-up until 1997; 157 cases identified through cancer registry; histologically confirmed, 79%	Self-administered questionnaire	*Intake (g/day)* None <5.4 5.4–13.4 13.5–27.7 ≥27.8 *p* for trend	 14 39 38 32 34	 1.0 1.39 (0.75–2.56) 1.39 (0.75–2.56) 1.24 (0.66–2.32) 1.40 (0.75–2.62) 0.71	Age, intervention arm, adjustment for other factors made little difference	

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Isaksson *et al.* (2002), Sweden, Swedish Twin Regsitry	Analytical cohort of 21 884 men and women recruited in 1961, aged 36–75 years; followed-up between 1969 and 1997; 176 cases identified through cancer registry; histologically confirmed, 90%	Self-administered questionnaire; alcohol consumption derived from 1967 questionnaire	*Alcohol intake (g/month)* None 1–209 ≥210	 52 86 11	 1.0 0.89 (0.61–1.30) 0.78 (0.39–1.55)	Age, sex, smoking	
Lin *et al.* (2002), Japan, Japan Collaborative Cohort	99 527 men and women, recruited 1988–90, undergoing health check, aged 40–79 years; follow-up until 1997 for mortality; 191 deaths (94 men, 97 women) with information on alcoholic beverages	Self-administered questionnaire	*Intake (g/day)* None Former 0–29 30–69 ≥60 *p* for trend	*Men* 26 6 35 20 7	*Men* 1.0 0.74 (0.30–1.82) 1.16 (0.66–2.04) 1.07 (0.56–2.06) 0.98 (0.39–2.46) 0.76	Age, smoking	No association in women; no association by duration or lifetime intake

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Inoue *et al.* (2003), Japan, HERPACC	Nested case–control study of hospital patients, aged 32–85 years, recruited 1988–99: follow-up until 2000; 200 cases (122 men, 78 women), 2000 controls (non-malignant), matched by age, sex	Self-administered questionnaire	*Alcohol drinking* Never Former Current	 111 37 52	 1.0 3.70 (2.28–6.00) 0.50 (0.34–0.73)	Age, sex, family history, diabetes, physical activity, bowel habits, raw vegetable intake	Increased risk in men and women, separately; the increased risk in former drinkers may be due to ill-health.

ATBC, α-Tocopherol β-Carotene; CI, confidence interval; HERPACC, Hospital-based Epidemiologic Research Program at Aichi Cancer Center; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study

However, where crude and multivariate data were presented together, adjustment for these factors appeared to make little difference to the estimates for alcoholic beverage intake.

There are very limited data on the effect of duration of alcoholic beverage drinking or cessation of drinking on the risk for pancreatic cancer; those studies that have reported risks for former drinkers compared with never drinkers have shown highly inconsistent results.

2.9.2 *Case–control studies (Table 2.49)*

Twenty-nine case–control studies have published quantitative data on the association of alcoholic beverage intake and the risk for pancreatic cancer. Most studies found no association (see Table 2.49). Several studies suggested that heavy alcoholic beverage consumption (≥15 drinks/week) may be associated with an increased risk for pancreatic cancer (Falk *et al*., 1988; Cuzick & Babiker, 1989; Ferraroni *et al*., 1989; Olsen *et al*., 1989; Silverman, 2001). Other studies have reported significant reductions in risk with increasing alcoholic beverage intake (Gold *et al*., 1985; Baghurst *et al*., 1991; Talamini *et al*., 1999).

There is no consistent evidence that intake of any specific type of beverage is associated with risk for pancreatic cancer.

The difference in findings may be partly due to differences in study design. In many of these case–control studies, a large proportion of cases were deceased, which resulted in interviews being conducted among the next of kin. Although some studies suggest that spouse proxies give reasonable estimates of alcoholic beverage intake, many interviews were conducted with a child, friend or other relative, which may result in substantial exposure misclassification and/or recall bias. Further, studies that only included cases that were histologically verified may not be representative of all cases and may lead to bias if high alcoholic beverage intake is associated with reduced access to medical care. In addition, selection bias due to low response rates, possible confounding by tobacco smoking, failure to exclude controls who had tobacco- and alcohol-related diseases and chance findings as a result of small sample size may also contribute to these discrepant results.

2.10 Cancer of the lung

A possible link between alcoholic beverage consumption and the risk for lung cancer has long been speculated; however, epidemiological evidence has been considered to be inconclusive. The data available to the previous IARC Working Group (IARC, 1988) did not allow the conclusion that the association between consumption of alcoholic beverages and lung cancer was causal.

Lung cancer is the most common and fatal cancer in the world. The major cause of lung cancer is tobacco smoking, to which 80–90% of cases are attributable. A high

Table 2.49 Case–control studies of pancreatic cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Williams & Horm (1977), USA, Third National Cancer Survey, 1969–71	7518 (all sites, men and women), aged ≥35 years; histological confirmation not stated; 57% randomly selected	Randomly selected patients with cancer of other non-related sites	Interviewer-administered questionnaire	*Glasses/ year* None 51 ≥52 None 51 ≥52	 *Men* 1.0 0.72 1.34 *Women* 1.0 0.58 0.59	Age, race, smoking	
MacMahon *et al.* (1981), Boston, Rhode Island, USA, 1974–79	369 (218 men, 151 women), aged ≤79 years; 100% histologically confirmed; response rate, ~68%	644 hospital-based, matched by physician, excluding pancreas/ liver disease and tobacco-/alcohol-related diseases; 42% other cancers; response rate, ~61%	Interviewer-administered questionnaire	*Alcohol drinking* Non-drinker Ever Regular	 1.0 0.9 (0.6-1.3) 0.8 (0.5-1.3)	Physician, time of hospitalization, age	No proxies used; no association in men or women separately, or by type of beverage
Manousos *et al.* (1981), Greece, 1976–77	50 (32 men, 18 women), all ages; 100% histologically confirmed; response rate not stated	206 hospital-based (non-malignant, excluding liver/ pancreas disease); response rate not stated	Not stated; standard record form obtained from patient	*Alcohol drinking (g/ day)* ≤10 >10	 1.0 0.7 (0.3–1.3)	Age, sex	

Table 2.49 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Durbec *et al.* (1983), France, 1979–80	69 (37 men, 32 women), aged 30–90 years; 100% histologically confirmed; response rate not stated	199 population-based (door-to-door); matched by age, sex, type of residence (no digestive diseases); response rate not stated	Interviewer-administered questionnaire	*Alcohol intake (g/day)* Per 10 g/day Duration (per year)	 1.24 (1.05–1.44) 0.72 (0.53–0.98)	Matching factors plus carbohydrate, fats; adjustment for smoking made no difference	
Wynder *et al.* (1983), USA, American Health Foundation, 1977–81	275 (153 men, 122 women), aged 20–80 years; 100% histologically confirmed; response rate, 45%	7994 hospital-based (non-tobacco-related diseases); matched by age, sex, race, ward; response rate, 35%	Interviewer-administered questionnaire	*Alcohol use (oz/day)* 0 <1 1–3 3–5 ≥5	*Men only* 1.0 1.2 (0.70–1.96) 1.1 (0.64–1.96) 1.0 (0.51–2.01) 1.6 (0.92–2.63)	Age, smoking	No association for women
Gold *et al.* (1985), Baltimore, USA, 1978–80	201 men and women; age range not stated; 62% histologically confirmed; response rate, 70%	201 hospital- and population-based; hospital (non-malignant) matched on age, sex, race, hospital, date of admission; population (random-digit dialling) matched on age, sex, telephone exchange area; response rate not stated	Interviewer-administered questionnaire	*Wine intake 1 year ago (glasses/week)* Never Ever	 1.0 0.52 (0.32–0.84) *p*-value=0.007 (population controls)	Matching factors plus religion, occupation, smoking	Relative risk, 0.86 (NS) for hospital controls; 75% of case interviews with proxies

Table 2.49 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Mack *et al.* (1986) Los Angeles, USA, 1976	490, aged <65 years; ~80% histologically confirmed; response rate, 67%	Population-based (neighbourhood algorithm); matched by age, sex, race, area; response rate not stated	Interviewer-administered questionnaire	*Alcohol (g/day)* Reference <40 40–79 ≥80	 1.0 0.7 (0.5–1.1) 0.8 (0.5–1.3) 1.2 (0.7–2.2)	Matching factors	~75% cases had proxy information; no association by smoking status
Norell *et al.* (1986), Sweden, 1982–84	99 (55 men, 44 women), aged 40–79 years; final diagnosis based on resection or autopsy (61%), radiology and biopsy (33%), or clinical and radiological evidence alone (6%); response rate, ~80%	138 population-based (birth records); matched by age, sex; 163 hospital (hernia); matched by age, sex; response rate, 85 and 90%	Self-administered questionnaire, followed by telephone interview if necessary	*Past intake (g/day)* 0–1 2–9 ≥10 0–1 2–9 ≥10	*Population controls* 1.0 0.7 (0.5–1.2) 0.6 (0.3–1.1) *Hospital controls* 1.0 0.5 (0.3–0.9) 0.5 (0.3–1.0)	Matching factors	16% of cases had proxy information
Voirol *et al.* (1987), Switzerland, 1976–80	88 (43 men, 45 women) confirmed by clinicians; age range not stated; 67% histologically confirmed	336 population-based; matched by age; response rate, 64%	Interviewer-administered questionnaire	*Beer (per dL intake)* None 1.3 *Wine (per dL intake)* None 1.8	 1.0 2.85 (significant) 1.0 0.86 (NS)		

Table 2.49 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Falk *et al.* (1988), Louisiana, USA, 1979–83	363; 82% histologically confirmed; response rate, 86%	1234 hospital-based (non-malignant); matched on age, sex, race; response rate, 87%	Interviewer-administered questionnaire	*Highest intake (drinks/ week)* None <6 6–11 12–26 ≥27	*Men only* 1.0 2.04 1.38 1.07 1.50	Age, respondent type, smoking, residence, income, diabetes, fruit intake	53% cases and 13% controls with proxy information; no association in women; no association by type of beverage
Cuzick & Babiker (1989), United Kingdom, 1983–86	216, all ages; 30% histologically confirmed; response rate not stated	212 hospital-based (non-malignant); 67 general practitioners; response rate not stated	Interviewer-administered questionnaire	*Intake 1 year ago (units/week)* None <4 4–14 ≥15 Former	 1.0 0.95 0.97 1.73 *p* for trend <0.1 2.71 (significant)	Age, sex, social class, urbanization, smoking	Increased risk for intake 10 years ago (≥15 units/ week: relative risk, 2.3); strongest association with beer
Ferraroni *et al.* (1989), Italy, 1983–88	214, aged <75 years; 100% histologically confirmed; response rate, >98%	1944 hospital-based (non-malignant, non-digestive tract disorders, not related to tobacco, alcohol or coffee intake, and not requiring long-term modification to diet); response rate, >98%	Interviewer-administered questionnaire	*Alcohol intake (drinks/day)* <3 3–6 >6 *p* for trend	 1.0 1.14 1.46 NS	Age, sex, social class, education, marital status, smoking, coffee intake	Most (>90%) drank wine only

Table 2.49 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Olsen *et al.* (1989), Minneapolis, USA, 1980–83	212 men (death as stated on death certificate), aged 40–84 years; 66% histologically confirmed; response rate, 85%	220 population-based (random-digit dialling); matched by age, race; response rate, >70%	Interviewer-administered questionnaire	*Intake 2 years before death (drinks/day)* 0 1 2–3 ≥4	 1.0 0.77 (0.47–1.30) 1.42 (0.67–3.03) 2.69 (1.00–7.27)	Age, education, diabetes, smoking, meat, vegetable intake	100% proxy information from cases and controls; increased risk for high intake of beer (≥4 drinks/ day)

Table 2.49 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Bouchardy *et al.* (1990), pooled analysis of studies in France, Italy, Switzerland, 1976-85	494 Italy: 245, aged <75 years; 100% histologically confirmed; recruited 1983–88; response rate, >97% France: 171; age range not stated (mean age, 63 years); 64% histologically confirmed; recruited 1982–85; response rate, >80% Switzerland: 91; age range not stated;67% histologically confirmed; recruited 1976–81; response rate, 16%	1704 Italy: 1082 hospital-based (non-malignant, non-digestive tract disorders, unrelated to tobacco or alcohol); response rate, >97% France: 268 hospital-based (first group cancer unrelated to tobacco, second group non-malignant unrelated to tobacco); matched by age, sex, interviewer; response rate not stated Switzerland: 383 population-based (through population register); matched by age, sex; response rate, 64%	Interviewer-administered questionnaire	*Alcohol intake (glasses/day)* None <2 <3 <4 4–5 6–7 ≥8 *p* for trend	 1.0 0.9 (0.6–1.2) 0.9 (0.6–1.2) 1.1 (0.7–1.7) 0.7 (0.5–1.1) 1.0 (0.6–1.6) 0.8 (0.5–1.3) NS	Age, sex, social class, smoking	No association for wine, beer or spritis; significant negative association with increasing alcohol intake in the French study, due to wine consumption; significant positive association with beer intake in the Swiss study; no difference by smoking status

Table 2.49 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Baghurst *et al.* (1991), Australia, 1984–87	104 (52 men, 52 women), all ages; verified through medical records; response rate, 62%	253 population-based (electoral roll); matched by age, sex; response rate, ~50%	Self-administered questionnaire checked by interviewer	*Intake 1 year before interview (g/day)* None 0–4.4 4.5–17.8 ≥17.9	 1.0 0.64 (0.34–1.23) 0.41 (0.20–0.82) 0.41 (0.19–0.87) *p* for trend=0.004	Age, sex, smoking	Proxy interview required for ~10% cases
Farrow & Davis (1990), Washington, USA, 1982–86	148 men, aged 20–74 years; 46% histologically confirmed; response rate, 68%	188 population-based (random-digit dialling); matched by age; response rate, 68%	Telephone-interview questionnaire	*Usual intake 3 years before diagnosis (drinks/week)* <4 4–14 ≥15	 1.0 0.7 (0.4–1.2) 0.8 (0.5–1.4)	Age, smoking, race, education	No association for type of beverage
Ghadirian *et al.* (1991), Canada, 1984–88	179 (97 men, 82 women), aged 35–79 years; all clinical or histological diagnoses; response rate, 60%	239 population-based (random digit-dialling and telephone directory listings); matched by age, sex, area; response rate not stated	Interviewer-administered questionnaire	*Total intake (g)* Never 2840 11 171 34 554 709 560	 1.0 0.59 (0.26–1.34) 1.0 (0.44–2.29) 0.71 (0.31–1.61) 0.65 (0.30–1.44)	Age, sex, education, response status	75% of case interviews with proxies (17% controls); no association for type of beverage

Table 2.49 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Jain *et al.* (1991), Canada, 1983–86	249 men and women admitted to hospital, aged 35–79 years; 69% histologically confirmed; response rate, 46%	505 population-based (residence lists); matched by age, sex, borough, proxy; response rate, 39%	Interviewer-administered questionnaire	*Lifetime intake* (g) None 0–32 600 32 600–162 150 ≥162 150 per 250 000 g	 1.0 0.91 (0.55–1.52) 0.78 (0.47–1.31) 0.86 (0.50–1.47) 0.94 (0.79–1.12)	Matching factors plus smoking, energy intake, fibre intake	78% cases had proxy interview, matched with proxy control; no association with type of beverage
Bueno de Mesquita *et al.* (1992), Netherlands, 1984–88	176 men and women, aged 35–79 years; 68% histologically confirmed; response rate, >90%	487 population-based (local registries); matched by age, sex; response rate, >65%	Interviewer-administered questionnaire	*Lifetime intake (g)* Never <22 471 22 472–128 971 ≥128 972	 1.0 0.97 (0.53–1.77) 0.93 (0.49–1.76) 1.25 (0.65–2.43) *p* for trend=0.55	Age, sex, response status, lifetime smoking, energy intake, vegetables	Significant negative association for white wine; 42% of case interviews with proxy (29% controls)
Lyon *et al.* (1992), Utah, USA, 1984–87	149 reviewed by medical records, aged 40–79 years; response rate, 88%	363 population-based (random-digit dialling, HCFA); matched by age, sex, county; response rate, 77%	Interviewer-administered questionnaire (by telephone)	*Alcohol use* Never Ever	 1.0 1.6 (1.08–2.38)	None	100% information from proxies

Table 2.49 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Mizuno *et al.* (1992), Japan, 1989–90	124 (68 men, 56 women); histological confirmation not stated; response rate not stated	124 hospital-based (non-malignant); matched by age, sex, hospital; response rate not stated	Questionnaire (not stated if self- or interviewer-administered)	*Frequency of intake (times/week)* None 1–2 1–2 3–5 Every day	 1.0 1.20 (0.51–2.85) 1.07 (0.35–3.26) 0.74 (0.28–1.95) 1.24 (0.56–2.71)	Matching factors	No association with age when drinking started duration, or quantity of sake or beer; controls included patients with digestive diseases
Kalapothaki *et al.* (1993), Greece, 1991–92	181 undergoing surgery (115 men, 66 women); 100% histologically confirmed; response rate, 90%	181 hospital-based (excluding disease related to diet, non-malignant, no gastrointestinal disease) and 181 visitors (residents of area and visitors to hospital); matched by age, sex, hospital; response rate, 93%	Interviewer-administered questionnaire	*Glasses/day* 0 <1 1–2 3–4 ≥4 per 1 glass/day	*Visitor controls* 1.0 0.94 (0.52–1.72) 1.09 (0.52–2.26) 0.62 (0.20–1.91) 0.81 (0.39–1.68) 0.96 (0.83–1.11)	Matching factors (for continuous variable, past residence, education, diabetes)	No association with hospital controls

Table 2.49 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Zatonski *et al.* (1993), Poland, 1985–88	110 (68 men, 42 women), confirmed by clinical and pathological records; 44% histologically confirmed; response rate, 77%	195 population-based (method not stated); matched on age, sex, residence; response rate, 87%	Interviewer-administered questionnaire	*Lifetime intake* Never Ever	 1.0 1.29 (0.67–2.48)	Age, sex, education, tea, coffee, smoking	71% of cases (0% of controls) used proxy; increased risk for spirits (Q4, 2.5; p=0.07), the most common drink consumed
Gullo *et al.* (1995), Italy, 1987–89	570 (319 men, 251 women), aged 22–79 years; 70% histologically confirmed	570 hospital-based (non-malignant); matched by age, sex, social class, region	Interviewer-administered questionnaire	*Alcohol (g/day)* 0 <50 50–100	 1.0 0.76 (0.56–1.04) 1.06 (0.63–1.77)	Age, sex	No association for men or women; most drank wine
Ji *et al.* (1995), China, 1990–93	451 (264 men, 127 women) identified through registry, aged 30–74 years; 57% histologically/surgically confirmed; response rate, 78%	1552 population-based (resident registry); matched by age, sex; response rate not specified	Interviewer-administered questionnaire	*Alcohol intake (g/week)* None <161 161–332.4 332.5–564 ≥565	*Men* 1.0 0.7 (0.4–1.3) 1.1 (0.7–1.8) 0.9 (0.5–1.4) 0.9 (0.5–1.4)	Age, income (women only: green tea, education)	Next of kin attended interviews for 38% of cases, 10% of controls; no association with duration, lifetime alcohol intake or type of beverage

Table 2.49 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Silverman *et al.* (1995); Silverman (2001), USA, 1986–-89	486 surviving men and women (307 white, 179 black), aged 30–79 years; confirmed through medical records; response rate, 46% (white) and 44% (black)	2109 (1164 white, 945 black) population-based: 1. aged 30–64 years (random-digit dialing); matched by age, sex, ethnicity; response rate, 78% for both white and black; 2. aged 65–79 years (HCFA), stratified random sample; response rate, 73% (white) and 78% (black)	Interviewer-administered questionnaire	*Alcohol consumption (drinks/ week)* Never 1–<8 8–<21 21–<57 ≥57 Never 1–<8 8–<21 21–<57 ≥57 *p* for trend Never 1–7 8–20 21–56 Never 1–7 8–20 21–56 *p* for trend	 *White men* 1.0 0.8 (0.5–1.44) 0.8 (0.4–1.3) 1.0 (0.6–1.9) 1.4 (0.6–3.2) *Black men* 1.0 0.6 (0.2–1.6) 1.2 (0.5–2.6) 0.6 (0.2–1.6) 2.2 (0.9–5.6) 0.04 *White women* 1.0 0.7 (0.4–1.1) 0.4 (0.2–0.9) 0.9 (0.3–3.0) *Black women* 1.0 1.1 (0.5–2.2) 1.8 (0.9–4.0) 2.5 (1.02–5.9) 0.03	Age, area, cigarette smoking, gallbladder disease, diabetes	Never/ever drinking not significant except for white women (0.6; 95% CI, 0.4–0.97); no significant differences by beverage type; similar association found in nonsmokers

Table 2.49 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Partanen *et al.* (1997), Finland, 1984–87	662 deceased men and women, aged 40–74 years; identified through cancer registry; response rate, 47%	1770 hospital-based (malignancies of the stomach, colon or rectum)	Self-administered questionnaire	*Distilled beverage intake in 1960s* None/ occasional Moderate Heavy *Wine/beer* None/ occasional Moderate Heavy	 1.00 1.17 (0.92–1.48) 1.22 (0.82–1.80) 1.00 1.16 (0.91–1.48) 1.61 (1.07–2.42)	Age, sex, tobacco smoking	
Tavani *et al.* (1997), Italy, 1983–92	361 men and women, aged 17–79 years; 100% histologically confirmed; response rate, ~97%	997 hospital-based (non-malignant, non-smoking-/alcohol-related); response rate, ~97%	Interviewer-administered questionnaire	*Usual intake (drinks/day)* None <4 >4–7 >7–8 >8 *p* for trend	 1.0 0.9 (0.7–1.3) 1.1 (0.7–1.7) 1.4 (0.7–2.7) 1.1 (0.5–2.2) 0.57	Age, sex, education, smoking, diabetes, pancreatitis, cholelithiasis	No proxy information; no association for type of beverage (90% of population drank wine) or duration

Table 2.49 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Soler *et al.* (1998), Italy, 1983–92	362 men and women, aged <75 years; 100% histologically confirmed; response rate, ~97%	1552 hospital-based (non-malignant); response rate, ~97%	Interviewer-administered questionnaire; total alcohol intake (frequency, duration, quantity provided)	*Total alcohol intake* Low Intermediate High	 1.0 0.83 (0.61–1.13) 1.20 (0.89–1.67)	Age, sex, area, education, smoking	No proxy interviews
Talamini *et al.* (1999), Italy, 1990–95	69 men (no pancreatitis); 100% histologically confirmed; response rate not specified	700 population-based (electoral roll) who had medical check-up, recruited 1985–87; response rate not specified	Interviewer-administered questionnaire	*Alcohol (g/day)* 0–40 41–80 > 80	 1.0 0.5 (0.2–1.0) 0.4 (0.2–1.0)	Smoking	

Table 2.49 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Villeneuve *et al.* (2000), multisite, Canada, 1994–97	583 (322 men, 261 women), aged 30–76 years; 100% histologically confirmed; response rate, 55%	4813 population-based (health insurance records, Ministry of Finance records, random-digit dialling); matched by age, sex; response rate, 65–71%	Self-mailed questionnaire with telephone follow-up	*Alcohol (drinks/ week)* 0 <3 3–<7 7–<14 ≥14 0 <3 3–<7 ≥7	 *Men* 1.0 0.83 (0.56–1.25) 0.86 (0.57–1.28) 1.20 (0.79–1.80) 1.36 (0.93–2.00) *Women* 1.0 0.90 (0.65–1.25) 0.59 (0.34–1.02) 0.95 (0.57–1.56)	Age, area, parity, coffe, smoking, energy intake, fat intake	Proxies used for 24% of cases
Lu *et al.* (2006), China, 2002–04	119 identified through hospital records and verified by pathology, surgical and clinical records; age range not stated; histological confirmation not stated; response rate not stated	238 population-based (procedure not stated); matched by age, sex, region, marital status; response rate not stated	Interviewer-administered questionnaire	*Alcohol duration (drink–years)* None ≤20 >20 *p* for trend	 1.0 1.003 (CI not stated) 3.68 (1.60–8.44) Significant [not reported]	Age, sex, smoking	Limited methodological details provided

CI, confidence interval; HCFA, Health Care Financial Administration; NS, not significant

correlation has been identified between use of tobacco and consumption of alcohol in many populations. As such, careful adjustment for smoking is one of the most important requirements for a valid interpretation of the effects of alcohol.

Factors important for causal inference, such as strength of the association, dose–response relationship, histological types, types of alcoholic beverage, and potential confounding by and interactions with tobacco smoking are considered here. The risks for lung cancer in relation to total alcoholic beverage consumption are summarized in Tables 2.50–2.52; the effects of alcoholic beverage consumption and the risk for lung cancer by histological types are presented in Tables 2.53 and 2.54; the effects of types of alcoholic beverage are presented in Tables 2.55–2.60; the combined or joint effects or effect modification of alcoholic beverage consumption and tobacco smoking are shown in Tables 2.61 and 2.62; the relationships between alcoholic beverage consumption and the risk for lung cancer among nonsmokers are shown in Tables 2.63 and 2.64.

2.10.1 *Total alcoholic beverage consumption*

(a) Cohort studies of special populations (Table 2.50)

All six studies based on cohorts of alcoholics—populations that have excessive alcoholic beverage intake—reported elevated mortality from lung cancer (Schmidt & Popham, 1981; Adami *et al*., 1992a; Tønnesen *et al*., 1994; Sigvardsson *et al*., 1996; Sørensen *et al*., 1998; Boffetta *et al*., 2001). However, due to the lack of control for tobacco smoking in all studies, the possibility that the observed association might be largely explained by the confounding effect of tobacco smoking can not be ruled out.

(b) Cohort studies of the general population (Table 2.51)

Among 20 cohort studies of the general population that provided tobacco smoking-adjusted risk estimates for total alcoholic beverage use, 10 reported an elevated risk for lung cancer associated with alcoholic beverage consumption, although it was seldom significant. Of the studies that examined high levels of alcoholic beverage intake (≥3 or ≥5 drinks/day), some reported elevated risks that became statistically significant at the highest category of alcoholic beverage consumption, all in men (Prescott *et al*., 1999; Lu *et al*., 2000a; Balder *et al*., 2005). Studies that used low drinking levels (e.g. 1–2 drinks/day) as the highest category did not find a significant association between these relatively low exposures and risk for lung cancer (Kono *et al*., 1986; Stemmermann *et al*., 1990; Breslow *et al*., 2000; Freudenheim *et al*., 2005).

Most cohort studies that reported a positive association also demonstrated a significant dose–response relationship. Other studies observed no association between alcoholic beverages and the risk for lung cancer at the highest level of consumption for both genders (Korte *et al*., 2002 [Cancer Prevention Study, II]; Nishino *et al*., 2006; Rohrmann *et al*., 2006) and in women (Prescott *et al*., 1999).

Table 2.50 Cohort studies of total alcoholic beverage consumption and lung cancer in special populations

Reference, location, name of study	Cohort description	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Schmidt & Popham (1981), Ontario, Canada, Cohort of Alcoholics	9889 men admitted for alcoholic treatment in 1951–70 in Ontario, Canada; mortality follow-up, 1951–71; mortality and cause-specific mortality ascertainment, death records and death certificates; 96% follow-up	Alcoholic Local reference US veteran reference	89	**SMR** 1.7 (p<0.01) 2.7 (p<0.01) 4.4 (p<0.01) 2.2 (p<0.01) 0.98	Age Total 1–9 cigs/day 10–20 cigs/day 21–39 cigs/day	347 patients whose vital status could not be determined were assumed to be alive at the study cut-off date.
Adami *et al.* (1992a), Central Sweden, Cohort of alcoholics	9353 (8340 men, 1013 women) subjects with a hospital discharge of alcoholism; follow-up, 1965–84; case ascertainment, Nationwide Registry of Cause of Death	Alcoholic *Men* *Women* Age <50 years Age 50–64 years Age ≥65 years	 76 3	**SIR** 2.1 (1.7–2.6) 2.7 (0.6–8.0) 6.7 (2.2–15.7) 3.5 (2.4–4.9) 1.5 (1.0–2.0)	Age, calendar year	Estimates not adjusted for smoking; updated analysis in Boffetta *et al.* (2001); cancers occurring during the first year of follow-up were excluded
Tønnesen *et al.* (1994), Copenhagen, Denmark, Cohort of Alcoholics	18 307 alcoholics (15 214 men, 3093 women) treated at a public outpatient clinic in Copenhagen in 1954–87; cancer case ascertainment, Danish Cancer Registry, 95%; mortality follow-up through population registry	*Alcoholic* Men Women Total	 456 29 485	**SIR** 2.5 (2.3–2.7) 3.7 (2.5–5.4) 2.6 (2.3–2.8)	Age, sex, calendar period	Estimates not adjusted for smoking; reference, national cancer incidence

Table 2.50 (continued)

Reference, location, name of study	Cohort description	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Sigvardsson *et al.* (1996), Sweden, Temperance Boards Study	Nested case-control study; 15 508 alcoholic women identified from the Temperance Board records; comparison group of 15 508 women individually matched on day of birth, region; follow-up, [1947–77]; case ascertainment, Swedish Cancer Registry	Alcoholic	139 (bronchus, lung) 4 (lung, unspecified)	5.0 (3.3–7.4) 4.0 (0.5–36.0)	Age, region	Estimate not adjusted for smoking
Sørensen *et al.* (1998), Denmark, Cohort of 1-year Survivors of Cirrhosis	11 605 1-year survivors of cirrhosis identified from Danish National Registry of Patients that covered all hospital admissions in Denmark; follow-up, 1977–93; 7165 alcoholic cirrhosis (5079 men, 2086 women); case ascertainment, Danish Cancer Registry (100%)	Alcoholic	135	**SIR** 2.1 (1.8–2.5)	Age, sex, calendar period	Estimate not adjusted for smoking; reference, national incidence rates

Table 2.50 (continued)

Reference, location, name of study	Cohort description	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Boffetta *et al.* (2001), Sweden, Cohort of Alcoholics	173 665 (138 195 men, 35 470 women) patients with a hospital discharge of alcoholism, aged ≥20 years; mortality follow-up, 1965–95; case ascertainment 98% (National Cancer Registry)	*Alcoholic* Men Women Total	 1613 267 1880	**SIR** 2.2 (2.1–2.4) 4.2 (3.7–4.7) 2.4 (2.3–2.5)	Age, gender, calendar year	Estimates not adjusted for smoking; SIRs by histological type reported; reference, national incidence rates

CI, confidence interval; SIR, standardized incidence ratio; SMR standardized mortality ratio

Table 2.51 Cohort studies of total alcoholic beverage consumption and lung cancer in the general population

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Klatsky *et al.* (1981), California, USA, Kaiser-Permanente Study	8060 Kaiser-Permanente members who completed the self-administrated questionnaire; four groups of 2015 by level of alcoholic beverage drinking; follow-up, 1964–68 to 1976; cause-specific mortality ascertainment, California death index (82–92% death catchments)	Self-administered questionnaire	*Drinks/day* 0 ≤3 3–5 ≥6 ≥6 versus ≤2	 15 7 16 24	**SMR** [1.0] [0.6] [1.1] [1.7] $p<0.01$	Matched on sex, race, presence or absence of established cigarette smoking habit, examination date, age	Matching on smoking based on intensity; subjects were not removed if smoking habit could not be matched.

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Kvåle *et al.* (1983), Norway, Three cohorts	16 713 subjects from three different cohorts who responded to a mailed questionnaire: 1. 7966 men from general population sample; 2. 3409 men from sibling roster of migrants to the USA; and 3. family members of patients in a case–control study (2410 men, 2928 women); follow-up, 1967–69 to 1978; cancer case ascertainment, Cancer Registry of Norway; 67% histologically confirmed as primary tumour: response rate, ~80%	Mailed questionnaire	*Men* Low Medium High	 24 33 10	 1.0 Not provided 1.3 (p=0.37)	Age, cigarette smoking (never, former and current smokers of 1–9, 10–19 and ≥20 cigs/day), region, urban/ rural place of residence, socioeconomic group	Analysis for 10 602 men with information on smoking; interaction between alcoholic beverage and vitamin A intake statistically significant (p<0.05); definitions for low, medium and high alcohol intake not provided

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Pollack *et al.* (1984), Hawaii, Japan-Hawaii Cancer Study	8006 Japanese men born between 1900 and 1919 (also subjects for the Honolulu Heart Study); follow-up, 1965–68 to 1980; 100% case catchments; cancer case ascertainment, hospital records, death certificates and the Hawaii Tumor Registry; 100% histologically confirmed	Baseline interview questionnaire	**Type of beverage** *Beer* *Wine* *Liquor*	Not provided	 See Table 2.55 See Table 2.57 See Table 2.59	Age, cigarette-smoking status (never, former and current smokers), alcohol content of the other two types of beverage (if significant)	Association between total alcoholic beverage consumption and risk for lung cancer not available; no significant interaction between cigarette smoking and alcoholic beverage consumption found; updated analysis in Stemmermann *et al.* (1990);

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Kono *et al.* (1986), western Japan, Cohort of Male Japanese Physicians	5135 male physicians in western Japan; follow-up, 1965–83; vital status, 99%; cancer death ascertainment, death certificate; response rate, 51%	Baseline mailed questionnaire	Non-drinker Former drinker Occasional drinker *Daily drinker* <27 mL alcohol/ day ≥ 27 mL alcohol/ day per 27 mL/day	24 5 12 17 16 	1.0 0.6 (0.2–1.5) 0.4 (0.2–0.8) 0.8 (0.4–1.4) 0.9 (0.5–1.7) [0.9] [0.7–1.1]	Age, smoking (non-, former and current smoker consuming <10, 10–19 or >20 cigs/day)	

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Stemmermann *et al.* (1990), Hawaii, Japan-Hawaii Cancer Study	7572 Japanese men born between 1900 and 1919 (also subjects for the Honolulu Heart Study); follow-up, 1965–68 to 1989; 100% case catchments; cancer case ascertainment, hospital records, death certificates, and the Hawaii Tumor Registry; cancer diagnoses not histologically confirmed excluded	Baseline interview questionnaire	*Alcohol (oz/ month)* 0 <5 5–14 15–39 ≥40	209	 1.0 0.8 (0.5–1.2) 0.9 (0.6–1.5) 1.4 (1.0–2.1) 1.1 (0.7–1.6) *p* for trend=0.09	Age, current smoking status (never, former, current smokers), age started smoking (current smokers), number of cigarettes smoked per day (current smokers), maximum number of cigarette smoked per day (former smokers), years of smoking with maximum number per day (former smokers)	Risk for lung cancer found not to be influenced by the type of alcoholic beverage consumed 1 oz = 0.0296 L

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Chow *et al.* (1992), USA, Lutheran Brotherhood Insurance Society	17 818 white men, aged ≥35 years, life insurance policy holders of the Lutheran Brotherhood Insurance Society; follow-up, 1966–86; vital status, 77%; case ascertainment, death certificate; response rate, 69%	Mailed questionnaire at baseline	**Times/month** *Beer* *Liquor*		 See Table 2.55 See Table 2.59	Age, industry/ occupation, smoking status (never tobacco, other tobacco only, occasional/ past daily cigarette use of 1–19, 20–29, ≥30, current daily cigarette use of 1–19, 20–29, ≥30)	Relative risk for total alcoholic beverage consumption and risk for lung cancer not available
Potter *et al.* (1992), Iowa, USA, Iowa Women's Health Study	41 837 women, aged 55–69 years, drawn from the 1985 driver's licence list and responded to a mail survey in 1986; follow-up, 1986–88; cancer case ascertainment, Health Registry of Iowa, 100%; nested case–control study; controls randomly selected from the non-patient population; response rate, 43%	Mailed questionnaire	**Glasses/day** *Beer* *Liquor*		 See Table 2.55 See Table 2.59	Smoking (pack–years)	Nested case–control study; odds ratio for total alcoholic beverage consumption not available

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Doll *et al.* (1994), United Kingdom, British Male Doctors Study	12 321 male physicians born between 1900 and 1930 and returned the 1978 questionnaire; follow-up, 1978–91; cause-specific mortality ascertainment, death certificates	Mailed questionnaire	*Units/week* None 1–7 8–14 15–21 22–28 29–42 ≥ 43 *χ^2 test value of alcohol effect* None versus 1–14 Trend*	163	**Mortality ratio** [1.0] [1.6] [1.4] [0.9] [0.9] [1.3] [2.1] 0.9 (p>0.05) 0 (p>0.05)	Mortality standardized for age, smoking (never smokers, current smokers of 1–14, 15–24, 25 or more cigs/day, other current smokers, former smokers), year of death, history of previous disease	Relative risk for alcohol use on lung cancer mortality not given; mortality ratio calculated from the standardized mortality given in paper * Trend of 1–14 versus 15–28 versus ≥29 units/ week
Murata *et al.* (1996), Japan, Chiba Gastric Screening Cohort	17 200 men who participated in Chiba gastric screening in 1984; follow-up, 1984–93; cancer case ascertainment, Chiba Cancer Registry; histological confirmation not given; nested case–control study	Self-administered questionnaire at baseline (prior to screening)	*Cups/day (27 mL ethanol/day)* 0 0.1–1.0 1.1–2.0 ≥ 2.1	 38 28 31 10	 1.0 1.0 [0.6–1.8] 2.4 [1.3–4.4] 1.8 [0.7–4.5]	Age, sex, city/ county of address	Nested case–control study; controls individually matched 2:1 to cases by age, sex, city/county of address; odds ratio for alcoholic beverage drinking by smoking status reported

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Omenn *et al.* (1996), USA, β-Carotene and Retinol Efficacy Trial	Randomized, double-blinded, placebo controlled trial; 14 254 smokers (7982 men, 6272 women) and 4060 men occupationally exposed to asbestos; recruiting period, 1988–1994; end of study, 1995; case ascertainment, participant report and clinical record review; 81% histologically confirmed	Self-reported, collected routinely	**Placebo group** *Non-drinkers* *Drinkers* Below median alcoholic beverage intake 3rd quartile of intake 4th quartile of intake >30 g/day alcohol >50 g/day alcohol	63 16 39 29 20 9	[1.0] [0.6] [0.9] [0.7] [0.8] [0.8]	Crude incidence rate ratio	Adjusted relative risk not provided; median alcohol intake for men, 3.0 g/day; 75th percentile, 18.7 g/day; median alcohol intake for women, 1.2 g/day; 75th percentile, 11.1 g/day

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Omenn *et al.* (1996) (contd)			**Intervention group**				
			Non-drinkers	68	[1.0]		
			Drinkers				
			Below median alcoholic beverage intake	29	[1.0]		
			3rd quartile of intake	35	[0.7]		
			4th quartile of intake	64	[1.3]		
			>30 g/day alcohol	43	[1.4]		
			>50 g/day alcohol	21	[1.4]		
Bandera *et al.* (1997), New York, USA, New York State Cohort	48 000 (27 544 men and 20 456 women) long-term residents of New York State; follow-up, 1980–87; case ascertainment, New York State Cancer Registry	Mailed questionnaire at baseline	**Drinks/month**			Age, education, cigarettes/ day, years of smoking, total energy intake	Tertile range not reported
			Men				
			1st tertile	124	1.0		
			2nd tertile	95	0.8 (0.6–1.0)		
			3nd tertile	176	1.1 (0.9–1.4) *p* for trend=0.001		
			Women				
			1st tertile	34	1.0		
			2nd tertile	43	1.2 (0.7–1.8)		
			3nd tertile	53	1.0 (0.6–1.6) *p* for trend=0.80		

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Yong *et al.* (1997), USA, First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study	10 068 subjects; follow-up, 1971–75 to 1992; follow-up, 96%; cancer case ascertainment, hospital records and death certificate	Baseline interview	Non-drinkers >5 g/day	Not given	1.0 1.2 (0.9–1.6)	Age, smoking status and pack–years smoked (8 categories), race, education, physical activity, body-mass index, total calorie intake	Alcoholic beverage consumption not the main focus of this study
Zhang *et al.* (1997) Zoucheng, Shandong, China	7809 men and 7994 women from probabilistic sample of general population in three counties, aged >20 years; mortality follow-up, 1982–94; cause-specific mortality ascertainment, county disease prevention and control centre	Baseline questionnaire, interviewer-administered	*Drinking/ smoking* No/No Yes/No No/Yes Yes/Yes	 1.0 3.1 4.2 2.5		Crude relative risk	No dose–response found for frequency, amount or duration of drinking; lung-cancer mortality found in crude analyses

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Prescott *et al.* (1999), Copenhagen, Denmark Three longitudinal population studies	Conducted in 1964–94: the Copenhagen City Heart Study, the Centre of Preventive Medicine, and the Copenhagen Male Study; 28 160 (15 107 men, 13 053 women) included; cancer follow-up, 99% (Danish Cancer Registry); response rate, 77%	Self-administered questionnaire	**Drinks/week** *Men* <1 1–6 7–13 14–20 21–41 >41 *Women* <1 1–6 7–13 14–20 21–41 >41	 52 85 106 65 114 58 63 82 30 11 7 1	 1.0 0.9 (0.6–1.2) 1.0 (0.7–1.4) 0.9 (0.6–1.3) 1.2 (0.9–1.7) 1.6 (1.1–2.3) *p* for trend=0.002 1.0 0.9 (0.6–1.3) 1.0 (0.6–1.6) 1.0 (0.5–1.9) 1.0 (0.5–2.2) 0.8 (0.1–5.8) *p* for trend=0.94	Age, study cohort, education, smoking (current smoking: pack–years, duration of smoking)	No interaction between smoking and total consumption or type of alcoholic beverage found

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Woodson *et al.* (1999), southwestern Finland, α-Tocopherol β-Carotene Cancer Prevention Study	27 111 white male smokers, aged 50–69 years in southwestern Finland; cancer incidence follow-up, 1985–94; cancer case ascertainment, Finland Cancer Registry and the Register of Causes of Death; 100% case ascertainment; 93% histologically confirmed; response rate, 93%	Self-administered food-use questionnaire at baseline	*Ethanol (g/day)* Non-drinkers Q1 0.04–5.2 Q2 5.3–13.3 Q3 13.4–27.6 Q4 27.7–278.5	1059 154 233 234 208 230	 1.2 (0.9–1.4) 1.0 1.0 (0.8–1.2) 0.9 (0.8–1.1) 1.0 (0.8–1.2) *p* for trend=0.89	Age, body-mass index, years smoked, cigarettes per day, intervention group	Relative risk for alcoholic beverage drinking, reported also by type of alcoholic beverage and by smoking categories
Breslow *et al.* (2000), USA, National Health Interview Survey	Sub-cohort of 20 004 adults, 18 years or older, who completed the Cancer Epidemiology Supplement (8363 men, 11 641 women); follow-up, 1987–95; case ascertainment, National Death Index and Death certificate; response rate, 86%	Cancer Epidemiology Supplement questionnaire (in-home interview)	*Servings/week* Q1 0 Q2 0.02–0.5 Q3 0.5–4.4 Q4 >4.4	 52 23 32 50	 1.0 0.7 (0.4–1.3) 1.0 (0.6–1.6) 1.3 (0.8–2.0) *p* for trend <0.101	Age, gender, smoking duration (years), packs per day smoked	Deaths arising within the first year of follow-up excluded

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Lu *et al.* (2000a), Yunnan, China, Cohort of Yunnan Tin Corporation Miners	7965 miners followed between 1992 and 1997, aged ≥40 years; 10 years of high-risk professional activity; completed the baseline questionnaire; did not have lung cancer; cases identified by expert panel	Interviewer-administered questionnaire	*Alcohol (g/day)* Non-drinkers <50 50–99 ≥100	 137 29 62 71	 1.0 1.0 (0.7–2.0) 1.4 (1.0–1.9) 1.5 (1.1–2.0)	Age, employment history, smoking	[From abstract and tables]

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Djoussé *et al.* (2002), Massachusetts, USA, Framingham Cohort Study (1948) and Framingham Offspring Study (1971)	In 1948, 5209 subjects aged 28–62 years at first examination; in 1971, 5124 children of the original cohort participated; study included 4265 subjects from the original cohort and 4973 from the offspring cohort; mean follow-up: original cohort, 32.8 years; offspring cohort, 16.2 years; cancer case ascertainment, self-report, hospitalization surveillance and National Death Index; 100% histologically confirmed	Follow-up examination	*Average intake (g/day)* 0 0.1–12 12.1–24 >24	269 44 100 39 86	 1.0 1.2 (0.7–2.1) 1.1 (0.6–2.1) 1.3 (0.7–2.4)	Age, sex, smoking status, pack–years of cigarette smoking, year of birth	Nested case–control study; controls selected using the risk–set sampling method and matched by age, pack–year of cigarette smoking, sex, year of birth, smoking status; for former smoker cases, controls also matched by year since quitting smoking

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Korte *et al.* (2002), USA, Cancer Prevention Study (CPS) I and II	Pooled analysis including unpublished results from the CPS I and II; CPS I, 379 575 men, 489 741 women; CPS II, 226 871 men, 230 552 women		**Ethanol (g/ month)**	Not provided		Smoking	
			CPS I				
			Men				
			Non-drinker		1.0		
			1–499		0.9 (0.8–1.0)		
			500–999		1.0 (0.9–1.1)		
			1000–1999		1.2 (1.1–1.3)		
			≥2000		1.4 (1.2–1.6)		
			Women				
			Non-drinker		1.0		
			1–499		1.0 (0.8–1.2)		
			500–999		1.2 (0.9–1.6)		
			1000–1999		1.8 (1.3–2.3)		
			≥2000		2.3 (1.4–3.9)		
			CPS II				
			Men				
			Non-drinker		1.0		
			1–499		0.9 (0.8–1.0)		
			500–999		1.0 (0.9–1.2)		
			1000–1999		1.0 (0.9–1.1)		
			≥2000		1.2 (1.0–1.4)		
			Women				
			Non-drinker		1.0		
			1–499		0.9 (0.8–1.1)		
			500–999		1.1 (0.9–1.3)		
			1000–1999		1.3 (1.0–1.5)		
			≥2000		1.1 (0.8–1.5)		

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Korte *et al.* (2002) (contd)	Meta-analysis of cohort studies including 8 published studies and unpublished data from CPSI and CPSII		*Ethanol (g/ month)* Non-drinker 1–499 500–999 1000–1999 ≥2000		 1.0 1.0 (0.9–1.0) 1.0 (0.9–1.1) 1.2 (1.0–1.3) 1.4 (1.2–1.6)	Smoking	
Balder *et al.* (2005), Netherlands, Netherlands Cohort Study on Diet and Cancer	58 279 men in 204 municipalities in Netherlands, aged 55–69 years; cancer follow-up, 1986–95; case ascertainment, Netherlands Cancer Registry and Netherlands Pathology Registry; case–cohort design (2335 men randomly sampled from the large cohort)	Mailed questionnaire	*Median intake (g/day)* Q1 0 Q2 2.2 Q3 9.3 Q4 23 Q5 42	 183 241 337 333 311	 1.0 1.1 (0.8–1.5) 1.2 (0.9–1.7) 1.1 (0.8–1.5) 1.6 (1.1–2.2) *p* for trend=0.03	Age, total energy intake (kJ), current cigarette smoker (yes/no), number of cigarettes smoked per day, years of smoking cigarettes, higher vocational or university education, family history of lung cancer, physical activity, body-mass index	

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Freudenheim *et al.* (2005), pooled analysis of 7 prospective studies	α-Tocopherol β-Carotene Cancer Prevention Study (men), Canadian National Breast Screening Study (women), Health Professional Study (men), Iowa Women's Health Study (women), Netherlands Cohort Study (women and men), New York State Cohort (women and men), Nurses' Health Study (women); total, 399 767 participants (137 335 men, 262 432 women)	Diet assessment by questionnaire	**Intake (g/day)** *Men* None >0–<5 5–<15 15–<30 ≥30 *Women* None >0–<5 5–<15 15–<30 ≥30	 254 373 432 324 379 467 344 252 130 182	**Pooled relative risk** 1.0 0.9 (0.7-1.0) 1.0 (0.8-1.2) 0.8 (0.6-1.1) 1.2 (0.9-1.6) *p* for trend=0.03 1.0 0.8 (0.7-0.9) 0.8 (0.7-1.0) 0.9 (0.7-1.1) 1.2 (0.9-1.4) *p* for trend=0.03	Education, body-mass index, energy intake, smoking status (never, past, current), smoking duration for past and current smokers, cigarettes smoked daily for current smokers; for specific alcoholic beverage, other two alcoholic beverage types were also adjusted in the model	Pooled relative risk for histological type reported; relative risk for alcohol drinking by smoking status reported; study-specific relative risk reported

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Nishino *et al.* (2006), Japan, Japan Collaborative Cohort	110 792 inhabitants, aged 40–79 years, of 45 study areas throughout Japan; follow-up, 1988–99; 28 536 men included in the analysis	Self-administered questionnaire at baseline	Never drinkers	91	1.0	Age, smoking (current smoking: 6 categories of number of pack–years; former smoking: 5 categories for number of years since quitting), family history of lung cancer, intake of green vegetables, oranges and fruit other than oranges	Analysis for men only; relative risks by smoking status reported
			Ever drinkers	286	1.0 (0.7–1.3)		
			Current drinkers (ethanol g/day)				
			24.9	113	0.8 (0.6–1.1)		
			25.0–49.9	85	0.9 (0.6–1.3)		
			50.0	38	1.0 (0.6–1.5)		
					p for trend = 0.32		
			Former drinkers	50	1.7 (1.2–2.5)		

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Rohrmann *et al.* (2006), 10 European countries, European Prospective Investigation into Cancer and Nutrition	521 457 from 10 European countries; most study centres recruited from the general population; other sources of recruitment included members of insurance plans, blood donors, mammographic screening, employees of enterprises, civil servants; 478 590 subjects included in the analysis (142 798 men, 335 792 women); baseline, 1992–2000; end of follow-up, 1999–2003; cases ascertainment, cancer registry and active follow-up; 97% histologically confirmed	Dietary instruments developped specifically for each country	**Ethanol (g/day)** *Both genders* Intake at recruitment Non-drinker 0.1–4.9 5–14.9 15–29.9 30–59.9 ≥60 Mean lifelong intake Non-drinker 0.1–4.9 5–14.9 15–29.9 30–59.9 ≥60	 146 310 232 169 184 78 30 228 229 201 117 82	 1.22 (1.0–1.5) 1.0 0.8 (0.6–0.9) 0.8 (0.7–1.0) 1.0 (0.8–1.2) 0.9 (0.7–1.1) *p* for trend=0.31 1.0 (6.7–1.5) 1.0 0.8 (0.7–1.0) 1.0 (0.8–1.2) 0.9 (0.7–1.1) 1.3 (0.9–1.7) *p* for trend=0.12	Results stratified by age, sex, study centre; hazard ratios adjusted for smoking status, smoking duration, height, weight, fruit consumption, red meat consumption, processed meat consumption, education, physical activity at work, total non-ethanol energy intake	Relative risks reported by histological type and by smoking status; interaction *p*-value reported

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Rohrmann *et al.* (2006) (contd)			*Men*				
			Intake at recruitment				
			Non-drinker	61	1.1 (0.8–1.6)		
			0.1–-4.9	121	1.0		
			5–14.9	118	0.7 (0.5–0.9)		
			15–29.9	108	0.8 (0.6–1.0)		
			30–59.9	128	0.9 (0.7–1.1)		
			≥60	70	0.8 (0.6–1.1)		
			Mean lifelong intake				
			Non-drinker	9	1.4 (0.7–2.9)		
			0.1–4.9	57	1.0		
			5–14.9	106	0.8 (0.5–1.1)		
			15–29.9	135	0.9 (0.7–1.3)		
			30–59.9	104	0.8 (0.6–1.2)		
			≥60	80	1.2 (0.8–1.8)		
			Women				
			Intake at recruitment				
			Non-drinker	85	1.3 (1.0–1.7)		
			0.1–4.9	189	1.0		
			5–14.9	114	0.8 (0.6–1.0)		
			15–29.9	61	0.9 (0.7–1.2)		
			30–59.9	56	1.1 (0.8–1.5)		
			≥60	8	0.9 (0.4–1.8)		

Table 2.51 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Rohrmann *et al.* (2006) (contd)			Mean lifelong intake				
			Nondrinker	21	0.9 (0.5–1.4)		
			0.1–4.9	171	1.0		
			5–14.9	123	0.8 (0.7–1.1)		
			15–29.9	66	1.1 (0.8–1.5)		
			30–59.9	13	0.9 (0.5–1.6)		
			≥60	2	1.3 (0.3–5.5)		

CI, confidence interval; oz, ounce (1 oz = 29.6 mL); SIR, standardized incidence ratio; SMR, standardized mortality ratio

A meta-analysis (Korte *et al*., 2002) found a significantly increased risk for lung cancer with an ethanol intake of at least 2000 g per month (≥5 drinks/day): the weighted odds ratio from case–control studies was 1.5 (95% CI, 1.0–2.3) and the weighted relative risk from cohort studies was 1.4 (95% CI, 1.2–1.6). [The weighted odds ratio for case–control studies was based on only one study and the relative risk for cohort studies on only three studies. These results should therefore be interpreted with some caution.]

It should be noted that most studies examined the effects of recent drinking patterns (case–control studies) or of the drinking patterns at baseline (cohort studies). The exposure studied most extensively was the frequency of drinking. Other parameters of exposure to alcoholic beverages, such as duration and age at initiation of drinking and the relevant exposure period, were not reported.

(c) Case–control studies (Table 2.52)

Twenty-one case–control studies reported tobacco smoking-adjusted odds ratios for total alcoholic beverage consumption and the risk for lung cancer. Four of the seven population-based studies (Carpenter *et al*., 1998; Hu *et al*., 2002; Freudenheim *et al*., 2003; Benedetti *et al*., 2006) reported no significant association between any level of alcoholic beverage consumption examined and the risk for lung cancer. However, most of them used categories that reflected a relatively low level of drinking (e.g. 1 drink/day or less often; highest level of drinking, >2 drinks per day, but the median frequency for this category was unclear). Three hospital-based studies (De Stefani *et al*., 1993; Dosemeci *et al*., 1997; Rachtan, 2002) that used non-drinkers as the baseline comparison group found a significant association between consumption of more than one drink per day and the risk for lung cancer. Dosemeci *et al*. (1997) found an elevated risk for lung cancer and a dose–response with increasing frequency of consumption, duration of drinking and cumulative measures in bottle–years. One hospital-based study (Zang & Wynder, 2001) did not find an association for cumulative alcoholic beverage intake (frequency×duration), or for ≥7 oz of 'whiskey-equivalents' of alcohol per day [approximately ≥68 g of ethanol per day] (odds ratio, 1.1; 95% CI, 1.0–1.4). [The Working Group noted that the baseline comparison group in this study included people who consumed less than one alcoholic beverage per day.] De Stefani *et al*. (2002) also reported a null association for adenocarcinoma of the lung.

In addition, among nine case–control studies of lung cancer published in the Chinese literature, five adjusted for or stratified by tobacco smoking. Five studies reported a positive association between alcoholic beverage consumption and the risk for lung cancer and point estimates that ranged from 1.5 to 6.6 but none reported the levels of consumption.

Table 2.52 Case–control studies of total alcoholic beverage consumption and lung cancer risk in the general population

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Williams & Horm (1977), USA, 1969–71	7518 (3436 men, 3856 women for the alcohol and tobacco smoking analysis) from Third National Cancer Survey (TNCS); age range not given; histological confirmation unclear; response rate, 57%	Intracancer controls from TNCS; patients with cancers thought to be unrelated to tobacco and alcohol use	Personal interview	**Oz/week × years** *Men* Non-drinker <51 ≥51 *Women* Non-drinker <51 ≥51	 1.0 p>0.05 0.9 p>0.05 1.0 p>0.05 1.0 p>0.05 1.1 p>0.05 0.7 p>0.05	Age, race, smoking	Controls included colon and liver cancer; non-drinkers defined as those who never drank at least once a week for 1 year; odds ratios for alcoholic beverage types reported
Herity *et al.* (1982), Ireland	59 men [patients at St Luke's hospital in Dublin], aged 44–83 years; histological confirmation unclear; response rate not given	152 male cancer patients, source not described, aged 21–83 years; response rate not described	Structured questionnaire in interview	Non-drinkers or ≤90 g of alcohol/day for 10 years >90 g of alcohol/day for 10 years	1.0 1.5 (0.4–5.2)	Stratified for non- or light smokers (≤20 cigs/day for 43 years)	Controls included cancer of gastrointestinal tract; interaction between alcohol drinking and smoking reported

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Kabat & Wynder (1984), USA, 1971–80	134 (37 men, 97 women) never-smoking patients; 100% histologically confirmed; response rate not given	134 (37 men, 97 women) hospitalized with non-tobacco-related diseases; individually matched to cases by age, sex, race, hospital, date of interview (±2 years), non-smoking status; response rate not given	In-hospital interview with a standardized questionnaire	No significant differences in alcohol intake were found between cases and controls of either sex (no numbers reported)			Nonsmoker defined as someone who had never smoked as much as one cigarette, pipe or cigar per day for a year; most controls had a cancer diagnosis (~60%).
Koo (1988), Hong Kong, China, 1981–83	88 never-smoking hospitalized Chinese women; age not given; 100% histologically confirmed; response rate not given	137 never-smoking Chinese women in the community; individually matched by district, house type before the exclusion of ever smokers	In-hospital (cases) or in-home (controls) interview	<1 time/week ≥1 time/week	1.0 1.9 (0.9–3.7) *p* for trend =0.076	Age, no. of live births, schooling	Never smokers were defined as those who had smoked less than 20 cigarettes or pipes in the past; odds ratio by histological type reported.

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Mettlin (1989), New York, USA, 1982–87	569 (355 men, 214 women) hospitalized, aged 35–90 years; 100% histologically confirmed; response rate not given	569 cancer-free hospitalized; matched on age, sex, residence	Self-administered questionnaire	**Times/week** *Beer* *Wine* *Liquor*	 See Table 2.56 See Table 2.58 See Table 2.60	Age, residence, sex, smoking history [probably pack–years], β-carotene intake index, education	Odds ratio for total alcoholic beverage consumption not available
Pierce *et al.* (1989), Melbourne, Australia, 1984–85	71 hospitalized men; mean age, 67.3 years; 100% cytologically or histologically confirmed; response rate; 100%	70 hospitalized cancer-free men; mean age, 66.5 years; individually matched to cases by age (±5 years); response rate, 100%	In-hospital interview	Drinks/week Duration (years)	1.0 (0.99–1.01) 1.0 (0.96–1.03)	Age; not clear whether smoking was adjusted	[The Working Group noted methological concerns and inconsistencies in the article]

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Bandera *et al.* (1992), New York, USA, 1980–84	280 hospitalized white men, aged 35–79 years; 100% histologically confirmed	564 neighbourhood controls; matched on age, sex, neighbourhood; response rate, 42%	In-person interview at home	**Total alcohol (1 year prior)** *0–40 pack–years* 0–21 drinks/ month ≥22 drinks/ month *p* for trend=0.1 *≥41 pack–years* 0–21 drinks/ month ≥22 drinks/ month *p* for trend=0.03	 1.0 0.9 (0.6–1.6) 1.0 1.6 (1.0–2.5)	Age, education smoking (pack–years)	Odds ratios for alcoholic beverage types reported; categories of alcoholic beverage consumption were based on distribution in combined sample of cases and controls

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
De Stefani *et al.* (1993), Uruguay, 1988–90	327 hospitalized men, aged 25–84 years; 100% histologically confirmed; response rate, 100%	350 men hospitalized with non-neoplastic condition (non-alcohol- related) as well as non-tobacco-related cancer, aged 25–84 years; response rate, 100%	Interviewer-administered questionnaire	*Ethanol (mL/day)* Lifetime abstainers 1–60 61–176 >176	 1.0 1.4 (0.9–2.0) 1.6 (0.9–2.0) 2.2 (1.3–3.0) *p* for trend =0.002	Age, residence, education, smoking (pack–years); for specific alcoholic beverages, other types of alcoholic beverage also controlled for	Histological type examined but data not reported; odds ratios for alcoholic beverage types reported; odds ratios for alcohol drinking by smoking status reported; tertile cut-off points for alcohol consumption based on the distribution in the combined sample of cases and controls; only one nonsmoking case

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Mayne *et al.* (1994), New York, USA, 1982–85	413 (212 men, 201 women) nonsmokers identified via the medical records department, pathology department and the tumour registry, aged 31–80 years; 99% histologically confirmed; interview conducted for 76% of all eligible	413 population selected from driving license files; individually matched on age, sex, county of residence, smoking history; response rate: two potential controls had to be contacted to obtain one control for the case, on average	Interviewer-administered questionnaire (home interview, food-frequency questionnaire for alcohol use)	Beer /month Q1 Q2 Q3 Q4	 1.0 (ref) 1.1 (p>0.05) 0.9 (p>0.05) 1.2 (p>0.05)	Age, sex, county of residence, smoking history, cigs/day smoked by former smokers, religion, education, body-mass index, income	Nonsmokers included never smokers and former smokers; 44% of cases were never smokers; one-third of case–control pairs used proxy respondents; passive smoking was found not to confound the dietary association and was therefore not included in the final model; odds ratio for total alcoholic beverage consumption not available

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Dosemeci *et al.* (1997), Istanbul, Turkey, 1979–84	1210 hospitalized men; 67% histologically confirmed; response rate not given (information obtained by hospital at time of admission)	829 hospitalized men including selected cancers reported not to be related to smoking or alcohol use, and subjects found to have no cancer	Standardized data-collection instrument at time of admission	Never drinker Ever drinker *Alcohol/week* 1–35 cL 36–140 cL >140 cL *Duration* 1–10 years 11–20 years >20 years *Bottle–years (35 cL of hard liquor)* 1–34 35–90 >90	1.0 1.6 (1.2–2.1) 1.6 (0.8–2.9) 1.7 (1.1–2.7) 1.7 (1.0–2.9) *p* for trend <0.001 1.8 (0.9–3.5) 1.6 (1.0–2.7) 2.1 (1.0–4.5) *p* for trend =0.001 1.7 (0.9–3.0) 1.9 (1.0–3.7) 1.6 (0.9–3.0) *p* for trend =0.004	Age, smoking (pack–years)	Interaction between alcoholic beverage drinking and smoking reported; odds ratio for specific histological type reported; odds ratio among smokers only reported
Rachtan & Sokolowski (1997), Cracow, Poland, 1991–94	118 hospitalized women; age not reported; 100% histologically confirmed; response rate not given	141 healthy women selected among next of kin of patients admitted to the same hospital without tobacco-related cancer; age not given; response rate not given	Interviewer-administered structured questionnaire	**Frequency** *Beer* *Wine* *Vodka*	 See Table 2.56 See Table 2.58 See Table 2.60		Odds ratios for total alcoholic beverage consumption not available; updated analysis in Rachtan (2002)

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Carpenter *et al*. (1998), Los Angeles, USA, 1991–94	261 (153 men, 108 women) hospitalized, aged 40–84 years; 100% histologically confirmed; response rate, [69%]	615 (416 men, 199 women) population; frequency matched for age, gender, race; response rate, [50%]	In-person interview	*Recent consumption* Never to 3 drinks/month 1–6 drinks/week 1–2 drinks/day >2 drinks/day *Consumption between age 30 and 40 years* Never to 3 drinks/month 1–6 drinks/week 1–2 drinks/day >2 drinks/day	1.0 0.5 (0.3–0.8) 0.9 (0.5–1.5) 1.1 (0.5–2.5) *p* for trend =0.06 1.0 0.6 (0.4–1.0) 0.7 (0.4–1.2) 0.7 (0.3–1.4) *p* for trend =0.54	Age, gender, race, saturated fat consumption, tobacco smoking (pack–years), years since quitting tobacco smoking; for specific alcoholic beverages, other types of alcoholic beverages also controlled for in the model	Histological type-specific odds ratio reported; odds ratio for alcoholic beverage types reported; subjects were Caucasians and African-Americans; study restricted to subjects who had complete information on smoking, recent alcoholic beverage consumption, past alcohol consumption, diet; period for 'recent consumption' not defined

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Zang & Wynder (2001), 8 metropolitan areas, USA, 1969–94	1763 hospitalized men; age not given [probably <50–≥70 years]; histological confirmation not clear, > [87%] if not 100%; response rate not given	4436 hospitalized men (included non-tobacco-related cancers and non-neoplastic diseases; excluded patients diagnosed with alcohol-related illness); age not given; pair-matched on age, sex, race, hospital, time of hospital admission before applying the exclusion criteria; response rate not given	Interviewer-administered questionnaire (exposure starting at least 1 year prior to the current illness)	*Current pattern ('whiskey-equivalent' oz alcohol/day)* <1 1–3.9 4–6.9 ≥7 Continuous variable *Lifetime exposure ('whiskey-equivalent' oz alcohol drink per day × years of drinking)* <4 4–16 17–27 28–64 65–103 ≥104 Continuous variable	 1.0 1.1 (0.9–1.3) 1.2 (0.9–1.4) 1.1 (1.0–1.4) 1.1 (1.0–1.1) 1.0 1.0 (0.8–1.2) 1.2 (0.9–1.5) 1.1 (0.9–1.4) 1.2 (0.9–1.5) 1.1 (0.9–1.3) 1.0 (1.0–1.1)	Body-mass index, current no. of cigarettes smoked per day; for lifetime exposure to alcohol, age also adjusted	Caucasian only; odds ratios for specific histology reported; odds ratios for alcohol drinking by smoking categories reported

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
De Stefani *et al.* (2002), Montevideo, Uruguay, 1998–2000	160 hospitalized men, aged 30–89 years; 100% histologically confirmed adenocarcinomas; response rate, 97%	520 men hospitalized for non-tobacco-, non-alcohol-related non-neoplastic conditions; frequency-matched on age, residence, urban/rural status; response rate, 93%	In-person interview	*Ethanol (mL/day)* Non-drinkers 1–60 61–120 >120	 1.0 0.8 (0.4–1.5) 1.1 (0.6–2.1) 1.2 (0.6–2.1) *p* for trend =0.34	Age, residence, urban/ rural status, education, family history of lung cancer in first-degree relatives, body mass index, smoking status, cigarettes per day, years since quit, age started smoking	Adenocarcinoma only; drinkers were defined as those who ingested alcohol at least 1 day per week regularly; odds ratios for alcoholic beverage types reported
Hu *et al.* (2002), 8 provinces, Canada, 1994–97	161 never-smoking women from the Provincial Cancer Registry, aged 20–>70 years; 100% histologically confirmed; response rate, 62%	483 population-based cancer-free; frequency-matched by age, sex, province; response rate, 71%	Questionnaire mailed to cases and controls	*Servings/week* 0 1 >1	 1.0 0.8 (0.5–1.4) 0.8 (0.5–1.2) *p* for trend =0.25	10-year age groups, province, education, social class	Study restricted to never smokers; definition for never smoking not described; odds ratios for alcoholic beverage types reported

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Korte *et al.* (2002)	Meta-analysis on alcoholic beverage consumption and risk for lung cancer		No. of studies	*Ethanol (g/month)*	Pooled odds ratio	Smoking	Pooled odds ratios from case–control studies only (including studies presented in this table)
				Non-drinker	1.0		
			3	1–499	0.6 (0.5–0.8)		
			5	500–999	1.3 (1.0–1.7)		
			2	1000–1999	1.1 (0.5–2.8)		
			1	≥2000	1.9 (1.4–2.5)		
			7	Overall	1.4 (1.1–1.8)		
Pacella-Norman *et al.* (2002), Johannesburg, South Africa, 1995–99	146 (105 men, 41 women) hospitalized, aged 18–74 years; 90% confirmed by histology, heamotology or cytology; response rate not given	2174 (804 men, 1370 women) hospitalized with non-tobacco-related cancer, aged 18–74 years; response rate not given	Nurse-administered interview (questionnaire)	*Men*		Age, place of birth, education, work category, missing values, heating fuel, smoking and snuff use (smoking adjusted for past–current smoking, current smoking by cigs/day)	Subjects were black; controls included patients with colon cancer
				Non-drinkers	1.0		
				<1 time/week	0.3 (0.1–1.1)		
				1–3 times/week	0.7 (0.3–1.5)		
				Most days/week	0.7 (0.4–1.3)		
				Women			
				Non-drinkers	1.0		
				<1 time/week	1.3 (0.5–3.3)		
				1–3 times/week	0.8 (0.3–2.6)		
				Most days/week	0.8 (0.3–2.1)		

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Rachtan (2002), Cracow, Poland, 1991–97	242 hospitalized women; age range not given; 100% histologically confirmed; response rate not given	352 healthy women from next-of-kin of patients admitted to the same hospital without tobacco-related cancer; age not given; response rate not given	Interviewer-administered structured questionnaire	*Average vodka intake (g)* Non-drinkers <100 g ≥100 g	 1.0 2.2 (1.3–3.8) 7.8 (2.9–21.2) *p* for trend <0.001	Age, pack–years of smoking, passive smoking, siblings with cancer, tuberculosis, place of residence, occupational exposure to coal and other dusts, rubber, acid mist, solvents, metals, other chemicals, consumption of milk, butter, margarine, cheese, meat, fruit, vegetables, carrots, spinach	Odds ratios for vodka for histological type reported; odds ratios for total alcohol drinking by smoking status reported; estimates unadjusted for smoking for beer and wine intake reported

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Freudenheim *et al*. (2003), New York, USA, 1996–98	168 hospitalized (111 men, 57 women), aged 35–79 years; 100% histologically confirmed; response rate, 48%	3351 (1546 men, 1805 women) population, aged 35–79 years; frequency-matched for age, sex, race for cases in three case–control studies; response rate, 65%	Interviewer-administered questionnaire	*Lifetime consumption (L)* 0 ≤82 >82 *Recent consumption (previous 12–24 months)* 0 ≤2.5 >2.5	 1.0 1.1 (0.5–2.6) 1.1 (0.5–2.7) *p* for trend =0.44 1.0 1.0 (0.4–2.4) 1.4 (0.5–3.4) *p* for trend =0.41	Age, education, race, sex, body-mass index, vegetable intake, fruit intake, total energy intake excluding alcohol, packs smoked per year, years smoked, index of passive exposure to smoke at home, work and in other settings	Odds ratios for alcoholic beverage types reported; [discrepancy in number and sex of cases in paper]

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Gajalakshmi *et al.*(2003), Tamil Nadu and Kerala, India, 1993–99	778 men from two cancer centres, aged ≤34–≥75 years; 100% histologically confirmed; response rate not given	3430 men (1503 non-tobacco-related cancers, 1927 healthy) recruited from the two cancer centres, aged ≤34–≥75 years; response rate not given	Interviewer-administered standard questionnaire	*Total alcohol* Never Former Current *Non-Indian alcohol* Never Former Current *Indian alcohol* Never Former Current	 1.0 0.9 (0.7–1.3) 1.7 (1.3–2.1) 1.0 0.8 (0.5–1.2) 1.3 (1.0–1.7) 1.0 0.9 (0.6–1.3) 1.8 (1.4–2.4)	Age, education, centre, smoking pack–years	Cancer controls included colon cancer; alcohol drinkers defined as people who drink alcohol at least once a day for at least 6 months; former drinker defined as drinkers who had stopped drinking for more than 1 year before interview; odds ratios restricted to never smokers reported

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Ruano-Ravina *et al.* (2004), Northwest Spain, 1999–2000	132 (118 men, 14 women) hospitalized, mean age, 64.2 years; 100% histologically confirmed; response rate, 100%	187 (164 men, 23 women) hospitalized (non-tobacco-related minor surgery); mean age, 62.5 years; frequency-matched on sex; response rate, 100%	Interviewer-administered questionnaire	*Beer* *Wine* *Liquor*	See Table 2.56 See Table 2.58 See Table 2.60	Age, sex, occupation, smoking habit (total lifetime tobacco consumption in thousands of packs), total alcoholic beverage intake	Odds ratio for total alcoholic beverage consumption not available

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Benedetti *et al.* (2006), Montreal, Canada, Study I: early 1980s Study II: mid 1990s	Study I: 699 hospitalized men, aged 35–70 years; [100% histologically confirmed]; response rate, 65% Study II: 1094 (640 men, 454 women) hospitalized, aged 35–75 years; [100% histological confirmation]; response rate, 76%	Study I: 507 men population-based; frequency-matched by age, residence to all cancer cases (all cancer cases arise from the hospitals); response rate, 69% Study II: 1468 (861 men, 607 women) population-based; stratified to the age and sex distribution of cases; response rate, 67%	Interview (proxy was allowed)	*Study I men* <1 drink/week 1–6 drinks/week ≥7 drinks/week *Study II men* <1 drink/week 1–6 drinks/week ≥7 drinks/week *Study II women* <1 drink/week 1–6 drinks/week ≥7 drinks/week	 1.0 1.2 (0.8–1.8) 1.3 (0.9–1.9) 1.0 1.0 (0.7–1.4) 1.2 (0.9–1.8) 1.0 0.4 (0.2–0.5) 0.7 (0.5–1.1)	Age, smoking status, cigarette–years, time since quitting, respondent status, ethnicity, census tract income, years of schooling	Odds ratios for specific histological type reported; odds ratios for alcoholic beverage types reported; odds ratios for alcohol drinking by smoking categories reported (light, moderate, heavy); odds ratios based on median drink–year cut-off reported

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Studies in the Chinese literature							
Zhang *et al.* (1989), JinZhou, Liaoning, 1988–89	105 hospitalized; age, sex distribution not given; histological confirmation not given; response rate not given	210 hospitalized (105 cancer, 5 cancer-free); age, sex distribution not given; response rate: not given	In-hospital interview	*Alcohol drinking* No Yes		Alcohol drinking variable no longer significant after adjusting for smoking, chronic bronchitis, exposure to toxic substances, coal burning, depression, cooking, education, family history of cancer	No adjusted odds ratio for alcohol use reported
Zhang *et al.* (1990), Dandong, Liaoning, 1987–88	Six cause of deaths (including lung cancer) identified between 1987 and 1988, aged >17 years; proxy probably used for cases; response rate not given	Random sample of 2500–3000 from general population; source not well described; age not given; response rate not given	[Interview?]	*Drinking/ smoking* No/No Yes/No No/Yes Yes/Yes	 1.0 2.2 (0.5–10.3) 6.2 (1.8–20.9) 10.6 (3.3–34.5)	Urban/rural, sex, age	

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Zhang *et al.* (1992), Lanzhou, Gansu, 1982–88	70 (58 men, 12 women) hospitalized from 8 hospitals in Lanzhou for over 10 years, aged 21–77 years; 100% histologically confirmed; response rate not given	70 hospitalized; 1:1 matched on age, sex, occupation; response rate not given	Interviewer-administered questionnaire	*Alcohol drinking* No Yes	 1.0 2.3	Smoking, coal burning	95% CI or *p*-value not provided [although probably significant]
Cui *et al.* (2001b), Jiangyan, Jiangsu, 1995–96	181 male [hospitalized] survivors, aged 24–86 years; 76% histologically confirmed; response rate not given	181 men selected from the healthy relatives or neighbours who had lived in the same area or worked with cases; matched on age	Interviewer-administered questionnaire	*Alcohol drinking* No Yes	 1.0 2.3 (1.2–8.4)	Smoking, respiratory disease, depression, body-mass index	

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Zhang *et al.* (2002), Kunmin, Yunnan, NR	118 (91 men, 27 women) hospitalized, mean age, 58 years; 100% histologically confirmed; response rate not given	118 healthy; matched on sex, occupation, ethnic group, age, residence	Interviewer-administered questionnaire	*Alcohol drinking* No Yes		[Alcohol drinking variable not significant in multivariate analysis]	No adjusted odds ratio for alcohol use reported
Chen *et al.* (2003b), Tianjin, before 1996	193 (sex not given) hospitalized, aged 30–76 years; 68% histologically confirmed; response rate: not given	259 (sex not given) randomly selected from a community in Tianjin, aged 30–75 years; response rate not given	Interviewer-administered questionnaire	*Alcohol drinking* No Yes		Alcohol drinking variable no longer significant after adjusting for smoking	No adjusted odds ratio for alcohol use reported

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Chen *et al.* (2003c); Huang *et al.* (2004), Guangzhou, Guangdong, 2000–02	91 hospitalized; age and sex distribution not given; 100% histologically confirmed; response rate not given	138 (91 hospitalized non-cancers and 47 healthy employees of Guangdong Pharmacy School); residents of Guangdong; matched on age, sex; response rate not given	Questionnaire	*Alcohol drinking* No Yes No Yes No Yes	*All lung* 1.0 3.3 (1.7–6.4) *SCC* 1.0 3.9 (1.8–8.2) *AC* 1.0 2.5 (1.0–6.3)	Crude odds ratio	Subjects overlapped with Chen *et al.* (2004).
Wu *et al.* (2003); Chen *et al.* (2004), Guangzhou, Guangdong, 2000–01	91 (60 men, 31 women) incident hospitalized, aged 22–84 years; histological confirmation not given; response rate not given	91 (60 men, 31 women) hospitalized without cancer or pulmonary diseases; matched by age; response rate not given	Questionnaire	*Alcohol drinking* No Yes	1.0 6.6 (1.5–28.3)	Education, smoking (cigs/day), ventilation for cooking fume, consumption of animal oil, carrot intake, family history of lung cancer	Same subjects as in Chen, M.-X. *et al.* (2003)

Table 2.52 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Zou *et al.* (2005), Dayao, Yunan, 1987–2001	53 cases (46 men, 7 women) identified by retrospective cohort, mean age, 62 years; histological confirmation not clear (all confirmed with histological or image diagnosis); response rate not given	159 from the cohort, aged ≥30 years; local residents; men age, 65 years; matched to cases (1:3 ratio) on age, sex, residence, education; response rate not given	Interviewer-administered questionnaire	*Alcohol drinking* No Yes	 1.0 1.2 (0.5–2.7)	Using asbestos stove, cigarette smoking, tea drinking	Nested case–control study Proxy respondent used for subjects who died; alcohol drinking variable not defined

AC, adenocarcinoma; CI, confidence interval; NR, non reported; SCC, squamous-cell carcinoma

2.10.2 *Histological type (Tables 2.53 and 2.54)*

Two cohort studies, one pooled analysis and seven case–control studies presented smoking-adjusted risk estimates for alcoholic beverages by histological type of lung cancer. There appears to be no consistent pattern for the effect estimates of alcoholic beverages on the main lung cancer types: squamous-cell carcinoma, adenocarcinoma and small-cell lung cancer (Tables 2.53 and 2.54). A positive association with squamous-cell carcinoma was reported in three case–control studies (Dosemeci *et al*., 1997; Zang & Wynder, 2001; Rachtan, 2002). A positive relationship between alcoholic beverage consumption and adenocarcinoma was reported in four case–control studies (Carpenter *et al*., 1998; Zang & Wynder, 2001 [lifetime exposure]; Rachtan, 2002; Benedetti *et al*., 2006 [only in men]). In a study in which only the cases of adenocarcinoma were included (De Stefani *et al*., 2002), no association was observed between alcoholic beverage consumption and this histological type, despite the large number of cases.

In a pooled analysis of seven cohort studies (Freudenheim *et al*., 2005), some association was found for adenocarcinoma and small-cell lung cancer among men, and for adenocarcinoma among women. In a more recent study that was not included in the pooled analysis (Rohrmann *et al*., 2006), virtually no association was observed for any lung cancer type among both men and women. [Estimates for lung cancer subtype were mostly based on small numbers of cases, which leads to difficulties in interpreting results due to wide confidence intervals and the possibility of chance findings.] Currently available data do not provide any conclusive evidence for the risk of alcoholic beverage intake on lung cancer subtype.

2.10.3 *Types of alcoholic beverage*

Findings from studies examining risk estimates for the consumption of different types of alcoholic beverages (i.e. beer, wine, and hard liquor) indicate that they may have different effects on lung cancer risk.

(a) Beer (Tables 2.55 and 2.56)

Among the six cohort studies that examined the effects of beer drinking on risk for lung cancer, two found a positive association for drinking one serving of beer per day in women (Potter *et al*., 1992) or two or more servings per day in men (Prescott *et al*., 1999) (Table 2.55). In the latter study, the point estimate for women was of similar magnitude as that in men (relative risk, 1.4 for men and 1.5 for women), but the confidence interval was wide (95% CI, 0.7–3.1).

In a pooled analysis that combined data from seven prospective cohort studies (Freudenheim *et al*., 2005), a positive association with a significant dose-reponse relationship was found between beer drinking and the risk for lung cancer among women, but not among men. The risk almost doubled for women who consumed ≥15 g ethanol

Table 2.53 Cohort studies of alcoholic beverage consumption and lung cancer by histological type

Reference	Subject and histology	Exposure categories	Risk ratio (95% CI)	Comments
Boffetta *et al.* (2001)	*Men*	Alcoholic	**SIR**	Adjusted for age, gender, calendar year; estimates not adjusted for smoking; SIR reference, national incidence rates; SCLC cases also included in 'other and unspecified type'
	SCC		2.4 (2.3–2.6)	
	AC		2.1 (1.9–2.4)	
	SCLC		1.1 (0.5–2.1)	
	Other and unspecified type		2.1 (2.0–2.3)	
	Women	Alcoholic		
	SCC		5.3 (4.1–6.8)	
	AC		3.3 (2.6–4.1)	
	SCLC		1.9 (0.4–5.6)	
	Other and unspecified type		4.4 (3.7–5.3)	
	Both genders	Alcoholic		
	SCC		2.6 (2.4–2.8)	
	AC		2.3 (2.1–2.5)	
	SCLC		1.2 (0.6–2.2)	
	Other and unspecified type		2.3 (2.2–2.5)	

Table 2.53 (continued)

Reference	Subject and histology	Exposure categories	Risk ratio (95% CI)						Comments
		Alcohol g/day	>0–<5	5–<15	15–<30	≥30	*p* for trend		
Freudenheim *et al.* (2005)	*Men*								Reference, 0 g/day; adjusted for education, body-mass index, energy intake, smoking status, smoking duration, cigarettes/day
	SCC		0.9 (0.7–1.2)	1.0 (0.8–1.3)	0.8 (0.6–1.2)	1.1 (0.5–2.1)	0.64		
	AC		1.1 (0.8–1.4)	1.2 (0.9–1.6)	1.0 (0.7–1.5)	1.4 (1.0–2.1)	0.10		
	SCLC		1.1 (0.8–1.5)	1.2 (0.9–1.6)	1.1 (0.8–1.5)	1.7 (1.2–2.3)	<0.01		
	Women								
	SCC		0.7 (0.5–1.1)	0.8 (0.6–1.0)	0.8 (0.6–1.2)	0.9 (0.6–1.5)	0.99		
	AC		0.9 (0.8–1.1)	0.9 (0.7–1.2)	1.0 (0.7–1.3)	1.4 (1.0–2.0)	<0.01		
	SCLC		0.8 (0.6–1.1)	0.8 (0.6–1.1)	1.0 (0.6–1.5)	0.9 (0.6–1.3)	0.94		
		Ethanol (g/day)	Non-drinker	5–14.9	15–29.9	30–59.9	≥60	*p* for trend	
Rohrmann *et al.* (2006)	*Men and women*								Reference, 0.1–4.9 g/day; all results stratified by age, sex, study centre; adjusted for smoking status, smoking duration, height, weight, consumption of fruit, red meat, processed meat, education, total non-ethanol energy intake
	SCC	Baseline intake	1.9 (1.2–2.9)	0.8 (0.6–1.2)	0.8 (0.5–1.3)	1.0 (0.6–1.5)	0.9 (0.5–1.6)	0.30	
	AC		1.1 (0.8–1.7)	0.9 (0.7–1.2)	1.1 (0.8–1.5)	1.3 (0.9–1.8)	1.2 (0.7–2.0)	0.19	
	SCLC		0.9 (0.5–1.6)	0.8 (0.5–1.2)	0.7 (0.4–1.1)	0.9 (0.5–1.4)	0.9 (0.5–1.7)	0.85	
	SCC	Mean lifelong intake	1.2 (0.5–2.8)	0.6 (0.4–0.9)	0.7 (0.5–1.2)	0.7 (0.4–1.2)	0.9 (0.5–1.8)	0.87	
	AC		1.0 (0.5–2.2)	0.9 (0.6–1.2)	1.3 (0.9–1.9)	1.1 (0.7–1.8)	1.4 (0.8–2.6)	0.16	
	SCLC		0.6 (0.1–2.6)	1.0 (0.6–1.6)	0.9 (0.6–1.6)	1.0 (0.5–1.9)	1.4 (0.7–2.8)	0.38	

AC, adenocarcinoma; CI, confidence interval; SCC, squamous-cell carcinoma; SCLC, small-cell lung cancer; SIR, standardized incidence ratio

Table 2.54 Case–control studies of alcoholic beverage consumption and lung cancer by histological type

Reference	Subject and histology	Exposure categories	Odds ratio (95% CI)				Comments
Koo (1988)		Times/ week	≥1	*p* for trend			Reference, <1 time/week; adjusted for age, no. of live births, schooling; restricted to never smokers
	Women						
	SCC + SCLC		2.1	0.141			
	AC + LCLC		1.4	0.460			
Dosemeci *et al.* (1997)	*Men*	Ever drank					Reference, never drinkers; adjusted for age, smoking
	SCC		1.6 (1.1–2.2)				
	SCLC		1.3 (0.8–2.1)				
	Others		1.9 (1.2–2.9)				
		Alcohol (cL/week)	1–35	36–140	≥141	*p* for trend	
	SCC		1.7 (0.8–3.5)	1.6 (0.9–2.8)	1.8 (1.0–3.6)	0.003	
	SCLC		1.8 (0.7–4.6)	1.2 (0.6–2.6)	0.8 (0.2–2.3)	0.419	
	Others		2.0 (0.8–5.0)	1.9 (0.9–3.8)	1.8 (0.8–4.3)	0.008	
		Duration (years)	1–10	11–20	≥21	*p* for trend	
	SCC		1.6 (0.7–4.0)	1.7 (1.0–3.1)	2.7 (1.2–6.2)	< 0.001	
	SCLC		2.0 (0.7–5.8)	1.2 (0.5–2.7)	1.6 (0.5–5.3)	0.139	
	Others		2.2 (0.7–6.3)	1.8 (0.8–3.7)	1.7 (0.5–5.7)	0.021	
		Bottle–years	1–34	35–90	≥91	*p* for trend	
	SCC		1.9 (1.0–3.9)	1.7 (0.8–3.9)	1.9 (1.0–3.9)	0.003	
	SCLC		1.7 (0.6–4.5)	1.8 (0.7–4.6)	0.7 (0.2–2.4)	0.298	
	Others		1.6 (0.6–4.3)	2.6 (1.1–6.3)	1.4 (0.5–3.7)	0.025	

Table 2.54 (continued)

Reference	Subject and histology	Exposure categories	Odds ratio (95% CI)			Comments
Carpenter *et al.* (1998)		Intake	1–6 drinks/ week	≥1 drink/day	*p* for trend	Reference, never to 3 drinks/month; adjusted for age, sex, race, saturated fat, pack–years smoked, years since quitting smoking; alcoholic beverage types mutually adjusted
	Men and women					
	AC	*Beer*	0.7 (0.4–1.3)	0.8 (0.4–1.6)	0.35	
	SCC + SCLC		1.0 (0.5–1.8)	0.8 (0.4–1.7)	0.32	
	Other cell types		1.0 (0.5–1.8)	0.6 (0.3–1.3)	0.13	
	AC	*Wine*	1.0 (0.5–1.8)	0.5 (0.2–1.6)	0.22	
	SCC + SCLC		0.6 (0.3–1.1)	0.5 (0.2–1.3)	0.11	
	Other cell types		0.8 (0.4–1.6)	0.8 (0.3–2.0)	0.49	
	AC	*Liquor*	1.0 (0.6–1.9)	1.4 (0.6–3.2)	0.54	
	SCC + SCLC		0.9 (0.5–1.6)	1.8 (0.9–4.0)	0.16	
	Other cell types		1.1 (0.6–1.9)	2.1 (0.9–4.5)	0.20	

Table 2.54 (continued)

Reference	Subject and histology	Exposure categories	Odds ratio (95% CI)						Comments
Zang & Wynder (2001)	'Whiskey–equivalent' (oz alcohol/day)		1–3.9	4–6.9	≥7	Continuous			Reference for current drinking, <1 oz alcohol/day; reference for lifelong exposure, <4 oz/day–year; adjusted for body-mass index, current cigarettes per day; dose–response used oz/day–year as continuous variable.
	Men								
	SCC		1.1 (0.9–1.5)	0.9 (0.7–1.3)	1.4 (1.1–1.8)	1.1 (1.0–1.2)			
	AC		1.1 (0.9–1.4)	1.3 (1.0–1.7)	1.0 (0.8–1.3)	1.0 (0.9–1.1)			
	SCLC		1.2 (0.8–1.7)	1.4 (0.9–2.2)	1.4 (1.0–2.0)	1.1 (1.0–1.3)			
	LCLC		1.2 (0.7–1.8)	0.7 (0.4–1.5)	1.2 (0.7–1.9)	1.0 (0.9–1.2)			
	Lifelong exposure (oz/day 'whiskey–equivalent' × years of drinking)		4–16	17–27	28–64	65–103	≥104	Continuous	
	SCC		1.0 (0.7–1.4)	0.8 (0.5–1.2)	1.1 (0.8–1.6)	1.1 (0.8–1.7)	1.2 (0.9–1.6)	1.0 (1.0–1.1)	
	AC		1.1 (0.8–1.5)	1.6 (1.1–2.3)	1.1 (0.8–1.5)	1.4 (1.0–2.0)	1.1 (0.8–1.5)	1.1 (1.0–1.1)	
	SCLC		1.1 (0.7–1.9)	1.0 (0.5–1.9)	1.0 (0.6–1.7)	1.5 (0.9–2.5)	1.3 (0.9–1.9)	1.0 (1.0–1.1)	
	LCLC		1.1 (0.6–2.0)	1.4 (0.7–2.8)	1.1 (0.6–2.0)	0.9 (0.4–1.8)	[0.9] (0.5–1.5)	1.0 (0.9–1.1)	

Table 2.54 (continued)

Reference	Subject and histology	Exposure categories	Odds ratio (95% CI)				Comments
De Stefani *et al.* (2002)		Ethanol (mL/day)	1–60	61–120	>120	*p* for trend	Reference, non-drinker; adjusted for age, residence, urban/ rural status, education, family history of lung cancer in first-degree relatives, body-mass index, smoking status, cigarettes per day, years since quitting, age at start of smoking
	Men						
	AC		0.8 (0.4–1.5)	1.1 (0.6–2.1)	1.2 (0.6–2.1)	0.34	
		Beer	1.1 (0.5–2.5)	0.6 (0.3–1.6)		0.31	
		Wine	0.6 (0.3–1.2)	0.6 (0.3–1.2)	0.4 (0.2–1.1)	0.29	
		Hard liquor	1.5 (0.8–2.6)	2.9 (1.4–6.2)	1.4 (0.7–3.0)	0.09	
Djoussé *et al.* (2002)	Alcohol (g/day)		0.1–12	12.1–24	>24		Reference, 0 g/ day; adjusted for age, sex, smoking status, pack–years of smoking, year of birth
	Men and women						
	SCC		0.4 (0.1–2.0)	0.4 (0.1–2.6)	0.3 (0.1–1.7)		
	AC		2.9 (0.8–10.9)	1.5 (0.3–8.1)	2.3 (0.5–10.5)		
	Others		0.7 (0.2–2.3)	0.8 (0.2–2.9)	0.8 (0.2–2.7)		

Table 2.54 (continued)

Reference	Subject and histology	Exposure categories	Odds ratio (95% CI)			Comments
Rachtan (2002)	Average vodka intake (g)		<100	≥100	*p* for trend	Reference, non-drinkers; adjusted for age, pack–years of smoking, passive smoking, consumption of milk, butter, margarine, cheese, meat, fruit, vegetables, carrots, spinach, siblings with cancer, tuberculosis, residence, occupational exposure
	Women					
	SCC		1.3 (0.6–2.9)	3.9 (1.0–15.2)	<0.001	
	AC		2.6 (1.2–6.1)	8.0 (1.7–37.7)	0.003	
	SCLC		1.9 (0.8–4.5)	11.8 (3.0–45.9)	<0.001	

Table 2.54 (continued)

Reference	Subject and histology	Exposure categories	Odds ratio (95% CI)		Comments
Benedetti *et al.* (2006)	Drinks/week		1–6	≥7	Reference, never weekly; adjusted for age, respondent status, ethnicity, smoking status, cigarette–years, socioeconomic status, years of schooling, years since quitting
	Men (Study I)				
	SCC		1.3 (0.8–2.2)	1.4 (0.9–2.2)	
	AC		1.8 (0.9–3.5)	2.0 (1.1–3.6)	
	SCLC		1.1 (0.6–2.1)	1.1 (0.6–2.0)	
	LCLC		0.9 (0.4–2.3)	0.5 (0.2–1.3)	
	Men (Study II)				
	SCC		1.3 (0.7–2.2)	1.4 (0.8–2.3)	
	AC		1.0 (0.6–1.7)	1.5 (1.0–2.5)	
	SCLC		1.1 (0.6–2.2)	1.3 (0.7–2.4)	
	LCLC		1.9 (0.7–4.6)	2.0 (0.8–4.9)	
	Women (Study II)				
	SCC		0.2 (0.1–0.4)	1.0 (0.5–2.1)	
	AC		0.5 (0.3–0.8)	0.9 (0.5–1.5)	
	SCLC		0.3 (0.2–0.7)	0.9 (0.4–2.1)	
	LCLC		0.3 (0.1–0.8)	0.4 (0.1–1.2)	

AC, adenocarcinoma; CI, confidence interval; LCLC, large cell lung cancer; SCC, squamous-cell carcinoma; SCLC, small-cell lung cancer

Table 2.55 Cohort studies of beer consumption and lung cancer

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Pollack *et al.* (1984)	Men	*oz/month*		Adjusted for age, cigarette smoking status (never, former and current smokers), alcohol content of the other two types of beverage (if significant) [values read from graph]
		Non-beer drinker	1.0	
		1–9	[0.7] [0.3–1.5]	
		10–99	[0.5] [0.2–1.4]	
		[100]–499	[1.1] [0.7–2.1]	
		≥500	[1.1] [0.7–2.1]	
Chow *et al.* (1992)	Men	*Times/month*		Adjusted for age, industry/occupation, smoking status (never any tobacco, other tobacco only, occasional/past use of 1–19, 20–29, ≥30 cigarettes/day, current use of 1–19, 20–29, ≥30 cigarettes/day)
		Never drank	1.0	
		<3	1.2 (0.8–1.9)	
		3–5	1.4 (0.8–2.3)	
		6–13	1.7 (1.0–2.9)	
		>13	1.1 (0.6–1.9)	
		Former drinker	1.8 (1.1–3.0)	
Potter *et al.* (1992)	Women	Non-drinker	1.0	Adjusted for smoking (pack–years)
		<1 glass/day	0.6 (0.3–1.2)	
		≥1 glass/day	1.9 (0.96–3.9)	
Woodson *et al.* (1999)	Men	*Ethanol (g/day)*		Adjusted for age, body mass index, years smoked, cigarettes per day, intervention group
		Non-drinker	1.0 (0.9–1.2)	
		Q1 0.01–1.6	1.0 (1.0)	
		Q2 1.7–4.5	0.8 (0.6–1.0)	
		Q3 4.6–11.5	0.9 (0.7–1.1)	
		Q4 11.6–242.6	0.9 (0.7–1.1)	
			p for trend=0.19	
Prescott *et al.* (1999)		*Drinks/week*		Adjusted for age, study cohort, education, smoking (current smoking: pack–years, duration of smoking), other types of alcoholic beverage
	Men	<1	1.0 (1.0)	
		1–13	1.1 (0.8–1.4)	
		>13	1.4 (1.0–1.8)	
	Women	<1	1.0 (1.0)	
		1–13	0.9 (0.6–1.3)	
		>13	1.5 (0.7–3.1)	

Table 2.55 (continued)

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Freudenheim *et al.* (2005) Pooled analysis of 7 prospective studies		*g/day*		Adjusted for education, body-mass index, energy intake, other types of alcoholic beverage, smoking status (never, past, current), smoking duration for past and current smokers, cigarettes smoked daily for current smokers
	Men	None	1.0	
		>0–<5	0.9 (0.8–1.1)	
		5–<15	0.8 (0.7–1.0)	
		≥15	1.1 (0.9–1.4)	
			p for trend=0.47	
	Women	None	1.0	
		>0–<5	0.8 (0.6–0.9)	
		5–<15	1.2 (1.0–1.5)	
		≥15	1.9 (1.5–2.4)	
			p for trend <0.001	

CI, confidence interval

from beer per day (approximately ≥1 beer per day; odds ratio, 1.9; 95% CI, 1.5–2.4), but the relative risk was 0.8 (95% CI, 0.6–0.9) for those with the lowest level of beer consumption (<5 g ethanol/day). A null association was reported in three studies (Pollack *et al*., 1984; Chow *et al*., 1992; Woodson *et al*., 1999), all of which were restricted to men. Chow *et al*. (1992) reported a relative risk of 1.7 (95% CI, 1.0–2.9) for drinking beer 6–13 times per month, and of 1.1 (95% CI, 0.6–1.9) for drinking beer more than 13 times per month.

Among 11 case–control studies that presented tobacco smoking-adjusted odds ratios for beer drinking compared with non-drinkers, three reported a positive association for the highest level of beer drinking used in the analyses (Bandera *et al*., 1992; De Stefani *et al*., 1993; Benedetti *et al*., 2006, in the first study in men only (Table 2.56).

(b) Wine (Tables 2.57 and 2.58)

Among 10 case–control studies (Table 2.58) that provided tobacco smoking-adjusted risk estimates for wine intake, only one reported a positive association for white wine intake (relative risk, 1.5; 95% CI, 0.5–4.4) but not for red wine or rosé (Ruano-Ravina *et al*., 2004). In contrast, a significant inverse association was observed between red wine consumption and risk for lung cancer in this study. Six other case–control studies reported odds ratios below 1 for wine consumption, although these were not always statistically significant.

Among the three cohort studies that reported risk estimates for wine drinking (Table 2.57), two reported a significant inverse association in men (Prescott *et al*., 1999; Woodson *et al*., 1999 [trend test]). In another study, drinking ≥50 oz of wine per month (approximately ≥10 glasses of wine per month) was associated with a twofold increased risk for lung cancer compared with non-wine drinkers (Pollack *et al*., 1984).

In a pooled analysis based on seven cohort studies (Freudenheim *et al*., 2005), an inverse association was detected by the trend test for men, but not for women.

None of the cohort studies reported relative risk estimates adjusted for dietary factors such as vegetable/fruit intake. Confounding by dietary factors may explain to current observations.

(c) Liquor (Tables 2.59 and 2.60)

Two of five cohort studies reported a positive association between liquor drinking and risk for lung cancer, adjusted for tobacco smoking (Table 2.59) (Pollack *et al*., 1984; Prescott *et al*., 1999 in men only). The strongest association was identified by Pollack *et al*. (1984), in which men who consumed ≥1 measure of whiskey per day were found to have a relative risk of 2.6 [95% CI, 1.3–5.0]. Prescott *et al*. (1999) found a borderline significant 50% increase in risk among men who consumed at least two drinks of liquor per day; no association was observed among women.

Table 2.56 Case–control studies of beer consumption and lung cancer

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Williams & Horm (1977)	Men	Non-drinker	1.0 (not given)	Adjusted for age, race, smoking; 'controls' were 'tobacco- and alcohol-unrelated' cancer; however, included colon and liver cancer
		<51 can–years	1.2	
		≥51 can–years	1.1	
	Women	Non-drinker	1.0	
		<51 can–years	0.8	
		≥51 can–years	1.1	
Mettlin (1989)	Men and women	*Times/week*		Adjusted for age, residence, sex, smoking history [pack–years or similar index of exposure], β-carotene intake index, education
		Never	1.0	
		<1	0.5 (0.4–0.8)	
		1–3	0.7 (0.5–1.1)	
		4–9	0.7 (0.5–1.2)	
		≥10	1.3 (0.8–2.1)	
Bandera *et al.* (1992)	Men	Drink/month		Adjusted for age, education, smoking (pack–years); no obvious interaction between beer consumption and smoking observed
		0	1.0	
		1–11	1.1 (0.7–1.7)	
		≥12	1.6 (1.0–2.4)	
			p for trend<0.01	
		0	1.0	Also adjusted for carotenoids and fat
		1–11	1.0 (0.7–1.6)	
		≥12	1.5 (1.0–2.2)	
			p for trend=0.009	
De Stefani *et al.* (1993)	Men	*Ethanol (mL/day)*		Adjusted for age, residence, education, smoking (pack–years), other types of alcoholic beverage
		Lifetime abstainers	1.0	
		1–9	0.7 (0.3–2.5)	
		10–59	1.4 (0.4–6.2)	
		>59	3.4 (1.3–15.2)	
			p for trend=0.02	

Table 2.56 (continued)

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Mayne *et al.* (1994)	Men and Women	*Monthly frequency* Q1 Q2 Q3 Q4	(not given) 1.0 (ref) 1.1 0.9 1.2 *p* for trend=NS	*p* value >0.05 for odds ratios of quartiles 2–4; adjusted for age, sex, county of residence, smoking history (never and former), cigarettes/day smoked in former smokers, religion, education, body mass index, income; ranges for quartiles not provided
Rachtan & Sokolowski (1997)	Women	Non-drinker Rarely 1–2/month At least once/week	1.0 1.1 (0.5–2.3) 1.8 (0.5–6.7) 3.3 (0.6–17.5) *p* for trend=0.126	Estimates only adjusted for age, not for smoking; updated analysis given in Rachtan (2002)
Carpenter *et al.* (1998)	Men and women	*Recent consumption* Never to 3 drinks/mth 1–6 drinks/week ≥1 drink/day *p* for trend=0.45 *Consumption between age 30 and 40 years* Never to 3 drinks/mth 1–6 drinks/week ≥1 drink/day *p* for trend=0.09	 1.0 0.4 (0.2–0.7) 0.9 (0.4–1.8) 1.0 0.9 (0.6–1.4) 0.7 (0.4–1.2)	Adjusted for age, gender, race, saturated fat consumption, tobacco smoking (pack–years), years since quitting tobacco smoking, other types of alcoholic beverage
De Stefani *et al.* (2002)	Men	*Ethanol (mL/day)* Non-drinker 1–60 >60 *p* for trend=0.31 Abstainer Beer only	 1.0 1.1 (0.5–2.5) 0.6 (0.3–1.6) 1.0 0.9 (0.1–5.6)	Adenocarcinoma only; adjusted for age, residence, urban/rural status, education, family history of lung cancer in first-degree relatives, body mass index, smoking status, cigarettes per day, years since quitting, age at start of smoking, other types of alcoholic beverage; [for exclusive consumption of a specific alcoholic beverage, total alcohol intake might also be adjusted for].

Table 2.56 (continued)

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Hu *et al*.(2002)	Women	*Servings/week*		Never smokers only; adjusted for age, province, education, social class
		0	1.0	
		≤0.5	1.2 (0.6–2.4)	
		>0.5	0.5 (0.2–1.1)	
			p for trend=0.17	
Rachtan (2002)	Women	*Frequency*		Adjusted for age only; estimates not adjusted for smoking
		Non-drinker	1.0	
		Rarely	1.0 (0.6–1.8)	[Unit of time not given]
		≥3 times/month	2.6 (1.5–4.5)	
			p for trend=0.002	
		Average amount (g)		
		Non-drinker	1.0	
		≥250	1.3 (0.8–2.0)	
		>250	9.0 (2.6–31.6)	
			p for trend<0.001	
		Drinking duration (years)		
		Non-drinker	1.0	
		≤29	1.0 (0.5–1.9)	
		≥30	2.0 (1.3–3.3)	
			p for trend=0.005	

Table 2.56 (continued)

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Freudenheim *et al.* (2003)	Men and women	*Lifetime consumption* (L)		Adjusted for age, education, race, sex, body mass index, vegetable intake, fruit intake, total energy intake excluding alcohol, packs smoked per year, years smoked, index of passive exposure to smoke at home, work, in other settings
		0	1.0	
		≤62	1.2 (0.7–1.9)	
		>62	1.4 (0.8–2.3)	
			p for trend=0.30	
		Consumption in previous 12–24 months (L)		
		0	1.0	
		≤1.6	0.8 (0.4–1.4)	
		>1.6	1.7 (1.0–2.9)	
			p for trend=0.05	
Ruano-Ravina *et al.* (2004)	Men and women	Non-drinker	1.0 (0.6–2.1)	Adjusted for age, sex, occupation, smoking habit (total lifetime tobacco consumption in thousands of packs), total alcoholic beverage intake
		Drinker	1.1 (0.97–1.02)	
		Continuous variable		
		Beer (weekly unit)	0.99	
Benedetti *et al.* (2006)	Men (Study I)	Never weekly	1.0	Adjusted for age, smoking status, cigarette–years, time since quitting, respondent status, ethnicity, census tract income, years of schooling
		1–6 drinks/week	1.2 (0.9–1.7)	
		≥7 drinks/week	1.5 (1.1–2.1)	
	Men (Study II)	Never weekly	1.0	
		1–6 drinks/week	1.0 (0.7–1.4)	
		≥7 drinks/week	1.0 (0.7–1.4)	
	Women (Study II)	Never weekly	1.0	
		1–6 drinks/week	0.3 (0.2–0.5)	
		≥7 drinks/week	0.9 (0.5–1.6)	

CI, confidence interval; NS, not significant

Table 2.57 Cohort studies of wine consumption and lung cancer

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Pollack *et al.* (1984)		*oz/month*		Adjusted for age, cigarette-smoking status (never, former, current smokers), alcohol content of the other two types of beverage (if significant) [read from graph]
		Non-wine drinker	1.0	
	8006 Men	1	[1.2] [0.6–2.6]	
		2–49	[0.8] [0.2–2.6]	
		≥50	2.2 [1.0–4.4]	
Prescott *et al.* (1999)		*Drinks/week*		Adjusted for age, study cohort, education, smoking (current smoking: pack–years, duration of smoking), other types of alcoholic beverage
	17 669 Men	<1	1.0	
		1–13	0.8 (0.6–1.0)	
		>13	0.4 (0.2–0.9)	
	13 525 Women	<1	1.0	
		1–13	0.9 (0.6–1.3)	
		>13	0.2 (0.0–1.3)	
Woodson *et al.* (1999)		*Ethanol (g/day)*		Adjusted for age, body mass index, years smoked, cigarettes per day, intervention group
	27 111 Men	Non-drinker	1.1 (0.9–1.3)	
		0.09–2.0	1.0	
		2.1–67.5	0.8 (0.6–1.1)	
			p for trend=0.02	
Freudenheim *et al.* (2005) Pooled analysis of 7 prospective studies		*g/day*		Adjusted for education, body mass index, energy intake, other types of alcoholic beverage, smoking status (never, past, current), smoking duration for past and current smokers, cigarettes smoked daily for current smokers
	Men	None	1.0	
		>0–<5	0.9 (0.8–1.1)	
		5–<15	0.7 (0.5–0.9)	
		≥15	0.9 (0.6–1.4)	
			p for trend=0.04	
	Women	None	1.0	
		>0–<5	0.9 (0.7–1.1)	
		5–<15	0.8 (0.5–1.1)	
		≥15	1.1 (0.8–1.5)	
			p for trend=0.99	

CI, confidence interval

Table 2.58 Case–control studies of wine consumption and lung cancer

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Williams & Horm (1977)	Men	Non-drinker	1.0 (not given)	Adjusted for age, race, smoking; 'controls' had 'tobacco- and alcohol-unrelated' cancer; however, controls included colon and liver cancer.
		<51 glass–years	0.6	
		≥51 glass–years	1.1	
	Women	Non-drinker	1.0	
		<51 glass–years	0.7	
		≥51 glass–years	1.1	
Mettlin (1989)	Men and women	*Times/week*		Adjusted for age, residence, sex, smoking history [pack–years or similar index of exposure], β-carotene intake index, education
		Never	1.0	
		<1	0.6 (0.4–0.8)	
		1–3	0.5 (0.3–0.8)	
		4–9	0.8 (0.5–1.5)	
		≥10	1.0 (0.4–2.5)	
Bandera *et al.* (1992)	Men	*Drinks/month*		Adjusted for age, education, smoking (pack–years); no obvious interaction between wine consumption and smoking observed
		0	1.0	
		1	1.0 (0.7–1.4)	
		≥2	0.7 (0.5–1.1)	
			p for trend=0.4	
De Stefani *et al.* (1993)	Men	*Ethanol (mL/day)*		Adjusted for age, residence, education, smoking (pack–years), other types of alcoholic beverage
		Lifetime abstainer	1.0	
		1–36	1.2 (0.7–2.2)	
		37–120	1.3 (0.7–3.1)	
		>120	1.5 (0.9–3.3)	
			p for trend=0.09	
Rachtan & Sokolowski (1997)	Women	Non-drinker	1.0	Estimates only adjusted for age, not for smoking; updated analysis given in Rachtan (2002)
		Rarely	0.9 (0.5–1.8)	
		1–2/month	1.1 (0.5–2.5)	
		At least 1/week	1.2 (0.2–8.5)	
			p for trend=0.958	

Table 2.58 (continued)

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Carpenter *et al.* (1998)	Men and women	*Recent consumption*		Adjusted for age, gender, race, saturated fat consumption, tobacco smoking (pack–years), years since quitting tobacco smoking, other types of alcoholic beverage
		Never to 3 drinks/month	1.0	
		1–6 drinks/week	0.7 (0.4–1.3)	
		≥1 drink/day	0.8 (0.3–1.9)	
			p for trend=0.66	
		Consumption between age 30 and 40 years		
		Never to 3 drinks/month	1.0	
		1–6 drinks/week	0.8 (0.5–1.3)	
		≥1 drink/day	0.6 (0.3–1.3)	
			p for trend=0.16	
De Stefani *et al.* (2002)	Men	*Alcohol (mL/day)*		Adenocarcinoma only; adjusted for age, residence, urban/rural status, education, family history of lung cancer in first-degree relatives, body mass index, smoking status, cigarettes per day, years since quitting, age at start of smoking, other types of alcoholic beverage; [for exclusive consumption of a specific alcoholic beverages, total alcohol intake might also be adjusted for].
		Non-drinker	1.0	
		1–60	0.6 (0.3–1.2)	
		61–120	0.6 (0.3–1.2)	
		>120	0.4 (0.2–1.1)	
			p for trend=0.09	
		Abstainer	1.0	
		Wine only	0.7 (0.4–1.4)	
Hu *et al.* (2002)	Women	*Servings/week*		Never smokers only; adjusted for age, province, education, social class
		0	1.0	
		≤0.5	0.7 (0.4–1.2)	
		>0.5	0.7 (0.4–1.2)	
			p for trend=0.10	

Table 2.58 (continued)

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Rachtan (2002)	Women	*Frequency*		Adjusted for age only; estimates not adjusted for smoking [Unit of time not given]
		Non-drinker	1.0	
		Rarely	1.3 (0.9–1.9)	
		≥3 times/month	2.0 (1.2–3.3)	
			p for trend=0.007	
		Average amount (g)		
		Non-drinker	1.0	
		≤70	1.1 (0.8–1.7)	
		>70	2.6 (1.6–4.4)	
			p for trend=0.001	
		Drinking duration (years)		
		Non-drinker	1.0	
		≤29	1.4 (0.8–2.4)	
		≥30	1.6 (1.1–2.3)	
			p for trend=0.021	
Freudenheim *et al.* (2003)	Men and women	*Lifetime consumption* (L)		Adjusted for age, education, race, sex, body mass index, vegetable intake, fruit intake, total energy intake excluding alcohol, packs smoked per year, years smoked, index of passive smoking exposure to smoke at home, work, in other settings
		0	1.0	
		≤19	0.9 (0.5–1.4)	
		>19	0.8 (0.5–1.3)	
			p for trend=0.06	
		Consumption in previous 12–24 months (L)		
		0	1.0	
		≤1.0	0.7 (0.4–1.3)	
		>1.0	0.7 (0.4–1.3)	
			p for trend=0.10	

Table 2.58 (continued)

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Ruano-Ravina *et al.* (2004)	Men and women	Non-drinker	1.0	Adjusted for age, sex, occupation, smoking habit (total lifetime tobacco consumption in thousands of packs), total alcohol intake
		White	1.5 (0.5–4.4)	
		Red	0.4 (0.2–1.0)	
		Rosé	0.4 (0.1–1.4)	
		All types	0.5 (0.2–1.4)	
		Continuous variable		
		Red (glasses/day)	0.9 (0.8–1.0)	
		White (glasses/day)	1.2 (1.0–1.4)	
		Rosé (glasses/day)	1.0 (0.8–1.1)	
Benedetti *et al.* (2006)	Men (Study I)	Never weekly	1.0	Adjusted for age, smoking status, cigarette–years, time since quitting, respondent status, ethnicity, census tract income, years of schooling
		1–6 drinks/week	1.4 (1.0–1.9)	
		≥7 drinks/week	0.7 (0.4–1.1)	
	Men (Study II)	Never weekly	1.0	
		1–6 drinks/week	0.6 (0.4–0.8)	
		≥7 drinks/week	0.8 (0.5–1.1)	
	Women (Study II)	Never weekly	1.0	
		1–6 drinks/week	0.3 (0.2–0.4)	
		≥7 drinks/week	0.7 (0.4–1.2)	

CI, confidence interval

In a pooled analysis (Freudenheim *et al*., 2005), a positive association was detected among men who drank one measure of liquor per day or more, with a significant dose–response relationship. No association was observed among women.

Liquor consumption was found to be positively associated with the risk for lung cancer in three (Carpenter *et al*., 1998; De Stefani *et al*., 2002; Rachtan, 2002) of 11 case–control studies that reported tobacco smoking-adjusted odds ratio estimates for liquor consumption (Table 2.60). The strongest association was found in the study by Rachtan (2002), in which Polish women who consumed ≥100 g alcohol from liquor per week (approximately one measure per day) had an eightfold greater risk for lung cancer than non-drinking women (95% CI, 2.9–21.2).

2.10.4 *Studies stratified by tobacco-smoking status (Tables 2.61 and 2.62)*

Studies based on never smokers may be the most valid approach to study the carcinogenicity of alcoholic beverages in the lung. In smokers, tobacco smoking may modify the effect of alcohol consumption and heterogeneity of risk may exist between populations with different smoking patterns. One of the proposed mechanisms for the carcinogenic effect of alcoholic beverages is that they may act as a solvent for tobacco-associated carcinogens. It is therefore important to examine the effect of alcoholic beverage consumption among both never smokers and smokers, and to study the interaction between these two risk factors. Tables 2.61 and 2.62 summarize the results from cohort and case–control studies that presented relative risks for alcoholic beverage use by smoking category.

Results from two cohort studies (Nishino *et al*., 2006; Rohrmann *et al*., 2006) did not seem to suggest an interaction between smoking status (never, former and current) and alcoholic beverage consumption, although a *p*-value for a formal test of interaction was not available. [These analyses may have the limitation that most of the cases of lung cancer were smokers.]

In a pooled analysis (Freudenheim *et al*., 2005), no obvious interaction was suggested following stratification by smoking status among women. A positive association was only found among male never smokers but not among male former or current smokers, which suggests a heterogeneity of the effect of alcoholic beverages by smoking status in men.

Since most cases of lung cancer are smokers, several cohort and case–control studies examined the effect of alcoholic beverages according to the amount smoked. Woodson *et al*. (1999) conducted a cohort study with detailed analyses of the effect of alcoholic beverage according to intake by smoking behaviour, characterized by the number of cigarettes per day, duration of smoking, frequency of inhaling and time since quitting. No obvious differences in the relative risks were found across these smoking categories. Most of the case–control studies reported significant positive associations only among smokers or greater risk estimates among heavier smokers than among lighter smokers (Herity *et al*., 1982; De Stefani *et al*., 1993; Dosemeci *et al*., 1997; Zang & Wynder, 2001; Benedetti *et al*., 2006 [men only]).

Table 2.59 Cohort studies of liquor consumption and lung cancer

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Pollack *et al.* (1984)	Men	*oz/month*		Adjusted for age, cigarette-smoking status (never, former, current smokers), alcohol content of the other two types of beverage (if significant); [read from graph]
		Non-whiskey drinker	1.0	
		1–4	[1.1] [0.6–2.0]	
		5–49	[1.0] [0.5–2.1]	
		≥50	2.6 [1.3–5.0]	
Chow *et al.* (1992)	Men	*Times/month*		Adjusted for age, industry/occupation, smoking status (never any tobacco, other tobacco only, occasional/past use of 1–19, 20–29, ≥30 cigarettes/day, current use of 1–19, 20–29, ≥30 cigarettes/day)
		Never drank	1.0	
		<3	1.3 (0.9–2.0)	
		3–5	1.3 (0.8–2.1)	
		6–13	1.3 (0.7–2.2)	
		>13	1.0 (0.5–1.8)	
		Former drinker	1.9 (1.1–3.1)	
Potter *et al.* (1992)	Women	Non-drinker	1.0	Adjusted for smoking (pack–years)
		≥1/day	1.1 (0.6–2.3)	
Woodson *et al.* (1999)	Men	*Ethanol (g/day)*		Adjusted for age, body mass index, years smoked, cigarettes per day, intervention group
		Non-drinker	1.1 (0.9–1.3)	
		Q1 0.01–2.6	1.0	
		Q2 2.7–10.6	1.0 (0.9–1.3)	
		Q3 10.7–22.7	1.1 (0.9–1.3)	
		Q4 22.8–160.0	1.1 (0.9–1.3)	
			p for trend=0.12	
Prescott *et al.* (1999)		*Drinks/week*		Adjusted for age, study cohort, education, smoking (current smoking: pack–years, duration of smoking), other types of alcoholic beverage
	Men	<1	1.0	
		1–13	1.2 (0.97–1.5)	
		>13	1.5 (0.99–2.1)	
	Women	<1	1.0	
		1–13	0.8 (0.6–1.2)	
		>13	0.7 (0.2–2.2)	

Table 2.59 (continued)

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Freudenheim *et al*. (2005) Pooled analysis of 7 prospective studies		*g/day*		Adjusted for education, body mass index, energy intake, other types of alcoholic beverage, smoking status (never, past, current), smoking duration for past and current smokers, cigarettes smoked daily for current smokers
	Men	None	1.0	
		>0–<5	1.2 (0.98–1.4)	
		5–<15	1.0 (0.8–1.2)	
		≥15	1.3 (1.1–1.7)	
			p for trend=0.04	
	Women	None	1.0	
		>0–<5	0.9 (0.7–1.0)	
		5–<15	0.8 (0.6–1.1)	
		≥15	1.0 (0.8–1.2)	
			p for trend=0.52	

CI, confidence interval

Table 2.60 Case–control studies of liquor consumption and lung cancer

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Williams & Horm (1977)	Men	Non-drinker	1.0 (not given)	Adjusted for age, race, smoking; controls included colon and liver cancer
		<51 jigger–years	0.9	
		≥51 jigger–years	1.1	
	Women	Non-drinker	1.0	
		<51 jigger–years	1.2	
		≥51 jigger–years	0.6	
Mettlin (1989)	Men and women	*Times/week*		Adjusted for age, residence, sex, smoking history [pack–years or similar index of exposure], β-carotene intake index, education
		Never	1.0	
		<1	0.7 (0.5–1.0)	
		1–3	0.9 (0.6–1.5)	
		4–9	0.6 (0.4–0.9)	
		≥10	0.7 (0.4–1.1)	
Bandera *et al.* (1992)	Men	*Drinks/month*		Adjusted for age, education, smoking (pack–years); no obvious interaction between liquor consumption and smoking was observed.
		0	1.0	
		1–8	0.6 (0.4–1.0)	
		≥9	1.1 (0.7–1.6)	
			p for trend=0.1	
De Stefani *et al.* (1993)	Men	*Ethanol (mL/day)*		Adjusted for age, residence, education, smoking (pack–years), other types of alcoholic beverage
		Lifetime abstainer	1.0	
		1–34	0.9 (0.6–1.6)	
		35–115	1.3 (0.8–2.6)	
		>115	1.1 (0.6–1.4)	
			p for trend=0.50	
Rachtan & Sokolowski (1997)	Women	*Vodka*		Adjusted for pack–years smoked, carrot intake, margarine on bread
		Non-drinker	1.0	
		1–2/month	2.6 (1.3–5.5)	
		At least 1/week	7.5 (0.8–71.0)	

Table 2.60 (continued)

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Carpenter *et al.* (1998)	Men and women	*Recent consumption*		Adjusted for age, gender, race, saturated fat consumption, tobacco smoking (pack–years), years since quitting tobacco smoking, other types of alcoholic beverage
		Never to 3 drinks/month	1.0	
		1–6 drinks/week	1.2 (0.7–2.2)	
		≥1 drink/day	1.9 (1.0–3.4)	
			p for trend=0.06	
		Consumption between age 30 and 40 years		
		Never to 3 drinks/month	1.0 (0.7–1.5)	
		1–6 drinks/week	1.0 (1.1–3.2)	
		≥1 drink/day	1.8	
			p for trend=0.06	
De Stefani *et al.* (2002)	Men	*Ethanol (ml/day)*		Adenocarcinoma only; adjusted for age, residence, urban/rural status, education, family history of lung cancer in first-degree relatives, body mass index, smoking status, cigarettes per day, years since quit, age at start of smoking, other types of alcoholic beverage; [for exclusive consumption of a specific alcoholic beverage, total alcohol intake might also be adjusted for].
		Non-drinker	1.0	
		1–60	1.5 (0.8–2.6)	
		61–120	2.9 (1.4–6.2)	
		>120	1.4 (0.7–3.0)	
			p for trend=0.09	
		Abstainer	1.0	
		Liquor only	2.1 (0.9–4.9)	
Hu *et al.* (2002)	Women	*Servings/week*		Never smokers only; adjusted for age, province, education, social class
		0	1.0	
		≤0.5	1.1 (0.6–2.1)	
		>0.5	1.1 (0.6–2.1)	
			p for trend=0.58	
Rachtan (2002)	Women	*Average amount (g)*		Adjusted for age, pack–years of smoking, passive smoking, siblings with cancer, tuberculosis, place of residence, occupational exposure, dietary factors [unit of time not given]
		Non-drinker	1.0	
		<100	2.2 (1.3–3.8)	
		≥100	7.8 (2.9–21.2)	
			p for trend<0.0001	

Table 2.60 (continued)

Reference	Subjects	Exposure categories	Relative risk (95% CI)	Comments
Freudenheim *et al.* (2003)	Men and women	*Lifetime consumption (L)*		Adjusted for age, education, race, sex, body mass index, vegetable intake, fruit intake, total energy intake excluding alcohol, packs smoked per year, years smoked, index of passive smoking exposure to smoke at home, work, in other settings
		0	1.0	
		≤28	1.2 (0.8–1.9)	
		>28	0.8 (0.5–1.2)	
			p for trend=0.44	
		Consumption in previous 12–24 months (L)		
		0	1.0	
		≤1.0	0.6 (0.3–1.2)	
		>1.0	0.9 (0.5–1.5)	
			p for trend=0.47	
Ruano-Ravina *et al.* (2004)	Men and women	Non-drinker	1.0	Adjusted for age, sex, occupation, smoking habit (total lifetime tobacco consumption in thousands of packs), total alcoholic beverage intake
		Drinker	1.6 (0.8–3.4)	
		Continuous variable		
		Liquor (weekly unit)	1.0 (1.0–1.1)	
Benedetti *et al.* (2006)	Men (Study I)	Never weekly	1.0	Adjusted for age, smoking status, cigarette–years, time since quitting, respondent status, ethnicity, census tract income, years of schooling
		1–6 drinks/week	1.4 (1.0–1.9)	
		≥7 drinks/week	1.2 (0.8–1.7)	
	Men (Study II)	Never weekly	1.0	
		1–6 drinks/week	0.9 (0.7–1.2)	
		≥7 drinks/week	0.9 (0.7–1.3)	
	Women (Study II)	Never weekly	1.0	
		1–6 drinks/week	0.4 (0.3–0.6)	
		≥7 drinks/week	1.7 (0.8–3.5)	

CI, confidence interval

Table 2.61 Cohort studies of alcoholic beverage consumption and lung cancer stratified by smoking status

Reference	Subjects and smoking status	Exposure categories	Risk ratio (95% CI)					Comments
Murata *et al.* (1996)	Ethanol (ml/day)		>0 and ≤27	>27				Reference, 0 mL/day; crude CI from data matched on age
	Men							
	Never smokers + former smokers		1.3 [(0.5–3.2)]	2.2 [(0.8–6.1)]				
	Current smokers		0.7 [(0.3–1.6)]	1.5 [(0.7–3.0)]				
Woodson *et al.* (1999)	Alcohol (g/day)		Non-drinker	5.3–13.3	13.4–27.6	≥27.7	*p* for trend	Reference, 0–5.2 g/day; all smokers; smokers defined as men who smoked 5 or more cigarettes per day; cut-offs for alcohol based on quartiles; adjusted for age, body mass index, years smoked, cigarettes per day, treatment group
	Men							
	Cigarettes/ day							
	<20		1.2 (0.8–1.7)	0.9 (0.7–1.3)	0.9 (0.6–1.3)	1.2 (0.8–1.7)	0.59	
	20–29		1.2 (0.9–1.6)	1.1 (0.8–1.4)	1.0 (0.7–1.3)	1.0 (0.8–1.4)	0.99	
	≥30		1.0 (0.6–1.6)	0.9 (0.6–1.3)	0.8 (0.5–1.2)	0.8 (0.5–1.2)	0.26	
	Years smoked							
	<32		1.4 (0.7–2.9)	1.1 (0.6–2.1)	1.1 (0.6–2.1)	1.0 (0.5–1.9)	0.87	
	32–40		1.4 (1.0–2.0)	1.1 (0.8–1.5)	1.1 (0.8–1.5)	1.3 (0.9–1.7)	0.16	
	>40		1.0 (0.8–1.3)	0.9 (0.7–1.2)	0.8 (0.6–1.0)	0.9 (0.7–1.1)	0.13	
	Inhaled							
	Seldom		1.4 (0.7–2.8)	0.8 (0.4–1.7)	0.7 (0.3–1.5)	0.7 (0.3–1.7)	0.37	
	Often		1.4 (1.0–2.0)	1.2 (0.9–1.5)	1.1 (0.8–1.5)	1.1 (0.8–1.5)	0.81	
	Always		1.0 (1.0–1.3)	0.9 (0.7–1.1)	0.8 (0.7–1.1)	1.0 (0.8–1.2)	0.84	
	Cessation							
	<3 years		1.2 (0.7–2.0)	0.8 (0.5–1.4)	1.1 (0.6–2.0)	0.9 (0.5–1.8)	0.67	
	>3 years		1.2 (0.6–2.6)	0.9 (0.4–1.8)	0.8 (0.4–1.7)	1.5 (0.7–3.2)	0.81	
	Never		1.2 (0.9–1.5)	1.0 (0.8–1.2)	0.9 (0.7–1.1)	1.0 (0.8–1.2)	0.16	

Table 2.61 (continued)

Reference	Subjects and smoking status	Exposure categories	Risk ratio (95% CI)				Comments
Freudenheim *et al.* (2005)	Alcohol (g/day)		>0–<5	5–<15	≥15	*p* for trend	Reference, 0 g/day; adjusted for education, body mass index, energy intake; for former smokers, also adjusted for smoking duration; for current smokers, also adjusted for smoking duration and cigs/day
	Men						
	Nonsmoker		1.5 (0.6–3.5)	2.5 (1.1–5.8)	6.4 (2.7–14.9)	<0.01	
	Former smoker		0.7 (0.5–1.0)	0.9 (0.7–1.2)	0.9 (0.7–1.3)	0.27	
	Current smoker		0.9 (0.5–1.4)	1.0 (0.8–1.4)	0.9 (0.7–1.2)	0.92	
	Current smoker (<20 cigs/day)		0.8 (0.4–1.7)	1.0 (0.7–1.5)	0.8 (0.5–1.1)	0.12	
	Women						
	Nonsmoker		1.0 (0.7–1.4)	0.9 (0.5–1.5)	1.4 (0.6–2.9)	0.98	
	Former smoker		0.7 (0.4–1.2)	0.9 (0.6–1.2)	1.1 (0.7–1.8)	0.26	
	Current smoker		0.8 (0.6–1.0)	0.9 (0.7–1.1)	1.1 (0.9–1.3)	0.02	
	Current smoker (<20 cigs/day)		0.6 (0.4–0.9)	0.8 (0.6–1.1)	0.9 (0.7–1.3)	0.42	

Table 2.61 (continued)

Reference	Subjects and smoking status	Exposure categories	Risk ratio (95% CI)						Comments
Nishino *et al*. (2006)	Ethanol (g/day)		Ever drinker	≤24.9	25.0–49.9	≥50	*p* for trend	Former drinker	Reference, never drinker; adjusted for age, family history of lung cancer, intake of green leafy vegetables, oranges, other fruits
	Men								
	Never smoker		1.2 (0.4–3.5)	1.1 (0.4–3.5)	0.4 (0.0–3.2)	1.2 (0.1–10.0)	0.61	4.2 (1.1–15.7)	
	Former smoker		0.7 (0.4–1.3)	0.6 (0.4–1.2)	0.7 (0.3–1.3)	0.3 (0.1–1.5)	0.13	1.4 (0.7–2.6)	
	Current smoker								
	≤20 cigs/day		0.9 (0.6–1.3)	0.8 (0.5–1.2)	0.8 (0.5–1.3)	1.1 (0.6–2.0)	0.99	1.3 (0.7–2.4)	
	>20 cigs/day		1.3 (0.7–2.5)	0.7 (0.3–1.7)	1.5 (0.7–3.0)	1.3 (0.6–2.9)	0.20	2.6 (1.1–6.1)	

Table 2.61 (continued)

Reference	Subjects and smoking status	Exposure categories	Risk ratio (95% CI)						Comments
Rohrmann *et al.* (2006)	Ethanol (g/day)		Non-drinker	5–14.9	15–29.9	30–59.9	≥60	*p* interaction	Reference, 0.1–4.9 g/day; all results stratified by age, sex, study centre; adjusted for height, weight, consumption of fruit, red meat, processed meat, education, total non-ethanol energy intake; for former smokers, also adjusted for smoking duration, time since quitting; for current smokers, also adjusted for smoking duration, cigs/day
	Men and women								
		Baseline intake							
	Never smoker		0.6 (0.3–1.2)	0.9 (0.6–1.5)	0.7 (0.3–1.4)	0.6 (0.2–1.8)			
	Former smoker		1.5 (1.0–2.2)	0.7 (0.5–1.0)	0.7 (0.5–1.0)	0.9 (0.6–1.3)	0.9 (0.5–1.7)	0.64	
	Current smoker		1.3 (1.0–1.7)	0.8 (0.6–1.0)	0.9 (0.7–1.2)	1.0 (0.8–1.3)	0.9 (0.7–1.2)		
		Mean lifelong intake							
	Never smoker		0.5 (0.2–1.2)	0.5 (0.3–0.8)	0.6 (0.3–1.5)	0.4 (0.1–3.0)	1.2 (0.1–13.6)		
	Former smoker		1.9 (0.9–4.2)	1.1 (0.8–1.6)	1.3 (0.9–2.0)	1.3 (0.8–2.2)	1.7 (0.9–3.5)	0.22	
	Current smoker		1.0 (0.6–1.8)	0.8 (0.6–1.0)	0.9 (0.7–1.2)	0.8 (0.6–1.1)	1.2 (0.8–1.7)		

CI, confidence interval

Table 2.62 Case–control studies of alcoholic beverage consumption and lung cancer stratified by smoking status

Reference	Subjects	Smoking status	Exposure categories	Odds ratio (95% CI)			Comments
Herity *et al.* (1982)			Intake (g/day for 10 years)	0–<90	≥90		[Assuming 20 cigarettes/pack]
	Men	0–<43 pack–years		1.0	1.5 (0.4–5.2)		
		≥43 pack–years		10.6 (4.6–24.1)	12.4 (5.4–28.4)		
Bandera *et al.* (1992)			Drinks/month	≥ 21	*p* for trend		Reference, 0–20 drinks/month; adjusted for age, smoking, education; no obvious interaction between beer, wine or liquor consumption and smoking observed
	Men	0–40 pack–years		0.9 (0.6–1.6)	0.10		
		>40 pack–years		1.6 (1.0–2.5)	0.03		
De Stefani *et al.* (1993)			Beer (mL/day)	1–9	10–59	≥60	Reference, non-drinkers; adjusted for age, residence
	Men	0–19 cigs/day		0.4 (0.1–2.2)	–	2.9 (0.5–15.7)	
		≥20 cigs/day		0.9 (0.4–2.0)	2.4 (0.6–8.9)	4.2 (1.4–12.6)	

Table 2.62 (continued)

Reference	Subjects	Smoking status	Exposure categories	Odds ratio (95% CI)				Comments
Dosemeci *et al.* (1997)			Duration (years)	Never drank	1–20	≥21		Reference, never smoker and never drinker
	Men	Never smoker		1.0	–	–		
		1–20 cigs/day		2.8 (2.1–3.6)	4.4 (2.6–7.3)	5.2 (2.0–14.6)		
		≥21 cigs/day		6.1 (4.0–9.3)	8.5 (2.5–14.3)	14.1 (3.9–61.2)		
Zang & Wynder (2001)			'Whiskey-equivalent' oz/day	0	1–5.9	≥6		Reference, non-drinkers and nonsmokers; data for current smokers only also reported
	Men	Nonsmoker		1.0	1.2 (0.7–2.1)	0.7 (0.2–2.0)		
		<20 cigs/day		6.2 (3.5–11.0)	7.4 (4.8–11.5)	8.3 (5.3–13.1)		
		20 cigs/day		13.8 (8.2–21.5)	14.6 (10.0–21.5)	15.4 (10.4–22.8)		
		>20 cigs/day		26.3 (18.0–38.6)	25.9 (18.4–36.4)	26 (18.6–36.5)		
Rachtan (2002)			Alcohol (g/week)	≥1–4	≥4–8	≥1–8	>8	Reference, <1 g/week; nonsmokers were never smokers
	Women	Nonsmoker		3.9 (1.8–8.3)	8.8 (2.8–27.3)		12.1 (3.9–36.9)	
		Current smoker				2.5 (1.2–5.1)	3.7 (1.7–8.2)	
		Current + former smoker				2.8 (1.5–5.1)	5.0 (2.5–9.9)	
			Vodka drinking	Non-drinker	Drinker			Reference, nonsmoker/non-drinker
		Nonsmoker		1.0	3.5 (1.9-6.4)			
		Smoker		10.5 (5.8-19.2)	20.2 (11.7-35.0)			

Table 2.62 (continued)

Reference	Subjects	Smoking status	Exposure categories	Odds ratio (95% CI)		Comments
Benedetti *et al.* (2006)		Cigarette–years	Drinks/week	1–6	≥7	Reference, never weekly; adjusted for age, respondent status, ethnicity, smoking status, cigarette–years, socioeconomic status, years of schooling, time since quitting. *Odds ratio for women consuming 1 or more beer weekly compared with women who never consumed beer on a weekly basis
			Total alcohol			
	Study I	<825		1.0 (0.5–1.8)	1.3 (0.7–2.4)	
	Men	825–1375		1.1 (0.6–2.0)	1.1 (0.6–2.0)	
		>1375		1.8 (0.8–4.3)	1.5 (0.8–3.1)	
			p for interaction	0.26	0.52	
	Study II	<675		0.3 (0.1-0.6)	0.7 (0.4–1.2)	
	Men	675–1270		1.4 (0.8–2.6)	1.9 (1.1–3.4)	
		>1270		1.9 (1.0–3.7)	1.6 (0.9–2.8)	
			p for interaction	0.00	0.06	
	Women	0		0.2 (0.0–0.6)	1.1 (0.4–3.3)	
		≤861		0.6 (0.3–1.1)	0.9 (0.5–1.8)	
		>861		0.2 (0.1–0.4)	0.5 (0.2–1.0)	
			p for interaction	0.70	0.54	
			Beer			
	Study I	<825		0.9 (0.5–1.6)	1.3 (0.7–2.3)	
	Men	825–1375		1.4 (0.8–2.5)	1.8 (1.0–3.0)	
		>1375		1.4 (0.7–3.0)	1.4 (0.7–2.6)	
			p for interaction	0.15	0.35	
	Study II	<675		0.6 (0.3–1.2)	0.9 (0.5–1.8)	
	Men	675–1270		1.1 (0.7–1.8)	1.4 (0.8–2.2)	
		>1270		1.3 (0.8–2.4)	0.9 (0.5–1.5)	
			p for interaction	0.00	0.88	
	Women	0		0.5 (0.3–0.9)*	–	
		≤861		0.3 (0.2–0.6)	0.7 (0.3–1.7)	
		>861		0.4 (0.2–0.7)	1.0 (0.4–2.7)	
			p for interaction	0.27	1.00	

Table 2.62 (continued)

Reference	Subjects	Smoking status	Exposure categories	Odds ratio (95% CI)		Comments
Benedetti *et al.* (2006) (contd)		Cigarette–years	Drinks/week	1–6	≥7	
			Wine	1.1 (0.6–1.7)	1.2 (0.6–2.4)	
	Study I	<825		1.3 (0.8–2.1)	0.3 (0.1–0.7)	**Odds ratio for women consuming 1 or more drinks of spirits weekly compared with women who never consumed spirits on a weekly basis
	Men	825–1375		1.9 (1.0–3.8)	0.6 (0.3–1.5)	
		>1375	*p* for interaction	0.16	0.19	
	Study II	<675		0.4 (0.2–0.8)	0.6 (0.3–1.2)	
	Men	675–1270		0.5 (0.3–0.8)	0.8 (0.5–1.4)	
		>1270		0.8 (0.5–1.3)	0.8 (0.4–1.6)	
			p for interaction	0.01	0.07	
	Women	0		0.2 (0.1–0.6)	0.7 (0.2–2.5)	
		≤861		0.3 (0.2–0.7)	1.2 (0.5–2.5)	
		>861		0.2 (0.1–0.4)	0.3 (0.1–0.7)	
			p for interaction	0.83	0.27	
			Spirits			
	Study I	<825		1.3 (0.8–2.2)	1.0 (0.5–2.2)	
	Men	825–1375		1.0 (0.7–1.6)	1.0 (0.5–1.8)	
		>1375		2.2 (1.1–4.1)	1.5 (0.7–3.0)	
			p for interaction	0.41	0.67	
	Study II	<675		0.6 (0.3–1.3)	1.4 (0.6–3.1)	
	Men	675–1270		1.1 (0.7–1.8)	1.2 (0.6–2.1)	
		>1270		0.9 (0.5–1.4)	0.7 (0.4–1.2)	
			p for interaction	0.19	0.25	
	Women	0		0.8 (0.5–1.5)**	–	
		≤861		0.5 (0.3–1.0)	1.0 (0.4–2.7)	
		>861		0.3 (0.2–0.6)	1.8 (0.5–6.0)	
			p for interaction	0.92	0.80	

CI, confidence interval

2.10.5 *Studies among nonsmokers (Tables 2.63 and 2.64)*

Residual confounding by tobacco smoking is a concern when interpreting the associations between alcoholic beverage intake and lung cancer. Restricting the analysis to never smokers appears to be an effective strategy to provide further insight on this topic, although secondhand tobacco smoke might still be a concern.

Korte *et al*. (2002) reported the unpublished data from the Cancer Prevention Study (CPS) I and II (Table 2.63). In CPS I, an increased risk for lung cancer was associated with drinking ≥500 g alcohol per month among both men and women who had never smoked. This association was not observed in CPS II.

A pooled study (Freudenheim *et al*., 2005), based on seven cohorts, found an elevated pooled relative risk for alcoholic beverage consumption among never-smoking men (a dose–response was also observed), but not among never-smoking women.

Two cohort studies published subsequently reported a null association among never smokers, with adjustment for dietary factors. Both studies examined higher levels of alcoholic beverage drinking than those studied previously (Nishino et al., 2006: ≥50 g of ethanol per day [~4 drinks/day]; Rohrmann *et al*., 2006: ≥60 g of ethanol per day [~5 drinks/day]), although the number of cases at these levels of drinking was small.

Seven case–control studies included never smokers only as the study subjects or stratified analyses to never smokers (Table 2.64). [Analyses stratified to never smokers often suffer from the small number of lung cancer cases that arise among never smokers and result in wide confidence intervals.] In the three studies based on populations of never smokers (Kabat & Wynder, 1984; Koo, 1988; Hu *et al*., 2002), no significant differences in alcoholic beverage intake were found between cases and controls. [One limitation of such a design is the lack of power to examine the risk associated with heavy drinking, as it is uncommon to find heavy drinkers among never smokers. For example, Hu *et al*. (2002) compared drinkers of 1 serving/week and >1 serving per week with non-drinkers which reflects the low drinking level in this group of women and which is likely to contribute to the null association observed in this study.] In contrast, Rachtan (2002) identified a significantly elevated risk associated with even a moderate level of alcoholic beverage intake among Polish women who never smoked (e.g. odds ratio, 8.8; 95% CI, 2.8–27.3 for 4–8 g alcohol per week [approximately 0.3–0.6 drinks/week]). A strong dose–response was also observed. [The magnitude of the risk estimates seems unlikely for these levels of alcoholic beverage drinking. This result may represent a chance finding, confounding or population/environmental characteristics that are specific to this study.]

2.10.6 *Population characteristics*

There are currently no sufficient data to examine whether the effect of alcoholic beverages differ among men and women and among populations of different ethnic origins. Studies that consisted of men only or women only are often not comparable due

Table 2.63 Cohort studies of alcoholic beverage consumption and lung cancer among nonsmokers

Reference	Subjects	Exposure category	No. of cases	Risk ratio (95% CI)	Comments
Murata *et al.* (1996)	Men	*Ethanol (mL/day)*	13	1.0	Nonsmokers included never smokers and past smokers; no other adjustment [crude CI calculated from data matched on age]
		Non-drinker	10	1.3 [0.5–3.2]	
		>0–≤27	8	2.2 [0.8–6.1]	
		>27			
Korte *et al.* (2002)	*CPS I*	*Ethanol (g/month)*	Not provided		Definition of nonsmokers in CPS I: lifetime never smokers; definition of nonsmokers in CPS II: <1 cigarette–year, pipe–year or cigar–year (<0.05 pack–years)
	Men	Non-drinker		1.0	
		1–499		1.1 (1.0–1.2)	
		≥500		1.4 (1.2–1.5)	
	Women	Non-drinker		1.0	
		1–499		1.2 (0.8–1.6)	
		≥500		2.0 (1.2–3.2)	
	CPS II				
	Men	Non-drinker		1.0	
		1–499		0.95 (0.6–1.6)	
		≥500		1.2 (0.7–2.2)	
	Women	Non-drinker		1.0	
		1–499		1.3 (0.9–1.9)	
		≥500		0.6 (0.3–1.2)	
Freudenheim *et al.* (2005)		*Alcohol (g/day)*			Adjusted for education, body mass index, energy intake
	Men	0	10	1.0	
		>0–<5	16	1.5 (0.6–3.5)	
		5–<15	18	2.5 (1.1–5.8)	
		≥15	30	6.4 (2.7–14.9)	
				p for trend<0.001	
	Women	0	90	1.0	
		>0–<5	68	0.98 (0.7–1.4)	
		5–15	17	0.9 (0.5–1.5)	
		≥15	8	1.4 (0.6–2.9)	
				p for trend=0.98	

Table 2.63 (continued)

Reference	Subjects	Exposure category	No. of cases	Risk ratio (95% CI)	Comments
Nishino *et al.* (2006)	Men	*Ethanol (g/day)*			Adjusted for age, family history of lung cancer, intake of green leafy vegetables, oranges, other fruits
		Never drinker	5	1.0	
		Ever drinker	13	1.2 (0.4–3.5)	
		Current drinker			
		<25.0	7	1.1 (0.4–3.5)	
		25.0–49.9	1	0.4 (0.0–3.2)	
		≥50.0	1	1.2 (0.1–10.0)	
				p for trend=0.61	
		Former drinker	4	4.2 (1.1–15.7)	
Rohrmann *et al.* (2006)	Men and women	**Ethanol (g/day)**			All results stratified by age, sex, study centre; adjusted for height, weight, consumption of fruit, red meat, processed meat, education, physical activity, total non-ethanol energy intake; definition for never-smoking not provided
		Baseline intake			
		Non-drinker	14	0.6 (0.3–1.2)	
		0.1–4.9	44	1.0	
		5–14.9	27	0.9 (0.6–1.5)	
		15–29.9	9	0.7 (0.3–1.4)	
		30–59.9	3	0.6 (0.2–1.8)	
		≥60	0		
		Mean lifelong intake			
		Non-drinker	7	0.5 (0.2–1.2)	
		0.1–4.9	43	1.0	
		5–14.9	14	0.5 (0.3–0.8)	
		15–29.9	6	0.6 (0.3–1.5)	
		30–59.9	1	0.4 (0.1–3.0)	
		≥60	1	1.2 (0.1–13.6)	

CI, confidence interval; CPS, Cancer Prevention Study

Table 2.64 Case–control studies of alcoholic beverage consumption and lung cancer among nonsmokers

Reference	Subjects	Exposure category	Exposed cases	Odds ratio (95% CI)	Comments
Kabat & Wynder (1984)	Men and women	Not specified	Not reported	No significant difference in alcoholic beverage intake found between cases and controls for either sex	No odds ratio reported; nonsmoker defined as someone who had never smoked as much as one cigarette, pipe or cigar per day for 1 year.
Koo (1988)	Women	<1 time/week ≥1 time/week	61 27	1.0 (0.93–3.70) 1.9 *p* for trend=0.076	Never smokers defined as those who had smoked less than 20 cigarettes or pipes in the past; adjusted for age, no. of live births, schooling.
Mayne *et al.* (1994)	Men and women	*Beer (times/ month)* Q1 Q2 Q3 Q4	Not given	 1.0 (not given) 1.1 0.9 1.2 *p* for trend=NS	Nonsmokers included never smokers (not smoked more than 100 cigarettes) and former smokers (had smoked at some time but had not smoked more than 100 cigarettes in the past 10 years); adjusted for age, sex, county of residence, smoking history, cigs/day smoked by former smokers, religion, education, body mass index, income
Zang & Wynder (2001)	Men	*Current 'whiskey–equivalent' (oz/ day)* 0 1–5.9 ≥6	 23 26 4	 1.0 1.2 (0.7–2.1) 0.7 (0.2–2.0)	Nonsmokers were those who had never smoked at least one cigarette per day for at least 1 year; adjusted for body mass index, age

Table 2.64 (continued)

Reference	Subjects	Exposure category	Exposed cases	Odds ratio (95% CI)	Comments
Hu *et al*. (2002)	Women	**Servings/week**			Nonsmokers were never smokers; adjusted for age, province, education, social class
		Total alcohol			
		0	86	1.0	
		1	36	0.8 (0.5–1.4)	
		>1	35	0.8 (0.5–1.2)	
				p for trend=0.25	
		Beer			
		0	127	1.0	
		≤0.5	17	1.2 (0.6–2.4)	
		>0.5	7	0.5 (0.2–1.1)	
				p for trend=0.17	
		Wine			
		0	100	1.0	
		≤0.5	30	0.7 (0.4–1.2)	
		>0.5	25	0.7 (0.4–1.2)	
				p for trend=0.10	
		Liquor			
		0	116	1.0	
		≤0.5	17	1.1 (0.6–2.1)	
		>0.5	21	1.1 (0.6–2.1)	
				p for trend=0.58	

Table 2.64 (continued)

Reference	Subjects	Exposure category	Exposed cases	Odds ratio (95% CI)	Comments
Rachtan (2002)	Women	*Total intake (g/ week)*			Nonsmokers were lifelong nonsmokers; for total alcohol, age was adjusted; for vodka intake, adjusted for age, passive smoking, consumption of milk, butter, margarine, cheese, meat, fruit, vegetables, carrots, spinach, siblings with cancer, tuberculosis, place of residence, occupational exposures
		<1	23	1.0	
		≥1–4	15	3.9 (1.8–8.3)	
		≥4–8	7	8.8 (2.8–27.3)	
		≥8	9	12.1 (3.9–36.9)	
				p for trend<0.001	
		Usual vodka intake(g)			
		Non-drinker	23	1.0	
		<100	25	2.3 (1.1–4.9)	
		≥100	6	15.0 (2.3–96.0)	
				p for trend<0.001	
Benedetti *et al*. (2006)	Women	**Drinks/week**			Nonsmokers defined as those who never smoked regularly; adjusted for age, respondent status, ethnicity, smoking status, cigarette–years, socioeconomic status, years of schooling
		Total alcohol			
		Never weekly	25	1.0	
		1–6	3	0.2 (0.0–0.6)	
		≥7	5	1.1 (0.4–3.3)	
		Beer			
		Never weekly	31	1.0	
		≥1	2	0.5 (0.3–0.9)	
		Wine			
		Never weekly	27	1.0	
		1–6	3	0.2 (0.1–0.6)	
		≥7	3	0.7 (0.2–2.5)	
		Liquor			
		Never weekly	29	1.0	
		≥1	4	0.8 (0.5–1.5)	

CI, confidence interval; NS, not significant

to the different levels of alcoholic beverage exposure in these studies. A few studies conducted analyses stratified by gender using the same exposure categories (Williams & Horm, 1977; Bandera *et al*., 1997; Prescott *et al*., 1999; Korte *et al*., 2002 [CPS I and CPS II]; Pacella-Norman *et al*., 2002; Freudenheim *et al*., 2005; Benedetti *et al*., 2006; Rohrmann *et al*., 2006). There was no obvious heterogeneity between genders based on results of total alcoholic beverage consumption and risk for lung cancer. However, heterogeneity may exist when level of smoking, type of alcoholic beverage and histological type of lung cancer are considered.

2.11 Cancer of the urinary bladder

Information on alcoholic beverage consumption and cancer of the urinary bladder was derived from five cohort (Table 2.65) and 18 case–control (Table 2.66) studies, which included more than 9000 cases in total.

Of the five cohort studies, one investigation in the Netherlands (Zeegers *et al*., 2001) found a relative risk of 1.6 in men who drank ≥30 g ethanol per day, but no trend in risk with dose. The corresponding value for women was 1.0. The other cohort studies, one among Danish brewery workers (Jensen, 1979) and three from selected populations in the USA (Mills *et al*., 1991; Chyou *et al*., 1993; Djoussé *et al*., 2004) found no association between various measures of alcoholic beverage consumption and risk for cancer of the urinary bladder.

In a multicentre case–control study conducted in 1978–79 in 10 areas of the USA (Thomas *et al*., 1983), which included 2982 incident cases, no association was found between urinary bladder cancer and total alcoholic beverage consumption (relative risk for ≥42 drinks per week, 0.99 in men and 0.66 in women) or consumption of beer (relative risk, 0.93 in both sexes combined), wine (relative risk, 0.60) or spirits (relative risk, 1.14). Of the subsequent case–control studies, nine showed some excess risk in (heavy) alcoholic beverage drinkers and eight showed no association. Moreover, the largest studies, conducted in Canada on 1125 cases (Band *et al*., 2005) and in Italy on 727 cases (Pelucchi *et al*., 2002a), also showed no association between various measures of alcoholic beverage consumption and risk for cancer of the urinary bladder.

An explanation for some apparently inconsistent epidemiological findings on alcoholic beverage consumption and cancer of the urinary bladder is that there are different correlates (including tobacco, coffee and diet) of alcoholic beverage drinking in various populations. Alcoholic beverage drinking, in part, may be positively correlated with cigarette smoking, a poorer diet or other recognized risk factors (i.e. social or occupational) for bladder cancer. Thus, residual confounding is possible.

A meta-analysis of 11 studies (two cohort and nine case–control) published between 1966 and 2000 (Bagnardi *et al*., 2001), which included a total of 5997 cases, found relative risks of 1.04 (95% CI, 0.99–1.09) for 25 g, 1.08 (95% CI, 0.98–1.19) for 50 g and 1.17 (95% CI, 0.97–1.41) for 100 g ethanol per day.

Table 2.65 Cohort studies of alcoholic beverage consumption and cancer of the urinary bladder

Reference, location, name of study	Cohort description	Exposure assessment	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Special population								
Jensen (1979), Denmark	14 313 Danish brewery workers employed at least 6 months in 1939–63; followed for cancer incidence and mortality in 1943–73; age not given; workers allowed 2.1 L of free beer/day (77.7 g pure alcohol)	Follow-up 1943–72	Cases and deaths ascertained through Cancer Registry (ICD-7)	All cancers Bladder cancer	1303 75	**SIR** (1.0–1.2) 0.9 (0.7–1.1)	Age, sex, area, time trends	Cancer morbidity and mortality compared with those in the general population

Table 2.65 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
General population								
Mills *et al.* (1991), USA, California Seventh-day Adventists	34 198 white, non-Hispanic Seventh-day Adventists, aged ≥25 years; followed through to 1982; newly diagnosed cancer cases identified by record linkage with the Los Angeles Cancer Surveillance Program and the Resource for Cancer Epidemiology in San Francisco; follow-up 99% complete	Detailed lifestyle and 51-item food-frequency questionnaire in 1976	Bladder (ICD-0, 188); 52 histologically confirmed (36 men, 16 women); 94% transitional-cell carcinomas	*Beer/wine/ liquor (frequency/ week)* <1 ≥1	 45 3	 1.0 (0.6–5.9) 1.5 (0.4–4.9)	 Age, sex Age, sex, smoking	

Table 2.65 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Chyou *et al.* (1993), USA, Japanese–American Cohort study (1965–68)	American men of Japanese ancestry, born 1900–19 and residing on Oahu, Hawaii; identified via the Honolulu Heart Program and through Service draft registration files; of 11 148, 8006 interviewed (72%) in 1965–68; data from 7995 men used; incident cancer cases identified via the Hawaii Cancer Registry; follow-up to May 1991	Interview on smoking history, usual frequency of consumption of 17 food items; a diet recall history (24 h) obtained	96 histologically confirmed cancers in the lower urinary tract (bladder, 83; renal pelvis, 8; ureter, 5); 91% transitional-cell carcinomas	*Total intake (g/day)* 0 <15 >15 *Beer (g/day)* 0 250 >250 *Wine* None Any *Spirits (g/day)* 0 <2 >2	 30 38 27 30 29 29 30 18 30 15 29	 1.0 1.3 (0.8–2.1) 1.2 (0.7–2.0) 1.0 1.4 (0.8–2.3) 1.1 (0.7–1.9 1.0 1.2 (0.7–2.3) 1.0 0.95 (0.5–1.8) 1.7 (0.98–2.8)		

Table 2.65 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Zeegers *et al.* (2001), Netherlands, Netherlands Cohort Study (1986–92)	58 279 men and 62 573 women from 204 municipal population registries, aged 55–69 years in 1986; follow-up, 6.3 years via record linkage with cancer registries and the Dutch database of pathology reports	Self-administered questionnaire; consumption of beer, red and white wine, sherry and other fortified wines, liqueur and liquor noted	Analysis based on 594 cancer cases (517 men, 77 women) of bladder, renal pelvis, ureter, urethra and 3170 sub-cohort members (1591 men, 1579 women)	*Total alcohol intake (g/day)*		**Men**	Age, smoking (status, amount and duration)	
				0	62	1.0		
				<5	108	1.5 (1.0–2.2)		
				5–<15	136	1.5 (1.0–2.2)		
				15–<30	109	1.2 (0.8–1.7)		
				≥30	102	1.6 (1.1–2.5)		
				Beer (g/day)				
				0	62	1.0		
				<5	174	1.4 (0.9–2.0)		
				5–<15	89	1.4 (1.0–2.2)		
				15–<30	22	1.7 (0.9–3.2)		
				≥30	10	1.1 (0.5–2.6)		

Table 2.65 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Zeegers *et al*. (2001) (contd)				*Wine (g/day)*				
				0	62	1.0		
				<5	151	1.5 (1.1–2.2)		
				5–<15	67	1.2 (0.8–1.9)		
				15–<30	25	1.1 (0.7–2.0)		
				≥30	11	1.7 (0.7–4.1)		
				Liquor (g/day)				
				0	62	1.0		
				<5	114	1.4 (1.0–2.1)		
				5–<15	89	1.4 (0.9–2.1)		
				15–<30	70	1.3 (0.8–1.9)		
				≥30	50	1.9 (1.2–3.2)		
				Total intake (g/ day)		**Women**		
				0	25	1.0		
				<5	29	0.97 (0.56–1.69)		
				≥5	33	0.75 (0.41–1.37)		

Table 2.65 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Djoussé *et al.* (2004), USA, Framingham Heart Study	Population-based; nested case–control study within the cohort started in 1948 with 5209 persons; of these, 205 excluded because alcohol data missing; in 1971, the children of the original cohort and their spouses were invited to join the Offspring Study; of the 5124 subjects in this cohort, 3 were excluded (missing alcohol data); mean age of 10 125 participants, 40.3 years (range, 5–70 years); 9821 subjects included; average follow-up, 27.3 years	Biennial examinations, asking about alcoholic beverage intake, smoking	133 confirmed incident cases of bladder cancer	*Total intake (g/day)* 0 0.1–6.0 6.1–12.0 12.1–24.0 24.1–48.0 >48 *Beer (drinks/week)* 0 <1 1–4 >4 *Wine (drinks/week)* 0 <1 1–4 >4 *Spirits (drinks/week)* 0 <1 1–4 >4	 14 43 21 14 22 8 48 20 23 31 49 42 17 14 21 20 28 53	 1.0 0.9 (0.5–1.8) 0.9 (0.4–1.9) 0.6 (0.3–1.3) 0.9 (0.5–1.9) 0.5 (0.2–1.2) 1.0 0.6 (0.3–1.2) 0.7 (0.4–1.3) 0.5 (0.1–0.8) *p* trend = 0.03 1.0 0.9 (0.5–1.6) 0.6 (0.3–1.2) 0.8 (0.4–1.7) 1.0 1.0 (0.5–2.0) 1.4 (0.4–2.9) 1.6 (0.9–3.1)	Age/sex, cohort, smoking status, pack–years of smoking; beverage-specific data also controlled for the other two types	

CI, confidence interval; ICD, International Classification of Diseases

Table 2.66 Case–control studies of alcoholic beverage consumption and cancer of the urinary bladder

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Mommsen *et al*. (1983), Denmark, 1977–79/80	212 (165 men, 47 women), mean age, 66.1 years (range, 42–85 years); newly diagnosed over 2 (men) or 3 years (women)	259 (165 men, 94 women) selected from the same area; matched with cases on sex, age, degree of urbanization, geographic area	Questionnaire and interview with physician on job history, use of alcohol, tobacco, coffee, sugar substitutes	Bladder	Alcohol drinking	193	2.3 (1.3–3.9)	Matching factors	
Thomas *et al*. (1983), USA, 1978–79	2982 newly diagnosed identified over a 1-year period from cancer registries in 10 areas in the USA; 100% histologically confirmed; participation rate, 73%	Population in same areas selected by random-digit dialling (2469; aged 21–64 years) and from files of Health Care Finance Administration (3313; aged 65–84 years); stratified on age, sex, geographic distribution; response rates, 84% (21–64 years) and 82% (65–84 years)	At-home interview with standardized questionnaire on job/ residential history, use of sweeteners and coffee, tobacco products; number of alcoholic servings in a typical winter week 1 year before	Bladder	**Servings per week** *All alcohol* 0 <3 4–6 7–13 14–27 28–41 ≥42 *Beer* 0 <3 4–6 7–13 14–27 28–41 ≥42	 835/426 216/92 228/75 335/62 359/59 139/9 114/2 1261 275 223 154 161 43 46	 *Men/women* 1.0 (1.0) 0.94 (0.80) 0.86 (0.93) 0.98 (0.77) 0.88 (0.97) 1.13 (0.87) 0.99 (0.66) *Men + women* 1.0 0.89 0.98 0.92 1.01 1.16 0.93	 Age, sex, race, smoking status, hazardous occupational exposure Age, race, smoking status, hazardous occupational exposure	[No CIs provided]

Table 2.66 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Thomas *et al*. (1983) (contd)					*Wine*				[No CIs provided]
					0	1261	1.0		
					<3	370	0.94		
					4–6	175	0.86		
					7–13	128	0.81		
					14–27	89	1.00		
					≥28	15	0.60		
					Spirits				
					0	1261	1.0		
					<3	294	0.78		
					4–6	259	0.91		
					7–13	255	0.95		
					14–27	235	0.99		
					28–41	53	1.04		
					≥42	51	1.14		

Table 2.66 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Claude *et al*. (1986), Germany, 1977–82	431 patients (340 men, 91 women) in three hospitals in Lower Saxony; mean age, 68.6 (men) and 69.7 years (women); refusal rate, 2%	Patients in the same hospitals; mean age, 69.7 (men) and 70.9 (women) years; matched 1:1 to cases by age (±5 years), sex; due to a lack of suitable patients >65 years, 21% recruited from homes for the elderly; about 70% of the men had prostate adenoma and infections	Interviews with a questionnaire on smoking, use of alcohol, coffee, drugs, medical history, radiation, urination habits, use of hair dyes, job history and exposures	Lower urinary tract (90% bladder); 89% transitional-cell carcinoma	*Beer (L/day)* 0.1–0.5 0.6–1.0 >1 *Wine (L/day)* 0.1–0.3 >0.30 *Spirits (L/week)* 0.1–0.5 >0.5 *Ever* Beer Wine Spirits	NR NR NR NR	*Men* 1.16 2.14 (p<0.05) 2.77 (p<0.05) 0.97 0.82 1.46 2.71 (p<0.05) *Women* 1.42 1.88 1.21	Smoking	Beer drinkers consumed ≥1 glass of beer (0.3 L) per day for ≥5 years; odds ratio for all beer drinkers, 1.6; odds ratio for nonsmokers among them, 0.8; odds ratio for beer drinkers who smoke, 1.7; also seen for spirits, not for wine; information on histology available

Table 2.66 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Kunze *et al*. (1986), Germany, 1977–82	340 patients from three hospitals in Lower Saxony; cancers of the bladder (309), pelvis (15), ureter (4), urethra (1) or multifocal tumours (11); 100% histologically confirmed; refusal rate, 2%	Patients in the same hospitals without any tumour primarily from urological departments; matched with cases on age, sex, hospital	Interviews at the hospital, about smoking, drinking, medical history, drug use, urinary habits, use of hair dyes.	Lower urinary tract (91% bladder, 4.4% pelvis, 1.2% ureter, 3.3% multi-focal)	*Beer (L/day)* <0.5 0.6–1.0 >1 *Wine (L/day)* <0.3 >0.30 *Spirits (L/week)* <0.5 >0.5 *Beer drinkers* Smoker Nonsmoker	NR	 1.16 2.14 (p<0.05) 2.77 (p<0.05) 0.97 0.82 1.46 2.71 (p<0.05) 1.6 (p<0.05) 1.7 (p<0.05) 0.8	Smoking	[Numerical data identical to Claude *et al*.(1986)]
Slattery *et al*. (1988), Utah, USA, 1977–82	419 patients identified via Utah Cancer Registry (all white); aged 20–84 years; 100% histologically confirmed carcinomas; completion rate, 76.3%	889 population-based selected by random-digit dialling (aged 21–64 years) or via Health Care Finance records (aged 65–84 years); matched 2:1 to cases by 5-year age group, sex; completion rate, 81.5%	Personal interviews on smoking, drinking, use of sweeteners, medical history, job history, demographics; intake of fluid noted for a typical winter week 1 year prior to interview	Bladder (ICD-0, 188)	*Alcohol (oz/week)* 0 1–30 ≥31 0 1–30 ≥31 *Alcohol (oz/week)* 0 0.1–3.64 ≥3.65 0 0.1–3.64 ≥3.65	 110 14 7 159 59 66 110 11 10 159 51 74	*Never smokers* 1.0 1.2 (0.6–2.2) 2.1 (0.8–5.4) *Ever smokers* 4.1 (2.5–6.7) 2.8 (2.1–3.9) 2.9 (2.0–4.4) *Never smokers* 1.0 1.0 (0.5–2.0) 2.4 (1.1–5.4) *Ever smokers* 3.8 (2.4–6.2) 2.8 (2.1–3.9) 3.0 (2.0–4.4)	Age, sex, diabetes, bladder infections	

Table 2.66 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Nomura *et al*. (1989), Hawaii, USA, 1979–86	261 patients of Caucasian or Japanese ancestry in 7 large hospitals on Oahu, Hawaii; 261 participated (195 men, 66 women), aged 30–93 years; 100% histologically confirmed; overall reponse rate 73%; 31 cases diagnosed in 1977–79	522 population-based identified from lists of the Health Surveillance Program; matched 2:1 for age (±5 years), sex, race, current residency on Oahu; 89% of those eligible	Interviews on smoking history, alcohol intake 1 year before the interview, job history, use of hair dyes	Lower urinary tract (90% bladder)	**Alcohol intake** *Drinks/week* *Men* Non-drinker Drinker 1–14 >15 *Women* Non-drinker Drinker 1–7 >8	 46 149 78 71 33 33 22 11	 1.0 1.2 (0.8–1.9) 1.1 (0.7–1.8) 1.3 (0.8–2.2) 1.0 0.9 (0.5–1.6) 0.7 (0.4–1.4) 1.5 (0.6–3.8)	Cigarette smoking (pack–years)	

Table 2.66 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Akdaş *et al*. (1990), Turkey, 1980–87	194 patients (168 men, 26 women) admitted to 2 hospitals, aged 24–80 years (mean age, 60 years); 100% histologically confirmed	194 patients in the same hospitals with no gross haematuria or cancer history; 91% had IVU done, showing a normal bladder; 57% had cystoscopy, showing absence of tumour; matched on age, sex	Interview on past and present residence, job history, socio-economic status, drinking habits (tea, alcohol, Turkish coffee), smoking habits, medical history, use of fertilizers or insecticides	Bladder	*Case control ratio* No drinking* Ever drinking Daily drinker *Drinking duration* 11–20 years >20 years >175 mL liquor/day		*Case control ratio* 0.67 1.67 $p<0.001$ $p<0.01$ $p<0.001$ $p<0.01$ $p<0.05$	Unadjusted Smoking	Risk for bladder cancer increased with intensity and duration of alcohol drinking * read from graph

Table 2.66 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Momas *et al*. (1994), France, 1987–89	219 men living in the Hérault district for >5 years diagnosed with primary bladder carcinoma, checked with the Hérault Cancer Registry; mean age, 67.8 years; papillomas and polyps excluded; 100% histologically confirmed; participation rate, 81% (53 died)	928 men living in Hérault region for >5 years, randomly selected from electoral rolls; aged >50 years; 558 of 692 in the telephone book agreed to be interviewed (80.6%); 236 of 329 not in phone book replied by mail (71.7%).	Interviews (direct or by phone) on past and present residence, level of education, jobs of >1 year, smoking/ drinking habits, intake of spiced food, sweeteners	Bladder (188)	*Lifelong intake of pure alcohol (kg)* <15 15–600 >600–1200 >1200	 7 47 57 50	 1.0 2.2 (0.9–5.6) 1.7 (0.7–4.3) 3.1 (1.2–8.2)		Stepwise logistic regression, using the largest possible data set in the regression model, i.e. with the set of persons having no missing values for any of the model variables
Nakata *et al*. (1995), Gunma Prefecture, China	303 men; mean age, 70.1 years	303 men from the general population from 15 areas of the Gunma prefecture; mean age, 70.2 years; age-matched (± 1 year)	Not reported	Bladder	History of drinking (yes/no)	191 190	1.0 (0.7–1.5) 0.9 (0.7–1.4)	Age Smoking	

Table 2.66 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Bruemmer *et al.* (1997), USA, 1987–90	427 Caucasian patients with invasive or non-invasive (in-situ or papillary) bladder cancer living in Washington State with no prior bladder cancer history; aged 45–65 years; 262 completed the interview; response rate, 62.4%	535 identified via random-digit dialling; matched to cases by sex, county of residence; 405 interviewed (79% of those eligible and selected)	Telephone interviews on demographics, history of cancer, smoking; fluid intake over a 10-year period before reference date (2 years before diagnosis)	Bladder (188)	*Alcoholic drinks (per day)*				
							Men		
					0	33	1.0		
					≤0.5	49	1.4 (0.7–2.7)		
					>0.5–2.0	57	1.2 (0.6–2.2)		
					>2	63	1.1 (0.6–2.1)		
							Women		
					0	19	1.0		
					≤0.5	22	0.4 (0.2–0.8)		
					>0.5–2.0	10	0.6 (0.2–1.6)		
					>2	9	0.5 (0.2–1.3)		

Table 2.66 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Donato *et al.* (1997), Brescia, Italy, 1990–92	172 patients (135 men, 37 women) diagnosed in a large hospital in Brescia; all but one histologically confirmed	578 patients (398 men, 180 women) in the same and two other hospitals with prostate adenoma, urolithiasis or obstructive uropathy; men age-matched (± 5 years) with cases; this could not be achieved for women	Questionnaire on education, history of smoking, coffee/alcohol drinking	Bladder (188)	*Alcohol drinking (g/day)* Non-drinker Former drinker Current drinker 1–20 21–40 41–60 >61 Non-drinker Current drinker 1–20 ≥21	 10 16 109 18 33 36 22 12 25 14 11	 *Men* 1.0 1.0 (0.4–2.7) 2.1 (1.0–4.8) 1.7 (0.6–4.7) 1.6 (0.6–3.8) 4.3 (1.7–11.0) 4.6 (1.6–13.4) *Women* 1.0 3.4 (1.2–9.7) 3.1 (1.0–9.3) 3.9 (1.1–13.7)	Age, place of residence, education, date of interview, smoking, coffee consumption	People who drank alcohol less than daily were considered non-drinkers
Probert *et al.* (1998), United Kingdom	116 patients with transitional-cell carcinoma recruited from haematuria clinics in two Bristol hospitals; tumours staged and graded by a clinical pathologist; 100% histologically confirmed	91 patients from the same clinics with benign haematuria or no bladder disease	Personal interview by the same person on job history, smoking history and status, coffee and alcohol use, place of residence	Bladder (188)	*Alcohol consumption* Wine Quantity/week Started drinking Beer Quantity/week 0 1–20 >20 *p* for trend	 34% 66% 62 37 15	*Cases/controls* [*odds ratio*] [1.59] 3.9/3.5 units 54.1/39.9 years [1.85] 11.9/9.6 units <0.05	 Crude Crude	No relative risks given

Table 2.66 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Pohlabeln *et al*. (1999), Hessen, Germany, 1989–92	300 patients (239 men, 61 women) newly diagnosed in 4 hospitals in Hessen; 89.6% bladder cancer; 100% histologically confirmed; 98.7% carcinomas; response rate, 92.6%	300 patients from the same hospitals with non-neoplastic diseases of the lower urinary tract; matched 1:1 on age (± 5 year), sex, area of residence; response rate, 98%	Questionnaire and interview on job history, active smoking history, dietary habits (foods/drinks) 10–15 years previously	Lower urinary tract	**Alcohol intake** *Total intake* Not daily 1–20 g/day 21–40 g/day >41 g/day Not daily Daily *Beer* Not daily 1–2 bottles/day ≥3 bottles/day Not daily ≥1 bottle/day *Wine* Not daily 1–2 glasses/day ≥3 glasses/day Not daily ≥1 glass/day	 102 74 35 28 52 9 119 96 24 58 3 211 24 4 55 6	 *Men* 1.0 1.10 (0.70–1.73) 0.83 (0.46–1.47) 1.71 (0.78–3.73) *Women* 1.0 2.84 (0.69–11.68) *Men* 1.0 1.05 (0.70–1.59) 1.82 (0.79–4.21) *Women* 1.0 4.53 (0.32–65.24) *Men* 1.0 1.18 (0.60–2.33) 2.48 (0.41–14.89) *Women* 1.0 2.29 (0.44–11.92)	Adjusted for smoking categories: none, 1–≤20, 20–≤40, >40 pack–years, cigar, pipe	1 bottle of beer = 2 glasses of wine = 20 g alcohol

Table 2.66 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
van Dijk *et al*. (2001), Netherlands, 1997–2000	120 patients (86% men) recruited at the Nijmegen University Medical Centre; 100% histologically confirmed; *ADH3* genotyping on 115 patients	133 patients (89% men) with benign prostatic hyperplasia and visitors to the urology ward; *ADH3* genotyping on 131 patients	Self-administered questionnaire on demographics, smoking/ drinking/ dietary habits, jobs, familiality of cancer, disease history	Bladder	*Alcohol intake* Moderate High ADH3 *genotype* $\gamma_1\gamma_2$ *and* $\gamma_2\gamma_2$ Moderate High ADH3 *genotype* $\gamma_1\gamma_1$ Moderate High	NR	 1.0 1.2 (0.6–2.4) 1.0 2.0 (0.9–4.5) 3.3 (1.3–8.8) 2.2 (0.8–5.8)	Adjustment unclear; moderate drinkers taken as reference	Moderate = 1–14 glasses per week; high = >14 glasses per week

Table 2.66 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Pelucchi *et al*. (2002a), Italy, 1985–92	727 patients with invasive transitional cell cancer (617 men, 110 women) in various hospitals in the Milan area and the Pordenone region; aged 27–79 years (median, 63 years); 100% histologically confirmed; refusal rate, 2.6%	1067 patients (769 men, 298 women) in the same hospitals, admitted for acute, non-neoplastic, non-urological or genital tract diseases; aged 27–79 years (median, 60 years); refusal rate, 2.2%	Questionnaire on smoking habits, intake of coffee and tea, medical history, family history of urological cancer, alcohol use, relevant occupational exposures	Bladder (188)	*Total intake (drinks/day)* Non-drinker Ever drinker <3 3–<6 ≥6 *Wine (drinks/day)* Non-drinker Ever drinker <3 3–<5 ≥5 *Beer* Never Ever *Spirits* Never Ever *Years of drinking* Never drinker 1–24 25–39 ≥40	 117 607 192 193 222 126 599 207 175 217 608 118 538 189 117 65 199 342	 1.0 0.8 (0.6–1.1) 0.8 (0.6–1.1) 0.8 (0.5–1.1) 0.8 (0.6–1.2) 1.0 0.9 (0.6–1.1) 0.9 (0.7–1.3) 0.8 (0.6–1.1) 0.9 (0.6–1.2) 1.0 0.7 (0.5–0.9) 1.0 0.9 (0.7–0.9) 1.0 0.7 (0.5–1.1) 0.7 (0.5–1.0) 1.0 (0.7–1.4)	Age, sex, study centre, education, smoking, tea or coffee consumption, green vegetable intake, occupation ‘at risk’	

Table 2.66 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Band *et al.* (2005), British Columbia, Canada, 1983–90	25 726 male patients aged ≥20 years listed in the British Columbia Cancer Registry, detailed questionnaire returned by 15 463 (60.1%); of these, 1129 bladder cancer patients responded (64.7%); 1125 cases had at least one matching control	8492 patients with cancer at all other sites, except lung (2998) and 'unknown sites' (708); matched on age, year of diagnosis	Questionnaire on lifetime job history (usual occupation/ industry, ever occupation), smoking/ drinking habits.	Bladder (188)	*Alcohol intake* Never Ever Unknown	 119 858 148	 1.0 0.9 (0.7–1.1) 1.2 (0.9–1.5)		Focus on identifying occupational cancer risks; similar alcohol use between cases and controls

Table 2.66 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Lu *et al.* (2005), Taiwan, China, 1997–98	103 (66 men, 37 women) patients in Kaohsiung; upper tract metastases or recurrent urinary neoplasm not eligible; 100% histologically confirmed; all genotyped for *N*-acetyl-transferase (*NAT2*); response rate, 100%	103 (68 men, 35 women) ophthalmic patients with non-neoplastic and non-urological diseases, and normal renal and liver function; all genotyped for *NAT2*; response rate, 100%	Interview with questionnaire on demographics, socioeconomic, dietary factors, jobs, smoking, betel quid use, alcohol use,	Bladder	*Alcohol drinking* No Yes NAT2 *genotype** Rapid Slow *Interaction alcohol use* NAT2 *genotype* No/Rapid No/Slow Yes/Rapid Yes/Slow	 98 5 52 24 12 15	*Odds ratio* 1.0 2.7 (1.3–5.9) 1.0 1.5 (0.8–2.8) 1.0 1.1 (0.5–2.1) 1.4 (0.6–3.5) 18.0 (2.3–142.8)	 *Adjusted for blackfoot disease-endemic area, alcohol drinking	
Baena *et al.* (2006), Spain	74 men admitted to the Department of Urology of the University Hospital of Cordoba over 1 year; mean age, 67.1 years	89 male patients in the same department, with non-malignant urological disease; mean age, 58.7 years	Interview with questionnaire on smoking/ drinking habits, diet and chronic diseases	Bladder	Alcohol drinking	60	[2.38] (p=0.036 in univariate analysis)	Crude	In multivariate analysis, alcohol was not an independent risk factor for bladder cancer, but no point estimates were given; unclear whether current or ever drinker.

CI, confidence interval; ICD, International Classification of Diseases; IVU, intravenous urography; NR, not reported

Given the likelihood of residual confounding and the absence of an association in large studies, there is no clear pattern of association between total alcoholic beverage consumption or consumption of various types of alcoholic beverage and the risk for cancer of the urinary bladder.

2.12 Cancer of the endometrium

2.12.1 *Cohort studies (Tables 2.67 and 2.68)*

Since 1988, three prospective cohort studies have examined the association between alcoholic beverage intake and the risk for endometrial cancer in special populations, namely women hospitalized or being treated for alcohol dependence (Adami *et al*., 1992a; Tønnesen *et al*., 1994, Sigvardsson *et al*., 1996; Weiderpass *et al*., 2001a; Table 2.67) and three have studied the association in the general population (Gapstur *et al*., 1993; Terry *et al*., 1999; Jain *et al*., 2000b; Folsom *et al*., 2003; Table 2.68) (see the Tables for overlapping study populations).

These studies were conducted in North America (Gapstur *et al*., 1993; Jain *et al*., 2000b; Folsom *et al*., 2003) and in Scandinavia (Adami *et al*., 1992a; Tønnesen *et al*., 1994; Sigvardsson *et al*., 1996; Terry *et al*., 1999; Weiderpass *et al*., 2001a).

Three studies (Gapstur *et al*., 1993, Terry *et al*., 1999; Jain *et al*., 2000b) presented risk estimates adjusted for multiple possible confounders (body size and reproductive factors), while only one (Jain *et al*., 2000b) adjusted the analysis of alcoholic beverages for smoking (ever/never). Smoking showed a non-significant protective effect in all of these studies.

In one study among alcoholics (Weiderpass *et al*., 2001a), there was an inverse association between alcoholic beverage consumption and endometrial cancer, but the analytical models did not include important covariates that may have confounded the association, such as cigarette smoking and body size. In the two other studies among alcohol-dependent populations, there was no evidence of an association. There was no evidence of an association between alcoholic beverage intake and the risk for endometrial cancer in the three cohort studies conducted in the general population (Gapstur *et al*., 1993; Terry *et al*., 1999; Jain *et al*., 2000b).

2.12.2 *Case–control studies (Table 2.69)*

Case–control studies that have investigated the relationship between alcoholic beverage consumption and the risk for endometrial cancer were carried out in Japan, North America and Europe.

Seven of these were hospital-based, particularly studies from southern Europe (La Vecchia *et al*., 1986; Shu *et al*., 1991; Austin *et al*., 1993; Levi *et al*., 1993; Parazzini *et al*., 1995a; Kalandidi *et al*., 1996; Petridou *et al*., 2002), two were based on cases and controls who were included in a cancer survey or registry database (Williams

Table 2.67 Cohort studies of alcoholic beverage consumption and endometrial cancer in special populations

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Adami *et al.* (1992a), Sweden, National Board of Health and Welfare/ Study of Alcoholics Women	9353 individuals (1013 women) with a diagnosis of alcoholism in 1965–83; follow-up for 19 years (mean, 7.7 years); all cancers in the first year of follow-up excluded	Registry-based	*Corpus uteri*	Women with diagnosis of alcoholism	3	**SIR** 1.4 (0.3–4.2)		
Tønnesen *et al.* (1994), Denmark, Cohort of non-hospitalized alcoholic men and women	18 307 male and female alcohol abusers admitted to an outpatient clinic in Copenhagen during 1954–87; 3093 women observed for 9.4 years	Registry-based	*Corpus uteri*	Alcohol abusers	3	0.4 (0.1–1.3)		

Table 2.67 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Sigvardsson *et al*. (1996), Sweden, Temperance Boards Study	Nested case–control study; records of 15 508 alcoholic women born between 1870 and 1961 obtained from Temperance Boards; controls matched for region and day of birth; incidence data from Swedish Cancer Registry	Registry-based	*Corpus uteri* (ICD-7, 172)	Alcohol abusers	30	0.7 (0.4–1.1)		

Table 2.67 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Weiderpass *et al.* (2001a), Sweden, National Board of Health and Welfare/ Study of Alcoholic Women	36 856 women (mean age, 42.7 years) hospitalized for alcoholism between 1965 and 1994 based on data from Inpatients Register; linkages to nationwide Registers of Causes of Death and Emigration and national Register of Cancer; average follow-up time, 9.6 years; the first year of follow-up was excluded from all analysis	Registry -based; linkages	Endometrium	Women with diagnosis of alcoholism	69	**SIR** 0.76 (0.59–0.96)	Age, calendar period	Enlarged population with longer follow-up than Adami *et al.* (1992a)

CI, confidence interval; ICD, International Classification of Diseases; SIR, standardized incidence ratio

Table 2.68 Cohort studies of alcoholic beverage consumption and endometrial cancer in general populations

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Gapstur *et al.* (1993), USA, Iowa Women's Health Study	25 170 women, aged 55–69 years, randomly selected from Iowa's 1985 drivers' licence list; cohort at risk, 24 848 women; questionnaire mailed in 1986; exclusions: prevalent cancer other than skin, prior hysterectomy, menstruation during the last year; 167 incident endometrial cancers	Mailed, self-administered questionnaire	Endometrium; *corpus uteri* (182.0) and *isthmus uteri* (182.1)	*Ethanol (g/day)* 0 <4.0 ≥4.0	 101 27 32	 1.0 (reference) 0.7 (0.5–1.1) 1.0 (0.7–1.6)	Age, body mass index, number of live births, age at menopause, non-contraceptive estrogen use	The same population as Folsom *et al.* (2003); Cox proportional hazard regression

Table 2.68 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Terry *et al.* (1999), Sweden, Swedish Twin Registry and Swedish Cancer and Death Registry	11 659 women born 1886–1925; follow-up through to 1992; record linkages to Swedish Cancer and Death Registries; 133 incident cases detected	Questionnaire concerning lifestyle factors, diet, physical activity, 1967	Endometrium	*Drinks/week* 0 <2 2–4 ≥4	 78 22 10 7	 1.0 (reference) 1.7 (1.0–2.8) 1.2 (0.6–2.4) 1.3 (0.6–2.8)	Age, physical activity, weight at enrolment, parity	
Jain *et al.* (2000b), Canada, National Breast Screening Study, 1980–85	56 837 women, aged 40–59 years, enrolled between 1980 and 1985; subcohort of 10% of randomly selected women from the main study in the dietary cohort; follow-up to 31 December 1993; 221 women diagnosed with incident adenocarcinoma	Self-administered questionnaire	Endometrium	*Alcohol consumption* 1 (low) 2 3 4 (high)	 65 62 41 53	 1.00 (reference) 1.01 (0.69–1.46) 0.78 (0.52–1.18) 1.00 (0.67–1.50)	Age, total energy intake, body mass index, ever smoked, oral contraceptive use, hormone-replacement therapy use, university education, live births, age at menarche	

Table 2.68 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Folsom *et al*. (2003), USA, Iowa Women's Health Study	23 335 women, aged 55–69 years, randomly selected from Iowa's 1985 drivers' licence list; follow-up from 1986 through 2000; 415 incident endometrial cancers detected	Baseline questionnaire	Endometrium	*Alcohol consumption* Yes No	 260 155	 1.00 (reference) 0.73 (0.59–0.89)	Age	$p<0.05$; p for difference from reference category
Beral *et al*. (2005), United Kingdom, Million Women Study	716 738 post-menopausal women in the UK without previous cancer or hysterectomy recruited into the Million Women Study in 1996–2001	Questionnaire	Endometrium	*Alcohol consumption* ≤10 g/week >10 g/week	 69 17	 1.77 (1.39–2.18) 1.81 (1.08–3.05)	Time since menopause, parity, oral contraceptive use, body mass index, region of residence, economic status	

CI, confidence interval; ICD, International Classification of Diseases

Table 2.69 Case–control studies of alcoholic beverage consumption and endometrial cancer

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Williams & Horm (1977), USA, The Third National Cancer Survey (cross-sectional study), 1967–71	7518 patients (all sites, men and women) interviewed; 57% selected randomly	Randomly selected patients with cancer of other, non-related sites	Interview	*Corpus uteri*	*Wine level* 1 2 *Beer level* 1 2 *Hard liquor level* 1 2 *Total alcohol oz–years level* 1 2	Relative odds 0.77 0.60 0.23 0.42 0.91 0.79 0.72 0.65	Age, race,	Consumers of alcohol were divided in categories 1 and 2 with 51 drink x years as level of division (years of alcohol consumption ≥ once per week
					Wine level 1 2 *Beer level* 1 2 *Hard liquor level* 1 2 *Total alcohol oz–years level* 1 2	 0.78 0.49 0.23 0.31 0.95 0.77 0.69 0.63	Age, race, smoking	

Table 2.69 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
La Vecchia *et al.* (1986), Milan, Italy, Jan. 1983– Jun. 1984	206 women, aged 75 years and less, admitted to the Obstetrics and Gynecology Clinics of the University, The National Cancer Institute and oncology, gynecology wards of the Ospedale Maggiore, Milan	206 women matched by 5-year range to cases, admitted to the same hospital network for acute conditions; women who undergone hysterectomy excluded	Structured questionnaire	Endometrium	*Alcohol consumption* (drinks/day) 0 <2 ≥2 and <3 ≥3 and <4 ≥4	 1.00 (reference) 1.59 (0.80–3.18) 1.57 (0.77–3.21) 3.44 (1.03–11.51) 4.33 (1.02–18.43) χ^2 trend=5.73 p=0.02	Various dietary items, interviewer, age, marital status, years of education, body mass index, parity, history of diabetes, hypertension, age at menarche, age at menopause, of oral contraceptives, hormone-replacement therapy use	
Cusimano *et al.* (1989b), Ragusa, Italy, 1 Jan. 1983–30 Jun. 1985	57 women from Ragusa and province (Italy/Sicily) diagnosed between 1 Jan. 1983 and 30. Jun 1985; aged 37–79 years; 100% histologically confirmed; participation rate; 95%	228 women from the same geographical region; aged 36–79. matched to cases by age (2.5-year range), type of health service consulted; women who had undergone hysterectomy excluded	Structured questionnaire; interview	Endometrium	*Alcohol consumption* No Yes	 1.00 (reference) 1.31 (0.73–2.34)		

Table 2.69 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Kato *et al.* (1989), Japan, 1980–86	417 women registered at Aichi Cancer Registry, diagnosed between 1980 and 1986; aged ≥20 years	8920 cancers at other sites excluding cancers known to be alcohol-related	Records from Aichi Cancer Registry with available data on alcohol drinking habits	*Corpus uteri*	*Alcohol drinking* Current versus none Daily versus less Occasional versus none Daily versus none Daily versus less	 0.67 (0.41–1.09) 0.46 (0.15–1.41) 0.74 (0.44–1.26) 0.44 (0.15–1.38) 0.53 (0.16–1.70)	Age	Possible bias due to control selection from cancer patients and the effect of alcohol consumption diminished; however, status of the controls' illness may have changed their alcohol drinking habit before diagnosis; lack of information on important risk factors.

Table 2.69 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Webster *et al.* (1989), USA, multicentre: Atlanta, Detroit, San Francisco, Seattle, states of Connecticut, Iowa, 1980–82	351 women newly diagnosed with primary epithelial endometrial cancer (from 1 December 1980 to 31 December 1982); aged 20–54 years; 100% histologically confirmed	2247 women selected by random-digit dialling, from same geographical areas as cases, during the same period; aged 20–54 years; frequency-matched by 5-year age groups	Structured questionnaire; interview at participants home.	Endometrium	*Alcohol consumption (g/week)* Non-drinker 1–49 50–149 ≥150	 1.83 (1.11–3.10) 1.61 (1.04–2.49) 1.11 (0.68–1.81) 1.00	Age, race, parity, oral contraceptive use, smoking	27% women unable to be interviewed
Shu *et al.* (1991), Shanghai, China, 1988–90	268 Shanghai residents diagnosed between 1 April 1988 and 30 January 1990; aged 18–74 years; data obtained from cancer registry in Shanghai; 98.5% histopatholo-gically confirmed; participation rate, 91.2%	268; matched to cases by age (2-year range) randomly; participation rate, 96.4%	In-person interview at participants' home; questionnaire	Endometrium	*Drinking* No Yes	 1.0 1.2 (0.6–2.6)		

Table 2.69 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Austin *et al.* (1993), Alabama, USA, 1985–88	168 women identified through University Hospital and private gynaecological–oncological practice in Birmingham between June 1985 and December 1988, aged 40–82 years; 100% histologically confirmed; participation rate, 93%	334 women attending the University optometry clinic, aged 40–82 years; intact uterus; frequency-matched by age, race; participation rate, 77%	Standardized and food-frequency questionnaires	Endometrium	*Alcohol category* Any type	*Relative rate* 0.64 (0.32–1.28) p=0.20	Age, race, education, body mass, index of central obesity, cigarette habit, use of replacement estrogens, number of pregnancies	
Levi *et al.* (1993), northern Italy and Switzerland,1988–9	274 patients from local cancer registry, aged 31–75 years; 100% histologically confirmed	572 women admitted to the same hospitals for acute, non-gynaecological, non-hormone-related, metabolic or neoplastic disorders, aged 30–75 years	Structured questionnaire/ interview at hospital	Endometrium	**Frequency of alcohol consumption** *Wine* Low Intermediate High *Beer* Low Intermediate High *Liquor* Low Intermediate High	*Odds ratios* 1.0 1.03 1.70 χ^2=5.67 p<0.05 1.0 0.99 2.43 χ^2=0.27 1.0 1.46 5.24 χ^2=4.39 p<0.05	Study centre, age	

Table 2.69 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Swanson *et al*. (1993), USA, 1987–90	400 women newly diagnosed in June 1987 to May 1990 from seven hospitals in Chicago, Hershey, Irwine and Long Beach, Minneapolis, Winston-Salem, aged 20–74 years; inclusion criteria: no previous treatment for the cancer and intact uterus; 100% pathologically confirmed; participation rate, 87.1%	297 women selected by random-digit dialling or Health Care Financing Administration; matched by age (5-year range), race, residence; participation rate, 65.6%	Short telephone interview	Endometrium	*Alcohol intake in adulthood (drinks per week)* None Any <1 1–4 >4	 1.00 0.82 (0.53–1.26) 0.75 (0.47–1.19) 1.04 (0.61–1.76) 0.72 (0.39–1.35)	Age, education, smoking status, age at menarche, use of oral contraceptives, Quetelet index, body fat distribution	13% of eligible cases and 35% of eligible controls not interviewed; bias if non-response associated with alcohol use; possible recall bias among cases due to their condition

Table 2.69 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Parazzini *et al.* (1995a), Milan, Italy, 1979–93 [population partially overlapping with La Vecchia *et al.* (1986)]	726 patients admitted to six greatest hospitals and clinics in Milan until 1 year before interview, aged 28–74 years; 100% histologically confirmed	2123 women admitted to the same network of hospitals for acute, non-malignant, non-gynaecological conditions, unrelated to hormonal diseases, aged 25–74 years; exclusion: women with hysterectomy	Standard questionnaire, by trained interviewers	Endometrium	*Total alcoholic beverages (drinks/day)* 0 >0–≤1 >1–≤2 >2	 1.0 (reference) 1.1 (0.9–1.4) 1.4 (1.1–1.8) 1.6 (1.2–2.2) χ^2 trend=11.33 p<0.001	Age, education, Quetelet index, parity, menopausal status, smoking, oral contraceptive and estrogen replacement therapy use, diabetes, hypertension, alcohol	Data on alcohol consumption may not represent a lifelong pattern; common weaknesses for hospital-based case–control study.
Kalandidi *et al.* (1996), Greater Athens, Greece, 1992–94	145 women diagnosed between 1992 and 1994, operated in two specialized cancer hospitals in Greater Athens; 100% histologically confirmed; participation rate, 83%	298 women, residents of Greater Athens, admitted at the same time to the greater hospitals in Athens for bone fractures or other orthopaedic conditions	Structured questionnaire; hospital interview	Endometrium	*Alcohol intake* No Yes	 1.0 (reference) 0.72 (0.44–1.37) p=0.67	Age, education, body mass index, occupation, age at menarche, menopausal status, oral contraceptive use, smoking, menopausal estrogens, coffee	

Table 2.69 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Goodman *et al.* (1997b), Oahu, Hawaii, USA, 1985–93	332 women diagnosed between 1 January 1985 and 1 June 1993, residents of Oahu and of Japanese, Caucasian, native Hawaiian, Filipino, Chinese origin, obtained from Hawaii Tumor Registry, aged 18–84 years; 100% histologically confirmed; participation rate, 66%	511 women selected randomly from lists of Oahu residents; matched to cases on ethnicity, age (range, 2.5 years); intact uteri; exclusions: hysterectomized women, mental incompetence; participation rate, 73%	Interviewer-administered standardized questionnaire	Endometrium	*Alcohol use* No Yes *Alcohol type (g ethanol equivalent)* Reference 0 0.2 17.8	 1.00 (reference) 0.90 (0.6–1.4) 1 0.8 0.8 0.8 *p* for trend=0.44	Pregnancy history, oral contraceptive use, unopposed estrogen use, diabetes, body mass index Carbohydrate or fat calories, pregnancy history, oral contraceptive use, unopposed estrogen use, diabetes, body mass index	

Table 2.69 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Newcomb *et al.* (1997), Wisconsin, USA, 1991–94	739 female residents of Wisconsin, diagnosed between 1991 and 1994, aged 40–79 years; identified by a state-wide mandatory cancer registry; limited to cases with listed telephone numbers and drivers' licences; 98% histologically confirmed ; participation rate, 87%	2313 women selected randomly from lists of licensed drivers; matched by age distribution; criteria: listed telephone number, no previous diagnosis of uterine cancer; participation rate, 85.2%	Structured telephone interview	Endometrium	*Recent consumption (drinks/week)* None Any <1 1–2 3–6 7–13 ≥14 *Continuous*	 1.00 1.07 (0.86–1.33) 1.22 (0.96–1.56) 0.86 (0.65–1.14) 1.11 (0.83–1.50) 0.81 (0.55–1.19) 1.27 (0.78–2.07) 1.00 (0.98–1.02) p=0.82	Age, smoking status, education, relative weight, hormone replacement therapy use, parity	Any possible information and recall bias unlikely to have an important effect on the results

Table 2.69 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Jain *et al.* (2000c), Ontario, Canada, 1994–98	552 women diagnosed in August 1994–June 1998 (adeno-carcinoma, carcinoma, cystadeno-carcinoma or mixed Mullerian carcinoma), aged 30–79 years; data from Ontario Cancer Registry (four areas: Toronto, Peel, Halton, York); 100% histologically confirmed; response rate, 70%	562 randomly selected women from property assessment lists; frequency-matched by age group, geographical areas (Toronto, Peel, Halton, York); selection criteria: intact uterus, no history of hysterectomy and listed with telephone number	Home interview, standardized questionnaire	Endometrium	*Intake (g absolute alcohol)* 0 <1.2 <8.3	*Odds ratio* 1.0 (reference) 0.85 (0.63–1.18) 0.72 (0.52–0.99) *p≤0.05* *p* trend=0.04	Total energy, age, body weight, ever smoked, diabetes, oral contraceptive use, hormone replacement therapy use, university education, live births, age at menarche	

Table 2.69 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
McCann *et al.* (2000), western New York, USA, 1986–91	232 women, aged 40–85 years; exclusions: women with more than one primary carcinoma and non-adenomatous carcinoma of the endometrium; 100% histologically confirmed; response rate, 51%	639 women randomly selected from the drivers' lists (<65 years) and from Health Care Finance administration (≥65 years); exclusions: hysterectomy and early menopause, before age 37 years; frequency-matched for age, county of residence	Interview: self-reported food-frequency questionnaire (2 years before) and additional telephone interview of controls	Endometrium	*Alcohol intake (g)* Q1 ≤0.5 Q2 0.6–2.1 Q3 2.2–9.0 Q4 >9.0	 1.0 (reference) 1.0 (0.6–1.6) 0.8 (0.5–1.3) 1.0 (0.5–1.8) p=0.58	Age, education, body mass index, diabetes, hypertension, smoking pack–years, age at menarche, parity, oral contraceptive use, menopausal status, post-menopausal estrogen use, total energy	Limitations due to low response rate among cases and controls

Table 2.69 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Weiderpass & Baron (2001), Sweden, 1994–95	709 born in Sweden and residing Sweden in 1 January 1994–31 December 1995 identified through six regional cancer registries, aged 50–74 years; intact uterus and no previous diagnosis of endometrial or breast cancer; 100% histologically confirmed by one pathologist (blinded); participation rate, 75%	3368 randomly selected from population register at the same time as cases; participation rate, 79.9%	Mailed questionnaire, or/and telephone interview	Endometrium	*Alcoholic beverage consumption (g/day)* Non-drinkers Drinkers >0–<1.59 1.6–3.99 ≥4	 1.00 (reference) 1.00 (0.83–1.21) 1.16 (0.90–1.49) 0.92 (0.70–1.20) 0.92 (0.70–1.20) p=0.44	Smoking, age, body mass index, parity, age at menopause, age at last birth, hormone replacement therapy use, oral contraceptive use, diabetes mellitus (self-reported)	

Table 2.69 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Petridou *et al.* (2002), Greater Athens area, Greece, 1999	84 women with no history of malignancy, resident in Greater Athens area, speaking Greek	84 women admitted at the same time as cases to the same hospital and department for small gynaecological operations; matched to cases for age; no history of malignancy, resident in Greater Athens, speaking Greek	Standardized questionnaire, interview	Endometrium	*Alcohol drinking* No Yes ≥2 glasses/ week	 1.00 (reference) 0.57 (0.23–1.42) p=0.23	Age, education, height, body mass index, age at menarche, ever pregnant, age at first pregnancy, number of children, abortions, menopausal status, alcohol, coffee, current smoking, appendectomy, cholecystectomy, thyroidectomy	Possible information and selection bias did not influence the validity of the results

CI, confidence interval; ICD, International Classification of Diseases

& Horm, 1977; Kato *et al*., 1989) and eight were population-based (Cusimano *et al*., 1989b; Webster *et al*., 1989; Swanson *et al*., 1993; Goodman *et al*., 1997b; Newcomb *et al*., 1997; Jain *et al*., 2000c; McCann *et al*., 2000; Weiderpass & Baron, 2001).

Ten studies (Cusimano *et al*., 1989b; Kato *et al*., 1989; Webster *et al*., 1989; Austin *et al*., 1993; Swanson *et al*., 1993; Parazzini *et al*., 1995a; Kalandidi *et al*., 1996; Newcomb *et al*., 1997; Weiderpass & Baron, 2001; Petridou *et al*., 2002) were designed to examine the association between alcoholic beverage intake, other lifestyle factors such as cigarette smoking, use of hormone-replacement therapy and other risk factors in the etiology of endometrial cancer. Six studies (La Vecchia *et al*., 1986; Shu *et al*., 1991; Levi *et al*., 1993; Goodman *et al*., 1997b; Jain *et al*., 2000c; McCann *et al*., 2000) were designed to evaluate nutritional factors in relation to the risk for endometrial cancer.

Confounding factors were considered in all of the above studies except for one (Cusimano *et al*., 1989b), although adjustment may have been incomplete in three studies (Williams & Horm, 1977 [age, race and smoking]; Shu *et al*., 1991 [pregnancies and weight]; Levi *et al*., 1993 [only adjusted for age and centre]). Interviews were conducted with or questionnaires were completed by the subjects in all studies.

The results of case–control studies were not consistent. Ten reported little or no association between alcoholic beverage consumption and the risk for endometrial cancer (Kato *et al*., 1989; Webster *et al*., 1989; Austin *et al*., 1993; Swanson *et al*., 1993; Kalandidi *et al*., 1996; Goodman *et al*., 1997b; Newcomb *et al*., 1997; McCann *et al*., 2000; Weiderpass & Baron, 2001; Petridou *et al*., 2002). Two found an inverse association (Williams & Horm, 1977; Jain *et al*., 2000c), which was significant in the latter study. Four studies reported an increased risk for endometrial cancer with higher alcoholic beverage consumption (La Vecchia *et al*., 1986; Cusimano *et al*., 1989b; Shu *et al*., 1991; Levi *et al*., 1993; Parazzini *et al*., 1995a); in two of these, the association was non-significant (Cusimano *et al*., 1989b; Shu *et al*., 1991), in one it was significant with a positive trend analysis (Parazzini *et al*., 1995a) and one (Levi *et al*., 1993) found a positive association relative to wine and liquor, but not to beer.

2.12.3 *Evidence of a dose–response*

There was no evidence of a trend of increasing risk for endometrial cancer with increasing alcoholic beverage consumption in the cohort studies.

In the case–control studies, there was no dose–response association between alcoholic beverage consumption and the risk for endometrial cancer in most studies. One study (Jain *et al*., 2000c) presented a negative dose–response association and one report showed a clear dose–response trend (Parazzini *et al*., 1995a). In another study, there was an indication of a dose–response in the association but no formal test for trend was presented (Webster *et al*., 1989).

2.12.4 *Types of alcoholic beverage*

Only one cohort study investigated the effect of specific types of alcoholic beverage (beer, wine, spirits) on the risk for endometrial cancer (Gapstur *et al*., 1993) and found no evidence of any association.

Seven case–control studies evaluated different alcoholic beverages in relation to risk for endometrial cancer (Williams & Horm, 1977; Austin *et al*., 1993; Levi *et al*., 1993; Swanson *et al*., 1993; Parazzini *et al*., 1995a; Goodman *et al*., 1997b; Weiderpass & Baron, 2001). The studies by Levi *et al*. (1993) and Parazzini *et al*. (1995a) showed an increased risk for endometrial cancer with increasing consumption of wine and hard liquor, but not beer. Overall, there were no consistent patterns of association between any specific type of alcoholic beverage and risk for endometrial cancer.

2.12.5 *Interactions*

Few studies presented information on possible interactions between alcoholic beverage intake and other variables. One cohort study investigated alcohol as an interacting factor with hormone-replacement therapy (Beral *et al.,* 2005). A positive association was found for Tibolone and an inverse association for continuous combined hormone-replacement therapy among women who consumed less than one drink daily.

Among the case–control studies, there was no consistent evidence of an interaction between alcoholic beverage consumption and different variables known or suspected to be associated with endometrial cancer, such as use of hormone-replacement therapy, body size, age, tobacco smoking, parity, education, physical activity, calory intake and other dietary aspects, oral contraceptive use or menopausal status.

2.13 Cancer of the ovary

2.13.1 *Cohort studies (Tables 2.70 and 2.71)*

Since 1988, four prospective cohort studies have examined the association between alcoholic beverage intake and the risk for ovarian cancer in special populations, namely women hospitalized or being treated for alcohol dependence (Adami *et al*., 1992a; Tønnesen *et al*., 1994, Sigvardsson *et al*., 1996; Lagiou *et al*., 2001; Table 2.70) and four have examined the association in the general population (Kushi *et al*., 1999; Kelemen *et al*., 2004; Schouten *et al*., 2004; Chang *et al*., 2007; Table 2.71). The studies were conducted in Europe (Denmark, the Netherlands and Sweden) and the USA. The studies in special populations presented results adjusted for age and calendar period only, whereas the population-based cohort studies presented results adjusted for a large variety of factors.

There was no evidence of an overall association between alcoholic beverage intake and the risk for ovarian cancer in these cohort studies.

Table 2.70 Cohort studies of ovarian cancer and alcoholic beverage consumption in special populations

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Comments
Adami *et al.* (1992a) Sweden, Cohort of people with a discharge diagnosis of alcoholism	Cohort of 9353 individuals (1013 women) with a discharge diagnosis of alcoholism in 1965–83; follow-up for 19 years (mean, 7.7 years); exclusion of cancer in the first year of follow-up	Registry-based	Women with diagnosis of alcoholism	4	**SIR** 1.9 (0.5–4.9)	
Tønnesen *et al.* (1994), Denmark, Cohort of non-hospitalized alcoholic men and women	18 307 male and female alcohol abusers who entered an outpatient clinic in Copenhagen during 1954–198?; 3093 women observed for 9.4 years	Registry-based	Alcohol abusers	6	0.9 (0.3–1.8)	
Sigvardsson *et al.* (1996), Sweden, Alcoholic women from the records of the Temperance Boards	Ovarian and fallopian tube cancer detected among 65 women	Registry-based	Alcohol abusers	65	1.2 (0.9–1.8)	
Lagiou *et al.* (2001), Sweden, Cohort of alcoholic women	Cohort of 36 856 women diagnosed with alcoholism between 1965 and 1994; mean duration of follow-up, 9.6 years, 317 518 person–years; first year of follow-up excluded from all analysis.	Registry-based	All women	76	**SIR** 0.86 (0.68–1.08) p=0.19	Expanded population and follow-up of the cohort reported by Adami *et al.* (1992a)

CI, confidence interval; SIR, standardized incidence ratio

Table 2.71 Cohort studies of ovarian cancer and alcoholic beverage consumption in the general population

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Kushi *et al.* (1999), Iowa, USA, Iowa Women's Health Study	29 083 women, aged 55–69 years (postmenopausal); follow-up 1986–95 (10 years); 139 incident cases of epithelial ovarian carcinoma; exclusions: cancer history other than skin, bilateral oopherectomy, incomplete questionnaire, energy intake implausibly high or low	Mailed self-administrated questionnaire (in 1986) and follow-up questionnaires (1987, 1989, 1992)	Ovary	*Alcohol consumption (g/day)* 0 0.9–3.9 4.0–10 >10	 78 43 8 10	 1.00 (reference) 1.37 (0.93–2.04) 0.61 (0.28–1.34) 0.49 (0.24–1.01) *p* trend=0.01	Age, total energy intake, number of live births, age at menopause, family history of ovarian cancer in a first degree relative, hysterectomy/ unilateral oopherectomy status, waist-to-hip ratio, level of physical activity, cigarette smoking, educational level	

Table 2.71 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Kelemen *et al.* (2004), Iowa, USA, Iowa Women's Health Study	27 205 women, aged 55–69 years (postmenopausal); follow-up, 1986–2000 (15 years); 147 incident epithelial ovarian cancers detected; association between ovarian cancer and alcohol in the context of folate consumption examined	Self-administered questionnaires	Ovary	*Alcohol consumption (g/day)* <0.01 0.01–3.9 4.00–9.9 ≥10	 48 75 12 12	 1.00 (reference) 0.78 (0.54–1.13) 0.75 (0.39–1.42) 0.58 (0.30–1.11) *p* trend=0.08	Age, folate, age at menopause, physical activity, postmenopausal hormone use, oral contraceptive use, family history of breast cancer, family history of ovarian cancer, known diabetes at baseline, smoking, carotene, vitamin C and vitamin E	

Table 2.71 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Schouten *et al.* (2004), Netherlands, The Netherlands Cohort Study	62 573 Dutch postmenopausal women, aged 55–69 years; started September 1986; follow up of sub-cohort of 2211 members; exclusion criteria: any cancer diagnosis other than skin, women who had undergone oopherectomy; follow-up biennially by mail to December 1995 (9.3 years); 235 cases of epithelial ovarian cancer detected; analysis based on 214 cases	Self-administered questionnaire	Ovary	*Alcohol consumption (categorical mean)* No (0) g/day 0.1–4 (1.9) g/day 5–14 (9.3) g/day ≥15 (26.3) g/day Total increment per 10 g alcohol	 57 74 28 21 	 1.00 (reference) 1.13 (0.79–1.63) 0.85 (0.53–1.37) 0.92 (0.55–1.54) *p* trend=0.54 1.01 (0.84–1.21)	Age, use of oral contraceptives, parity, height, body mass index, energy intake, current cigarette smoking	Possible limitation: misclassification of alcohol consumption (if any, expected to be non-differential); former-drinkers not separated from abstainers (small proportion)

Table 2.71 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Chang *et al.* (2007), USA, California Teachers Study	90 371 teachers; baseline assessment 1995–96; follow-up to end of 2003; excluded: women >85 years of age, with previous history of ovarian cancer, bilateral oopherectomy before baseline, when information not provided or invalid; 253 women diagnosed with epithelial ovarian cancer (227 invasive, 26 borderline)	Mailed questionnaire	Ovary (invasive and borderline)	**Year before baseline** *Total alcohol intake (g/day)* None <10 10–20 ≥20 *Alcohol from wine (g/day)* None <11.1 ≥11.1	 77 81 72 23 91 99 63	 1.00 (reference) 1.04 (0.76–1.42) 1.47 (1.06–2.03) 1.15 (0.71–1.84) *p* trend=0.19 1.00 (reference) 1.09 (0.80–1.50) 1.57 (1.11–2.22) *p* trend=0.01	Race, total energy intake, parity, oral contraceptive use, strenuous exercise, menopausal status/hormone replacement therapy, stratified by age at baseline; other alcohol types, race, total energy intake, parity, oral contraceptive/ hormone-replacement therapy use, strenuous exercise, menopausal status, stratified by age at baseline;	

Table 2.71 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Chang *et al*. (2007) (contd)				Interactions **Wine intake (g/day)** *Socioeconomic status: upper 25%* ≥11.1	39	1.96 (1.19–3.24) *p* trend=0.004	(contd) race, total energy intake, parity, oral contraceptive use, strenuous exercise, menopausal status/hormone replacement therapy, stratified by age at baseline	
				Lifetime strenuous physical activity ≤1.4 h None <11.1 ≥11.1	61 58 40	1.00 (reference) 1.07 (0.72–1.59) 1.68 (1.09–2.59) *p* trend=0.01		
				Parity: parous None <11.1 ≥11.1	71 73 48	1.00 (reference) 1.05 (0.73–1.50) 1.57 (1.06–2.34) *p* trend=0.02		
				Median age >50 years None <11.1 ≥11.1	68 72 51	1.00 (reference) 1.10 (0.76–1.57) 1.62 (1.09–2.39) *p* trend=0.01		
				Menopausal status: Peri/ postmenopausal None <11.1 ≥11.1	66 72 51	1.00 (reference) 1.16 (0.80–1.66) 1.72 (1.16–2.55) *p* trend=0.01		

Table 2.71 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Chang *et al*. (2007) (contd)				**Alcohol intake ≥11.1 g/day**				
				Oral contraceptive use				
				Never	29	1.70 (1.02–2.82)		*p* trend=0.03
				Ever	14	1.78 (0.85–3.72)		*p* trend=0.09
				Hormone therapy use				
				None	9	1.20 (0.51–2.78)		*p* trend=0.73
				Estrogen+progestin	16	1.17 (0.58–2.34)		*p* trend=0.45
				Estrogen only	15	2.03 (0.95–4.35)		*p* trend=0.06
				Cigarette smoking				
				Ever	27	1.42 (0.80–2.50)		*p* trend=0.24
				Never	36	1.77 (1.13–2.78)		*p* trend=0.01
				Total folate intake				
				≤473 µg/day	25	1.34 (0.78–2.30)		*p* trend=0.27
				>473 µg/day	37	2.07 (1.29–3.35)		*p* trend=0.002

CI, confidence interval; ICD, International Classification of Diseases

2.13.2 *Case–control studies (Table 2.72)*

Twenty-three case–control studies investigated the relationship between alcoholic beverage consumption and the risk for ovarian cancer in Australia, India, Japan, North America, Scandinavia and western Europe.

Twelve of these were hospital-based (West, 1966; Williams & Horm, 1977; Byers *et al*., 1983; Tzonou *et al*., 1984; Mori *et al*., 1988; Whittemore *et al*., 1988; Hartge *et al*., 1989; La Vecchia *et al*., 1992; Nandakumar *et al*., 1995; Tavani *et al*., 2001a; Yen *et al*., 2003; Pelucchi *et al*., 2005), one was based on cases and controls who were included in a cancer registry database (Kato *et al*., 1989) and 10 were population-based (Gwinn *et al*., 1986; Polychronopoulou *et al*., 1993; Kuper *et al*., 2000b; Goodman & Tung, 2003; McCann *et al*., 2003; Modugno *et al*., 2003; Riman *et al*., 2004; Webb *et al*., 2004; Peterson *et al*., 2006).

Confounding factors were considered in all studies, although adjustment was less extensive in studies published during the 1980s. Overall, the results of case–control studies do not suggest any association between alcoholic beverage consumption and the risk for ovarian cancer, although a few studies indicated either positive or negative associations.

2.13.3 *Evidence for a dose–response*

There was no consistent evidence of a trend of increasing risk for ovarian cancer with increasing alcoholic beverage consumption based on the cohort or case–control studies.

2.13.4 *Types of alcoholic beverage*

In two population-based cohort studies the association between types of alcoholic beverage was investigated (Schouten *et al*., 2004; Chang *et al*., 2007). Intake of wine during the year before baseline was associated with an increased risk for ovarian cancer in one study (Chang *et al*., 2007), but was not confirmed in the other (Schouten *et al*., 2004).

Seven case–control studies evaluated different alcoholic beverages in relation to the risk for ovarian cancer (Gwinn *et al*., 1986; La Vecchia *et al*., 1992; Tavani *et al*., 2001a; Goodman & Tung, 2003; Modugno *et al*., 2003; Webb *et al*., 2004; Peterson *et al*., 2006). Overall, there were no consistent patterns of association between any specific type of alcoholic beverage (beer, wine, spirits) and risk for ovarian cancer.

2.13.5 *Interactions*

Three of the cohort studies (Kelemen *et al*., 2004; Schouten *et al*., 2004; Chang *et al*., 2007) investigated possible interactions between alcoholic beverage intake and

Table 2.72 Case–control studies of ovarian cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
West (1966), Massachusetts, USA, 1959–60 (controlled case–history study)	92 (of 97) patients with primary ovarian malignancy, resident within a 50-mile radius of Boston, MA; aged 25–74 years; from 50 hospitals in Boston and greater Boston area, operated from 1 January 1959 until 31 March, 1960 (date of incidence = date of surgery); exclusions: women aged >75 years, women with co-existent malignancy of another organ, not metastatic from ovary	92 (of 97) hospital patients with benign ovarian tumour; matched for age, residence, day of surgery.	Interview based on the same protocol for cases and controls	Ovary	Use of alcohol	Data not shown p=0.28		No significant difference between alcohol users and non-users

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Williams & Horm (1977), USA, The Third National Cancer Survey (cross-sectional study), 1967–71	7518 cancer patients (all sites, men and women) interviewed; 57% selected randomly	Randomly selected patients with cancer of other, non-related sites	Interview	Ovary	*Wine level*	*Relative odds*	Age, race,	
					1	0.62		
					2	1.00		
					Beer level			
					1	0.54		
					2	0.88		
					Hard liquor level			
					1	0.61		
					2	0.93		
					Total alcohol oz–years level			
					1	0.88		
					2	0.87		
					Wine level		Age, race, smoking	
					1	0.49		
					2	0.85		
					Beer level			
					1	0.51		
					2	0.81		
					Hard liquor level			
					1	0.52		
					2	0.94		
					Total alcohol oz–years level			
					1	0.74		
					2	0.85		

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Byers *et al.* (1983), USA, 1957–65	274 white women patients, diagnosed within 2 years of interview, admitted to Roswell Park Memorial Institute, aged 30–79 years	1034 hospitalized white women admitted to same institute at the same time for non-malignant conditions, not related to the reproductive system or gastrointestinal system, or diagnosed with *diabetes mellitus* or thyroid disease, aged 30–79 years	Mailed questionnaire before admission to hospital, individual interview on the day of admission and second interview at admission by trained interviewer	Ovary	**Drinks per week** *At age 30–49 years* 0 <8 ≥9 *At age 50–79 years* 0 <8 ≥9 *At age 30–79 years* 0 <8 ≥9	 1.0 (reference) 0.84 0.56 1.00 (reference) 0.98 1.09 1.00 (reference) 0.92 0.83	Age	Possible selection bias does not account for the observed risks; possible recall bias; nearly all patients of advanced stage; analysis by stage not possible.
Tzonou *et al.* (1984), Athens, Greece, 1980–81	150 women with common and primary epithelial ovarian cancer, operated in any of 10 large hospitals of the Greater Athens area; 100% histologically confirmed; participation rate, 82.4%	250 women hospitalized at the same time in the Athens hospitals for first-time orthopaedic disorders, randomly chosen; participation rate, 100%	Standard questionnaire at interview by the same physician	Ovary	Non-drinkers Drinkers *Duration (years)* ≤9 10–19 20–29	(reference) 1.5 (0.9–2.5) 0.7 (0.2–2.2) 1.9 (0.7–4.8) 2.9 (1.1–7.6)	Age, parity, age at menopause, use of exogenous estrogens	

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Gwinn *et al.* (1986), Atlanta, Detroit, San Francisco, Seattle, the states of Connecticut, Iowa and New Mexico and the four urban counties of Utah, USA, December 1980–December 1982	433 women diagnosed between December 1980 and December 1982, lived in one of the study areas at the time of diagnosis, aged 20–54 years; 100% histologically confirmed; participation rate, 71%	2915 women identified by randomly selecting telephone numbers of households in the geographic areas where the cases lived, aged 20–54 years; matched by age (5-year intervals); no history of bilateral oophorectomy; response rate, 83.4%	Standard questionnaire in participants' homes by trained interviewers; questions about alcohol consumption habits in the last 5 years added to the questionnaire in August 1981	Ovary	*Average weekly consumption* Never drank Ever drank <50 g/week 50–149 g/week 150–249 g/week ≥250 g/week	 1.0 (reference) 0.9 (0.7–1.2) 1.0 (0.7–1.4) 0.8 (0.5–1.1) 1.0 (0.6–1.6) 0.5 (0.2–0.9)	Age, geographic region, religion, education, smoking, oral contraceptive use, parity, infertility, family history of ovarian cancer	Lack of information on drinking status for 13 cases and 50 controls (one drink=12.6 g alcohol)

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Mori *et al.* (1988), Hokkaido, Japan, 1980–81 and 1985–86	110 women with primary epithelial ovarian cancer, hospitalized in any hospital in Hokkaido; participation rate, 100%	220; two series: 110 patients from wards in hospitals in Hokkaido with diseases other than ovarian cancer; 110 identified from outpatients without any malignant gynaecological diseases; matched to cases by year of birth, year of the survey; participation rate, 100%	In-person interview	Ovary	*Consumption of alcoholic beverages* Less than once a week At least once a week	 1 (reference) 1.0 (0.6–1.9)	Unclear (none?)	

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Whittemore *et al.* (1988), San Francisco Bay area, USA, 1983–85	188 women from northern California diagnosed between January 1983 and December 1985 in one of the seven hospitals in Santa Clara County or at University of California San Francisco, Medical Center, aged 18–74 years	539; 280 hospitalized in one of the hospitals where cases were admitted, without overt cancer; 259 chosen from the general population by random-digit dialling; matched to cases by age (within 5-year intervals), race (white, black, oriental)	Structured home interviews by trained interviewers	Ovary	*Previous alcohol consumption* Non-drinker Drinker Non-drinker Heavy drinker (>20 drinks/ week)	 1 0.74 p=0.14 1 0.66 p=0.34	Observations not altered by adjustment for cigarette smoking or coffee consumption	No evidence of a trend in risk with increasing duration or amount of alcohol consumption; absence of data on diet may preclude examination of potential confounders.

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Hartge *et al.* (1989), Washington DC, USA, August 1978–June 1981	296 women with primary epithelial ovarian cancer, residents of metropolitan area of Washington DC, aged 20–79 years; diagnosis microscopically confirmed after operation; participation rate, 74%	343 women hospitalized at the same time and the same hospitals as cases, identified from hospital discharge lists; matched to cases by hospital, age, race; exclusion criteria: patients with psychiatric diagnosis and with diagnosis related to the major exposures of interest; patients with bilateral oophorectomy; participation rate, 78%	Standardized questionnaire by trained interviewers at participants' home shortly after diagnosis	Ovary	*Average weekly consumption* 0 Occasional drink 1–6 drinks 7–13 drinks ≥14 drinks	 1.0 (reference) 1.1 (0.7–1.9) 1.4 (0.8–2.3) 1.2 (0.7–2.2) 1.5 (0.8–2.8) p=0.14	Age, race	
Kato *et al.* (1989), Japan, 1980–86	417 women registered at Aichi Cancer Registry, diagnosed between 1980 and 1986, aged ≥20 years	8920 cases of cancer of other sites excluding cancers known to be alcohol-related	Records from Aichi Cancer Registry with available data on alcohol drinking habits	Ovary	*Alcohol drinking* Daily versus less	 0.38 (0.15–0.95) p<0.05	Age	Possible bias due to control selection from cancer patients; no information on important risk factors

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
La Vecchia *et al.* (1992), Milan, Italy, January 1983–May 1990 (overlaps with La Vecchia *et al.*, 1986)	801 women with incident ovarian cancer, aged 22–74 years; 100% histologically confirmed	2114 women admitted to a network of teaching or general hospitals in the greater Milan area for acute, non-neoplastic, gynaecological or hormone-related conditions diagnosed within the year before the interview, and not undergone bilateral oophorectomy, aged 24–74 years	In-person interview based on a standardized questionnaire during hospital admission	Ovary	*Alcohol consumption (drinks/day)* 0 <1 1<2 2<3 ≥3	 1.0 1.0 (0.7–1.4) 1.1 (0.9–1.4) 1.2 (1.0–1.5) 1.3 (0.9–1.8) $p \leq 0.05$ $\chi^2=4.29$	Age, education, smoking, menstrual and reproductive factors, oral contraceptive use, indicators of fat and green vegetable consumption	

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Polychronopoulou *et al.* (1993), Greater Athens, Greece, June 1989–March 1991	189 women residents of Greater Athens, operated for epithelial ovarian cancer in two hospitals, aged ≤75 years	200 residents of Greater Athens, visitors of patients hospitalized in the same wards as the cancer patients at the same time, aged <75 years; exclusion criteria: previous cancer diagnosis or at least one ovary removed; not matched by age	In-person interview questionnaire by resident doctor at each of the hospitals	Ovary	*Consumption of alcoholic beverages (glasses/day)* Never ≥1 1 1–2 >2	 1.00 0.85 (0.52–1.39) 1.06 (0.82–1.36) 0.94 (0.49–1.79) 1.62 (0.66–3.96) *p*=0.67	Age (10-year group) Age, years of education, age at menarche, weight before the onset, menopausal status, age at menopause, parity, age at first birth, smoking, coffee drinking	
Nandakumar *et al.* (1995), Bangalore, India, 1982–85	97 ever-married women obtained from the cancer registry in Bangalore; mean age, 48.3 years	194 women from the same area, attending a referral hospital for cancer or suspected cancer, with the diagnosis of no evidence of cancer; no hysterectomy; matched by age, material status, calendar time	Interview	Ovary	*History of alcohol consumption* No Yes	 1.00 (reference) 1.3 (0.2–8.0)	Age, marital status, calendar time, area of residence	Statistical analysis accounted for the matched design of the study

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Kuper *et al.* (2000b), eastern Massachusetts/ New Hampshire, USA, May 1992–March 1997	549 women born and resident in New Hampshire or Massachussetts, without any previous ovarian malignancy or bilateral oophorectomy, aged 50–74 years; reported to the regional Cancer Registries; specimens reviewed by one of authors; histological classification based on original histology of local pathologists; participation rate, 79%	516 identified by combination of random-digit dialling and selection from community lists; matched to cases by community of residence, age within 4 years	In-person interview self-administered food-frequency questionnaire	Ovary	*Drinks/day* 0 0–1 >1–2 >2–3 >3	 1.00 0.91 (0.67–1.23) 1.33 (0.88–2.01) 0.92 (0.50–1.69) 1.35 (0.80–2.26) p=0.20	Age, centre, material status, parity, body mass index, oral contraceptive use, family history of breast, ovarian and prostate cancer, tubal ligation, education, alcohol consumption, pack–years of smoking	Low participation rate for cases and controls, possible selection bias; heavy alcohol drinkers could be under-represented, especially among controls.

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Tavani *et al.* (2001a), Milan, Pordenone, Pauda, Gorizia, Latina, Naples, Italy, January 1992–September 1999	1031 women with incidental invasive epithelial ovarian cancer, aged 18–79 years; 100% histologically confirmed	2411 women admitted to the hospital for acute, non-neoplastic, non-hormone-related diseases and unrelated to known and potential risk factors for ovarian cancer, aged 17–79 years	Structured questionnaire, in-person interview at hospitals	Ovary	*Total alcohol (g/day)* Never drinker <12 12–<24 24–<36 ≥36	 1.00 (reference) 1.02 (0.80–1.30) 1.29 (1.00–1.67) 1.04 (0.80–1.36) 1.09 (0.76–1.57) χ^2 for trend=0.68 p=0.409	Study centre, year of interview, age, education, parity, age at menopause, oral contraceptive use, family history of ovarian or breast cancer, body mass index, energy intake	Limitations common to other hospital-based case–control studies

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Goodman & Tung (2003), Hawaii, Los Angeles, CA, USA, 1993–99	558 women resident in Hawaii or Los Angeles County for at least 1 year, no history of ovarian cancer before, identified through the rapid reporting systems of Hawaii Tumor Registry and Los Angeles County Cancer Surveillance Program, aged ≥18 years; 100% histologically confirmed; response rate, 62%;	607 women with no prior history of ovarian cancer and at least one intact ovary; from lists of female Oahu residents/Hawaii; if ≥65 years, supplemented by participants of Health Care Financing Administration in Oahu; in Los Angeles, >95% selected based on a neighbourhood walk procedure; frequency-matched to patients based on ethnicity, 5-year age group, study site; participation rate, 67%	Structured in-person interviews; reference date for cases, year before diagnosis; for controls, interview date	Ovary	*Total alcohol* Never drinker Ever drinker Former drinker Current drinker	 1.00 0.88 (0.67–1.16) 1.16 (0.82–1.64) 0.69 (0.50–0.96)	Age, ethnicity, education, study site, oral contraceptive use, parity, tubal ligation	Possibility of recall bias; participation rates not optimal and may have affected the validity of the findings.

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
McCann *et al.* (2003), western New York, USA, 1986–91	124 women with primary ovarian cancer, aged 40–85 years; 100% histologically confirmed	696; randomly selected from driver's licence lists for women <65 years and from Health Care Financing Administration for women ≥65 years of age; frequency-matched to cases on age (±5 years), county of residence	In-person interview	Ovary	*Alcohol intake (g/day)* <0.2 0.2–1.1 1.1–3.7 3.7–12.9 >12.9	 1.00 0.55 (0.30–1.02) 0.67 (0.36–1.25) 0.97 (0.54–1.73) 0.62 (0.34–1.12) $p<0.05$	Age, education, total months menstruating, difficulty becoming pregnant, oral contraceptive use, menopausal status, total energy	Small number of cases, possible recall and information bias, short time between diagnosis and interview
Modugno *et al.* (2003), Delaware Valley, USA, May 1994–July 1998	761 women from 39 hospitals around Delaware Valley diagnosed within 9 months before interview, aged 20–69 years, 100% confirmed by pathology; response rate, 88%	1352 women ascertained by random-digit dialling (aged ≤ 65 years) or through Health Care Financing Administration lists (aged 65–69 years); frequency-matched to cases by 5-year age groups, three-digit telephone exchanges	Standardized, in-person interview	Ovary	**Ethanol consumption** *Non-mucinous cancers* Never Ever Current Former *Mucinous cancers* Never Ever Current Former	 1.0 (reference) 1.03 (0.84–1.26) 0.96 (0.75–1.23) 1.12 (0.86–1.46) 1.0 (reference) 0.92 (0.61–1.40) 0.97 (0.60–1.57) 0.87 (0.51–1.49)	Age, parity, use of oral contraceptive, education, race, tubal ligation, smoking, family history of ovarian cancer	Possibility of error in the histological classification; possibility for selection bias among controls and under representation of heavy drinkers in the control group

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Yen *et al.* (2003), Taipei, Taiwan, China, 1993–98	86 women with primary epithelial ovarian cancer resident in Taiwan for at least 20 years, aged 20–75 years; hospital pathological records; exclusions: major gynaecological operation, hysterectomy, oophoerectomy	369 women hospitalized for non-malignant, non-gynaecological conditions, unrelated to hormones or digestive tract or to long-term modification of diet; matched by age (5-year range), hospital, admission date	In-person interviews at the hospitals	Ovary	*Alcohol consumption* No Yes	 1.0 (reference) 0.71 (0.20–2.51)	Age, income during marriage, education	Limitation on power of the test due to small sample involved; possible selection bias
Riman *et al.* (2004), Sweden, 1 October 1993–31 December 1995	655 women born and resident in Sweden, with primary, newly diagnosed epithelial ovarian cancer, aged 50–74 years; 100% histologically confirmed; participation rate, 79%	3899 women randomly selected from a national population registry and sampled simultaneously with cases; frequency-matched to the expected age distributions; exclusion: women with previous bilateral oophorectomy	Mailed, self-administered questionnaires and additional telephone interview with cases who failed to respond	Ovary	Alcohol consumption (g/day) Non-users <*5* ≥*5*	 1.0 (reference) 0.94 (0.77–1.14) 0.99 (0.75–1.29) *p*=0.80	Age, parity, body mass index, age at menopause, duration of oral contraceptive use, ever use of hormone replacement therapy; *p*-value for the likelihood ratio test of heterogeneity	Possible recall bias

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Webb *et al.* (2004), Australia (New South Wales, Victoria and Queensland), August 1990–December 1993	696 Australian women treated in the major treatment centres in New South Wales, Victoria and Queensland, aged 18–79 years; 100% histologically confirmed; participation rate, 89%	786 cancer-free women selected at random from the electoral roll; frequency-matched to the cases for age (within 10-year bands), urban/rural district of residence; women with reported history of ovarian cancer or bilateral oophorectomy excluded	Face-to-face interview and food-frequency questionnaire	Ovary	None 1/week 1–6/week 1–1.9/day ≥2/day	*Invasive cancers* 1.0 0.84 (0.62–1.14) 0.73 (0.53–1.02) 0.85 (0.53–1.36) 0.46 (0.27–0.79) p=0.009 p=0.05 (excluding non-drinkers)	Age (in years), age squared, education, body mass index, smoking (newer, past, current), duration of oral contraceptive use, parity, caffeine intake	
Pelucchi *et al.* (2005), Italy (four areas), 1992–99	1031 women admitted to the major teaching and general hospitals; 100% histologically confirmed	2411 women admitted to the same network of hospitals for acute, non-malignant and non-gynaecological conditions, unrelated to hormonal diseases or to long-term modifications of diet	Standard questionnaire during hospital stay by centrally trained interviewers; food-frequency questionnaire	Ovary	Non-drinkers/light alcohol drinkers (<1.8 g/ day) Moderate/heavy alcohol drinkers (≥1.8 g/day)	0.93 (0.76–1.14) χ^2=0.97 p=0.32 1.02 (0.86–1.23) χ^2=0.10 p=0.75	Age, study centre, year of interview, education, parity, body mass index, alcohol consumption, oral contraceptive use, physical activity, non-alcohol energy intake	Ovarian cancer risk for folate intake in alcohol strata (null results in brief)

Table 2.72 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Peterson *et al*. (2006), Massachusetts (excluding Boston) and Wisconsin, USA, 1993–95 and 1998–2001	762 English-speaking women from two case–control studies (new diagnosis reported to the respective state cancer registries with listed telephone numbers and drivers' licences) verified by self report if less than 65 years of age or Medicare beneficiaries if 65 years or older, aged 40–79 (1993–95) or 20–75 years (1998–2001); 63 cases excluded due to unclear pathological diagnosis and 7 due to missing data on alcohol consumption; participation rate, 66%	6271 randomly selected from lists of licensed drivers if less than 65 years and from rosters of Medicare beneficiaries compiled by the Health Care Financing Administration if 65 years or older; all women had publicly available telephone number; frequency-matched to the age distribution of ovarian cancer and breast cancer cases enrolled in a breast cancer study; participation rate, 80.6%	Structured telephone interview with interviewers blinded to case/control status of the subjects	Ovary	*Recent past* None Ever drank <1 drink/week 1–6 drinks/week ≥1 drink/day	 1.00 1.06 (0.87–1.29) 1.05 (0.84–1.32) 1.15 (0.92–1.42) 0.89 (0.70–1.20) p=0.77	Age, state of residence	Possible bias related to control selection and recall bias

CI, confidence interval; ICD, International Classification of Diseases

other variables. Some weak interactions were found by Chang *et al*. (2007) for women who drank more than one glass of wine daily and were over 50 years of age, post-menopausal, used estrogen only hormone therapy, belonged to a higher social class, were never smokers and had higher total folate intake. Among the case–control studies, there was no consistent evidence of interaction between alcoholic beverage consumption and different variables known or suspected to be associated with ovarian cancer, such as reproductive history, education, body size or diet.

2.14 Cancer of the uterine cervix

2.14.1 *Cohort studies (Table 2.73)*

A total of six prospective cohort studies have examined the association between alcoholic beverage intake and risk for cervical cancer, all of which were carried out in special populations, namely women who were treated for alcohol abuse or alchoholism (Prior, 1988; Adami *et al*., 1992a; Tønnesen *et al*., 1994; Sigvardsson *et al*., 1996; Weiderpass *et al*., 2001b) or worked as waitresses (Kjaerheim & Andersen, 1994).

These studies were conducted in Scandinavia (Adami *et al*., 1992a; Kjaerheim & Andersen, 1994; Tønnesen *et al*., 1994; Sigvardsson *et al*., 1996; Weiderpass *et al*., 2001b) and in the United Kingdom (Prior, 1988), and were all based on record linkages between existing databases, such as registries for hospitalizations and clinical care for alcoholism, and data from trade-union files. The cancer outcome was obtained by the respective cancer registries in each country/region. The comparison of incidence rates of cervical cancer was made between the special populations selected for the studies and women from the general population who were the same age as the study participants, during the same time periods.

All five studies conducted among women who were treated for alcohol abuse or alchoholism presented elevated risk estimates for invasive cervical cancer. However, none of them were able to adjust for known risk factors for cervical cancer, namely human papillomavirus (HPV) infections, number of sexual partners and tobacco smoking, or attendance of cervical cancer-screening programmes. It is possible that women who abuse alcohol have other behavioural patterns that may affect the risk for cervical cancer, such as non-compliance with screening, tobacco smoking and having a higher prevalence of HPV than the general populations in their respective countries.

2.14.2 *Case–control studies (Table 2.74)*

The association between alcoholic beverage intake and cervical cancer was evaluated in 12 case–control studies, seven of which were hospital-based (two from Italy, two from Thailand, one from Uganda and studies from United Kingdom and the USA), three were register- or cohort- based (from the USA and Zimbabwe), one was population-based (from Lesotho) and one was a large multicentre study from Latin America

Table 2.73 Cohort studies of alcoholic beverage consumption and cervical cancer in special populations

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Prior (1988), Birmingham, United Kingdom, Study of patients hospitalized for alcohol-related diseases	1110 patients (234 women) hospitalized in the Birmingham Region between 1948 and 1971 for alcohol-related conditions; follow-up to 1981; compared with the West Midlands Region	Hospital discharge record	*Cervix uteri* (ICD-8/180)	Cancer morbidity among women hospitalized for alcohol-related conditions	*Obs/Exp* 3	3.7 (p<0.05)		
Adami *et al.* (1992a) Sweden, Cohort of people with a discharge diagnosis of alcoholism	9353 individuals (1013 women) with a discharge diagnosis of alcoholism in 1965–83; follow up for 19 years (mean, 7.7 years); exclusion of cancer in the first year of follow-up	Registry based	*Cervix uteri*	Alcohol abusers	6	**SIR** 4.2 (1.5–9.1)		

Table 2.73 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Kjaerheim & Andersen (1994), Norway, Norwegian Cohort of Waitresses	5314 waitresses organized in the Restaurant Workers Union between 1932 and 1978; follow-up 1959–91	Employers lists from Restaurant Workers Union	*Cervix uteri* (ICD-7/171)			**SIR**		
				Waitresses versus women in Norway except Oslo	51	1.7 (1.3–2.3)		
				Type of restaurant				
				Alcohol serving	28	1.8 (1.3–2.5)		
				Non-alcohol serving	13	1.6 (0.8–2.7)		
				Years since first employment				
				0–9	20	1.5		
				10–19	22	1.8		
				≥20	9	1.8		
Tønnesen *et al.* (1994), Denmark, Cohort of non-hospitalized alcoholic men and women	18 307 alcohol abusers (men and women) who entered an outpatient clinic in Copenhagen during 1954–198?; 3093 women observed for 9.4 years	Registry based	*Cervix uteri*	Alcohol abusers	22	2.00 (1.2–3.0) ($p \leq 0.01$)		

Table 2.73 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Sigvardsson *et al.* (1996), Sweden, Temperance Boards Study	Nested case–control study; records of 15 508 alcoholic women born between 1870 and 1961 obtained from Temperance Boards; control matched for region and day of birth; incidence data from Swedish Cancer Registry	Registry based	*Cervix uteri* (ICD-7/171)	Alcohol abusers	187	3.9 (2.8–5.4)		

Table 2.73 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Weiderpass *et al.* (2001b), Sweden, National Board of Health and Welfare/ Study of Alcoholic Women	36 856 women (mean age, 42.7 years) registered and hospitalized with alcoholism between 1965 and 1994; data from Inpatients Register; linkages to nationwide Registers of Causes of Death and Emigration and national Register of Cancer; average follow-up time, 9.4 years	Registry based; linkages	*Cervix uteri in situ*			**SIR**		
				Total	502	1.7 (1.6–1.9)		
				Age at cancer diagnosis (years)				
				<35	180	1.5 (1.3–1.8)		
				35–49	246	1.8 (1.6–2.0)		
				50–59	55	2.4 (1.8–3.1)		
				≥60	21	2.7 (1.7–4.2)		
			Cervix uteri Invasive (ICD-7/171)	Total	129	2.9 (2.4–3.1)		
				Age at cancer diagnosis (years)				
				<35	16	3.2 (1.8–5.2)		
				35–49	40	2.4 (1.7–3.2)		
				50–59	35	3.7 (2.6–5.2)		
				≥60	38	2.9 (2.1–4.0)		

CI, confidence interval; ICD, International Classification of Diseases; Obs/Exp, observed/expected; SIR, standardized incidence ratio

Table 2.74 Case–control studies of invasive cervical cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Williams & Horm (1977), USA, The Third National Cancer Survey (cross-sectional study), 1967–71	57% randomly selected and interviewed from 7518 cancer patients from the Third National Cancer Survey (all sites)	Randomly selected patients with cancer of other, non-related sites	Interview	Cervix		**Relative odds**		Age, race
					Wine level			
					1	0.61		
					2	1.44		
					Beer level			
					1	1.29		
					2	1.29		
					Hard liquor level			
					1	0.61		
					2	0.79		
					Total alcohol oz–years level			
					1	0.88		
					2	0.81		
					Wine level			Age, race, smoking
					1	0.62		
					2	1.53		
					Beer level			
					1	1.22		
					2	1.20		
					Hard liquor level			
					1	0.54		
					2	0.76		
					Total alcohol oz–years level			
					1	0.82		
					2	0.73		

Table 2.74 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Harris *et al.* (1980), Oxford United Kingdom, 1974–79	237 women with abnormal cervical smears and who had undergone cervical punch biopsy or surgical conisation at two hospitals in Oxford (John Radcliffe and Churchill Hospital) between October 1974 and June 1979; 65 cases of carcinoma *in situ*	422 women who attended gynaecological clinics at the John Radcliffe Hospital or who received inpatient or outpatient gynaecological care at the Churchill Hospital during the same time period; small numbers of controls were patients receiving initial cervical smear at the Abington Health Centre; exclusions: women who had hysterectomy, history of cancer or a mental illness	Interview at the hospital prior to histological diagnosis	Cervix, cervical carcinoma *in situ*	**Alcohol consumption** *Carcinoma* in situ Never Monthly Weekly Daily	 1.0 0.83 0.87 1.23	Age (<30, 30–40, ≥40)	

Table 2.74 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Marshall *et al.* (1983), Buffalo, NY, USA	513 white women, patients admitted to the Roswell Park Memorial Institute between 1957 and 1965, diagnosed with cervical cancer during admission; diagnoses were histologically confirmed	490 white women matched to the cases by age (5-year group); ascertained from patient lists; diagnosed mainly with non-neoplastic diseases of sites other than genitourinary and gastrointestinal tract; for 234 of these patients, no diagnosis was established at discharge	Mailed pre-admission questionnaire; interview at admission; both were completed before diagnosis	Cervix	**Alcohol consumption** *Types of alcohol* None Beer Wine Distilled liquor Beer and wine Beer and distilled liquor Wine and distilled liquor All types of alcohol *Monthly consumption (drinks)* 0 1–10 11–20 21–30 ≥31	 1.0 (reference) 1.8 (1.2–2.7) 0.8 (0.3–1.6) 0.7 (0.4–1.1) 1.5 (1.2–2.0) 1.3 (0.8–2-0) 0.6 (0.3–1.2) 0.8 (0.5–1.3) 1.0 (reference) 1.0 (0.7–1.3) 1.1 (0.7–1.7) 1.3 (0.7–2.5) 1.2 (0.8–1.9)		

Table 2.74 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Martin & Hill (1984), Lesotho, 1950–74	257 hospital patients from 14 geographical areas diagnosed between 1950 and 1969, aged 23–86 years (average, 47.9 years); followed in 1970–74; diagnosis based on histological examination, cervical smear or very strong clinical evidence (invasive cervical cancer)	257 women free of cancer from the same or adjacent geographical areas (provided they were of the same character), aged 22–89 years	Questionnaire	*Cervix uteri*	*Indigenous alcohol consumption* Drinker versus non-drinker *European alcohols* Drinker versus non-drinker	2.4 χ^2=9.47 p<0.01 3.19 χ^2=6.95 p<0.01	Tobacco, European alcohol consumption Tobacco, indigenous alcohol consumption	The mycotoxin zearalenone in indigenous alcohols suggested to be correlated with cervical cancer; limitations: lack of quantities of alcohol consumption; cervical cancer patents represent a lower educational and social status than the rest of society in Lesotho.

Table 2.74 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Cusimano *et al.* (1989b), Italy, Ragusa, 1 Jan. 1983–30 Jun. 1985	39 women from Ragusa and province (Italy/ Sicily) diagnosed with cervical cancer between 1 Jan. 1983 and 30. Jun 1985, aged 35–79 years; 100% histologically confirmed (invasive); participation rate, 83%	156 women from the same geographical region, aged 30–76 years; matched to cases by age (2.5-year range), type of health service consulted; women who had undergone hysterectomy excluded	Structured questionnaire; interview	*Cervix uteri*	*Alcohol consumption* No Yes	 1.0 (reference) 0.72 (0.35–1.50)	'Adjusted for confounding variables' (unclear which ones: parity, number of spontaneous miscarriages, use of oral contra-ceptives, young age of proband's mother at birth)	

Table 2.74 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Herrero *et al.* (1989), Latin America: Colombia, Costa Rica, Mexico, Panama, Jan. 1986–June 1987	667 patients living in the study area for at least 6 months prior to diagnosis; diagnosed with incidental invasive squamous-cell carcinoma between January 1986 and June 1987 in hospitals in Bogota (Colombia)-the Ministry of Health cancer referral center, three Social Security hospitals in San Jose, Costa Rica, the Social Security's Oncology Hospital in Mexico City, Mexico, and The National Oncology Institute in Panama, aged <70 years; 100% histologically confirmed	1430 (1064 hospital, 366 community) randomly selected from the hospital patients in Bogota and Mexico City and both from referral hospitals and community in Costa Rica and Panama; matched by age (5-year range); women with history of hysterectomy or cancer, endocrine, nutritional, psychiatric, gynaecological, smoking-related diseases excluded	Interview	*Cervix uteri*	*Ethanol (g/week)* Non-drinker Occasional ≤48.6 >48.6	*Risk ratios* 1.0 (reference) 2.1 1.6 1.1	Smoking, number of sexual partners, other covariates	Study of smoking and cervical cancer where alcohol drinking was a confounder

Table 2.74 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Licciardone *et al.* (1989), Missouri, USA, 1984–86	331 white women identified by Missouri Cancer Registry between July 1984 and June 1986 (invasive cervical cancer)	993 white women randomly selected from Missouri Cancer Registry, reported at the same time (1984–86) for malignancies unrelated to smoking or alcohol; frequency matched to cases by age	Hospital records	*Cervix uteri* (ICD180)	*Alcohol consumption* Never drank Former drinker Light drinker (<2 drinks/day) Heavy drinker (≥2 drinks/day) Drinker (quantity unknown) Unknown	*Odds ratio* 1.00 (reference) 0.7 (0.2–2.9) 0.8 (0.5–1.2) 0.8 (0.4–1.6) 1.0 (0.5–1.8) 1.0 (0.6–1.7)	Age, smoking, alcohol consumption, stage at diagnosis	
Parkin *et al.* (1994), Bulawayo, Zimbabwe, 1963–77	1263 data records from cancer registry of Bulawayo (covering provinces Matabeleland North and South, Masvingo and Midlands); 86% squamous-cell carcinoma, 3.4% adenocarcinoma	2347 women with cancer at sites other than breast, *corpus uteri*, uterus unspecified	Standard questionnaire; interview of cases or relatives	*Cervix uteri*	*Alcohol intake* Never Occasional Frequent	 1.0 (reference) 1.4 (1.1–1.8) $p<0.05$ 1.6 (1.3–1.9) $p<0.001$ p trend<0.001	Age group, time period, province, education, age at first intercourse, number of full-term pregnancies	

Table 2.74 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Thomas *et al.* (2001a), Bangkok, Thailand, 1991–93	232 women admitted to public wards of Sirairaj Hospital, Bangkok, with diagnosis of cervical carcinoma between 1 September 1991 and 1 September 1993; born in 1930 or later and who lived in Thailand at least the past year; 100% histologically confirmed; squamous (190) and adenomatous (42) carcinoma; gave DNA specimen for study	Collected from the same hospital, up to 24 h after the case had been admitted; matched by age (5-year range); resident of the same region of the country as case; exclusion: women who were treated for diseases associated with use of steroid contraceptives	All cases and controls were interviewed at hospital; women gave a blood specimen	*Cervix uteri*	*Ever drank alcoholic beverages* No Yes No Yes	**Odds ratio** *HPV 16-positive* 1.0 (ref) 1.1 (0.7–1.6) *HPV 18-positive* 1.0 (ref) 1.5 (0.8–2.9)	Age	Study of risk factors for invasive cervical carcinoma with HPV types 16 and 18; controls in this analysis were women HPV-positive for types 16 and 18, respectively.

Table 2.74 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Thomas *et al.* (2001b), Bangkok, Thailand, 1991–93	190 women with invasive cervical cancer compared with 65 women with in-situ disease, admitted to public wards of Sirairaj Hospital in Bangkok between 1 September 1991–1 September 1993; born in 1930 or later and lived in Thailand at least the past year; 100% histologically confirmed	291 for invasive cancers and 124 for *in situ*; collected from the same hospital, up to 24 h after the case had been admitted; matched by age (5-year range), resident of the same region of the country as case; exclusion: women who were treated for diseases associated with use of steroid contraceptives	All cases and controls were interviewed at hospital	*Cervix uteri*	*Ever drank alcoholic beverages* No Yes	**Odds ratio** *Invasive* 1.0 (reference) 1.0 (0.7–1.5)	Age, HPV type or other/ unknown HPV type, or no HPV infection	Control group presented: women without in-situ lesions

Table 2.74 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Chiaffarino *et al.* (2002), northern Italy, 1981–93	791 women admitted to university and general hospitals, aged 17–79 years; diagnosis of incident invasive cervical cancer; exclusion: alcoholic women; 100% histologically confirmed; participation rate, >95%	916 women admitted to the same hospitals for acute conditions; exclusion: alcoholic women; participation rate, >95%	Structurized questionnaire; interview	Cervix uteri	*Total alcohol* Non-drinker Drinker Occasional Regular	 1.00 (reference) 1.23 (0.99–1.53) 1.21 (0.88–1.65) 1.24 (0.98–1.56) χ^2 trend=3.24 p=0.072	Age, year of interview, education, cervical screening history, smoking habit, menopausal status, number of partners, parity, oral contraceptive use, hormone replacement therapy use	Data from two case–control studies of Parazzini *et al.* (1992, 1997); residual confounding could not be excluded for modest association.
Newton *et al.* (2007), Kampala, Uganda, 1994–1998	343 HIV-seronegative women, 15 years old and older, with a provisional diagnosis of cervical cancer from all wards and outpatient clinics of the four main hospitals in Kampala, Uganda	359 controls diagnosed with other cancer at sites or type (except for cancer of the breast, ovary or the female genital tract) and benign tumours derived from wards and outpatients clinics of the main hospitals in Kampala, Uganda	Interview by trained counsellors; questions about social and demographic factors, sexual and reproductive history	*Cervix uteri*	*Alcohol consumption* Never Once/week 2–4/week Most days χ^2 trend=0.2 p=0.7	 1.0 (reference) 1.6 (1.1–2.5) 1.6 (0.9–2.7) 0.4 (0.2–0.9)	Age group	

CI, confidence interval; HIV, human immunodeficiency virus; HPV, human papillomavirus; ICD, International Classification of Diseases

that included both hospital and population controls. Seven studies did not show any or any significant relative risk among alcoholic beverage drinkers (Harris *et al.,* 1980; Marshall *et al.,* 1983; Cusimano *et al.,* 1989b; Licciardone *et al.,* 1989; Thomas *et al.,* 2001a; Chiaffarino *et al.,* 2002). Significantly elevated relative risks emerged from two case–control studies from Africa, in which adjustment for confounding was incomplete (Martin & Hill, 1984; Parkin *et al.,* 1994). In the study from Latin America, in which adjustment for possible confounders was adequate, there was an elevated risk for cervical cancer among occasional drinkers (confidence intervals not given) but no association with heavy drinking (Herrero *et al*., 1989). No consistent results with a higher risk among moderate drinkers were found in a study from Uganda (Newton *et al.,* 2007).

2.14.3 *Evidence of a dose–response*

The cohort studies did not present convincing evidence of a dose–response between risk for cervical cancer and duration of alcoholic beverage consumption, which was roughly estimated as years since cohort enrolment (first hospitalization/clinical treatment for alcoholism).

Two case–control studies from the USA and Latin America (Herrero *et al*., 1989; Licciardone *et al.,* 1989), in which at least smoking habits and number of sexual partners were adjusted for, showed no dose–response effect. In four other case–control studies in which there was some indication of a possible dose–response association (Harris *et al.,* 1980; Marshall *et al.,* 1983; Martin & Hill, 1984; Parkin *et al*., 1994), the adjustment for possible confounders was incomplete. In one study, such a trend was observed only among consumers of wine and other alcoholic beverages combined (Chiaffarino *et al*., 2002).

2.14.4 *Types of alcoholic beverage*

The cohort studies did not investigate the effect of specific types of alcoholic beverages (beer, wine, spirits) on risk for cervical cancer.

Almost all case–control studies that tried to evaluate specific types of alcoholic beverage (Marshall *et al.,* 1983; Martin & Hill, 1984; Chiaffarino *et al*., 2002) did not find consistent differences in risk for cervical cancer. Only Williams and Horm (1977) found an elevated risk for cancer of the cervix among beer drinkers.

2.14.5 *Interactions*

None of the cohort or case–control studies presented information on possible interactions between alcoholic beverage intake and other variables in the causation of cervical cancer. Information for histological subtypes was not given.

2.15 Cancer of the prostate

2.15.1 *Cohort studies*

(a) Special populations (Table 2.75)

Only one of the eight studies of special populations showed an association between alcoholic beverage consumption and cancer of the prostate. In a Danish study of alcohol abusers, higher numbers of prostate cancers were observed compared with those expected from the general population (Tønnesen *et al*., 1994).

(b) General population (Table 2.76)

Studies of prostate cancer that were conducted more recently generated concern when no attempt was made to distinguish between cases that were detected by screening, with a possibility that many might not have presented clinically during the lifetime of the individual in the absence of screening, and those that presented clinically and were more likely to be progressive. Among the 17 cohort studies, two specifically identified more advanced cases (Platz *et. al.*, 2004; Baglietto *et. al.*, 2006) but neither suggested any association between alcoholic beverage consumption and such cases of prostate cancer. A few of the other cohort studies that did not make this distinction suggested an increased risk for prostate cancer at elevated levels of alcoholic beverage consumption (Hirayama, 1992; Schuurman *et al*., 1999; Putnam *et al*., 2000; Sesso *et al*., 2001), but there was no consistent dose–response relationship and many other cohort studies showed no association.

2.15.2 *Case–control studies (Table 2.77)*

Five of the 33 case–control studies considered type of disease. Slattery and West (1993) considered ‘aggressive’ tumours, Hodge *et al*. (2004) studied ‘clinically important’ disease, Hayes *et al*. (1996) conducted stratified analyses by tumour grade and stage, Chang *et al*. (2005) considered localized and advanced disease and Schoonen *et al*. (2005) classified cases as less and more aggressive cancers. The remainder did not appear to make any distinction, although, in the study of Walker *et al*. (1992), 90% of the cases were advanced at presentation. The majority of the studies showed no association between alcoholic beverage consumption and prostate cancer. Of those that suggested a positive association, one (De Stefani *et al*., 1995) showed a borderline elevation of risk for high levels of consumption of beer, but the risk at high levels of total alcoholic beverage consumption was not significant; one (Hayes *et al*., 1996) showed significant elevations in risk for ‘heavy’ and ‘very heavy’ consumers of alcoholic beverages, with higher risks among those with poorly or undifferentiated tumours, or with regional or distant metastases; and another (Sharpe & Siemiatycki, 2001) reported an elevation in risk for those with long duration of drinking, and the greatest elevation in risk for those who started drinking at age <15 years.

Table 2.75 Cohort studies of alcoholic beverage consumption and cancer of the prostate[a] in special populations

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Sundby (1967), Oslo, Norway	1722 men treated for alcoholism in 1925–39; follow-up to 1963; 29 lost to follow-up, 1061 died before the end of study; 632 alive at the end of study	Not reported	Not reported	16	Not reported	Not reported	Expected number based on Oslo urban mortality data
Hakulinen *et al.* (1974), Finland	Male 'chronic alcoholics', >30 years of age, registered in 1967–70 when under custody of alcohol-misuse supervision, or when sent to a labour institute because of the vagrant law; mean annual number in registry=4370	Alcohol misusers registry; Finnish Cancer Registry; Social Welfare Board of Helsinki	Not reported	1	Not reported	Not reported	Two categories of drinkers examined: alcohol misusers and chronic alcoholics; quantity of drinking not reported

Table 2.75 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Adelstein & White (1976), England and Wales, 1953–64, UK Alcoholics Study	629 men discharged from four mental hospitals in 1953–57; 966 men diagnosed with alcoholism and admitted to hospital in 1964; of the total of 1595, 605 had died by July 1974	Patient discharge	Deaths from prostate cancer	3	Not reported	Not reported	
Jensen (1979), Denmark, Danish Brewery Workers	14 313 male Union members employed >6 months in a brewery in 1939–63; follow-up, 1943–73	Not reported	Brewery workers were allowed 2.1 L of free beer/ day (77.7 g pure alcohol/ day)	80	**SIR** 1.0 (0.8–1.2)	Age, sex, area, time trends	Cancer morbidity and mortality compared with those in the general population

Table 2.75 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Schmidt & Popham (1981), Ontario, Canada	9889 men admitted to clinical service for alcoholics in 1951–70; 7719 still alive after 1971	Not reported	Average daily intake of a sample from this group: 25.4 cL pure alcohol	11	**SMR** 1.09 (NS) CI not reported	Not reported	SMR based on age-standardized death rates in Ontario population; compared with US Veterans, SMR for prostate cancer was 1.24 (NS); 96% of a representataive sample of the clinical population drank >15 cL per day; ICD-7 177
Carstensen *et al*. (1990), Sweden, Swedish brewery workers	6230 men employed in the brewery industry in 1960; follow-up by linkage to Swedish Cancer Registry, 1961–79		Workers receive 3 bottles of beer/ day (1 L) free	112	1.06 (0.87–1.27)	Not reported	No information available on when a worker ceased working in the industry; ICD-7 177

Table 2.75 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Adami *et al.* (1992a), Sweden, Cohort of people with a discharge diagnosis of alcoholism	9353 individuals (8340 men) with a discharge diagnosis of alcoholism in 1965–83; mean age at entry, 49.8 years; at diagnosis, 68.1 years; follow-up through to 1984 (maximum, 19 years; mean, 7.7 years); first year of follow-up excluded	Registry based	No data on individual alcohol or tobacco use	68	**SIR** 1.0 (0.8–1.3)		Risk did not vary by length of follow-up
Tønnesen *et al.* (1994), Denmark, Alcoholic men and women	15 214 male alcoholics who entered an outpatient clinic in Copenhagen during 1954–87; average follow-up, 12.9 years	History of alcohol intake obtained by an experienced social worker and psychiatrist	Most subjects consumed about 200 g alcohol daily; consumption in Denmark was 26 g/ day in 1987 (per person >14 years)	91	1.4 (1.2–1.8) $p \leq 0.01$	Not reported	Subjects consumed more alcohol than previous cohort studies examining alcohol intake and prostate cancer; lack of consistency with previous studies may be due to higher intake.

CI, confidence interval; ICD, International Classification of Diseases; NS, not significant; Obs, observed; SIR, standardized incidence ratio; SMR, standardized mortality ratio

[a] Unless otherwise noted in the 'Comments', the ICD code for prostate cancer is 185

Table 2.76 Cohort studies of alcoholic beverage consumption and cancer of the prostate[a] in general populations

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Whittemore *et al.* (1985), USA, Harvard and University of Pennsylvania Alumni Study	33 915 male students who entered Harvard in 1916–50 and 13 356 male and 4076 female students examined at the University of Pennsylvania in 1931–40; followed for cancer mortality through to July 1978	College physical examination, questionnaires	Not reported	243	Not reported	Not reported	Data on collegiate alcohol consumption limited; prostate cancer not associated with collegiate alcohol use; ICD-7 177

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Mills *et al.* (1989), USA, Seventh-day Adventists study	60 000 Seventh-day Adventists in California identified by census questionnaire in 1974, aged >25 years; cancer incidence monitored among 35 000 non-Hispanic white Adventists for up to 6 years; response rate among non-Hispanic whites, 75% (much lower for others)	Lifestyle questionnaire in 1976; annual mailings enquiring about hospitalization, medical records, diagnosis; follow-up 99% complete	*Alcohol intake (any)* No Yes	 142 5	 1.0 0.7 (0.3–1.74)	Age	

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Stemmermann *et al*. (1990), Hawaii, USA, Americans of Japanese Ancestry	7572 Japanese men on Oahu island; examination and interview 1965–68; follow-up through to 1988	Questionnaire on diet, alcohol and tobacco use, socioeconomic factors, demographic variables	*Alcohol intake (oz/month)* 0 <5 5–14 15–39 >40	227 total cases; no. of cases by level of intake not reported	**SIR** 1.0 0.9 (0.6–1.3) 0.9 (0.6–1.3) 1.0 (0.7–1.5) 0.9 (0.6–1.5)	Age at exam 1, current smoker status, age started smoking (current smokers), number of cigarettes smoked per day (current smokers), ex-smoker status, maximum number of cigarettes smoked per day (ex-smokers), years of smoking with maximum number per day (ex-smokers)	Mean alcohol intake fell from 14.6 to 11.6 oz/ month for age groups 45–49 years to >65 years, respectively; incidence rates, adjusted for age and smoking, showed no relation with the amount of alcohol consumed; update of Pollack *et al* (1984) and Severson *et al* (1989).

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Hsing *et al*. (1990), USA, Lutheran Brotherhood Cohort Study	17 633 male white policy holders, aged ≥35 years, of the Lutheran Brotherhood Insurance Society	Response to a questionnaire (mailed) in 1966; followed-up until 1986	*Beer* Former drinker Current drinker *Liquor* Former drinker Current drinker	149 total deaths; no. of cases/ deaths by drinking level not reported	1.7 (1.0–2.9) 1.2 (0.8–1.7) 0.7 (0.3–1.5) 1.0 (0.7–1.4)	Smoking	Users defined as those who drank beer or liquor ≥6 times a year; information on dietary habits and alcohol/tobacco use was only obtained once, in 1966.
Hirayama (1992), Japan	265 118 adults (122 261 men), aged ≥40 years, representing 94.8% of the 1965 census population	Interview (1965) on diet, tobacco/ alcohol use, occupation and reproductive history; 17-year follow-up (1966–82)	Non-daily drinker/ nonsmoker Daily drinker/ nonsmoker Non-daily drinker/smoker Daily drinker/ daily smoker [no details reported]	Not reported	1.0 2.65 1.07 2.46 CI not reported	Age, smoking	Update of Hirayama (1989)

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Hiatt *et al.* (1994), California, USA, Health Plan Cohort	43 432 members of a prepaid health plan; received a health check-up in 1979–85	Questionnaire: current and past consumption of alcohol, number of drinks/ day, type of beverage	Non-drinker Former drinker Occasional drinker <1 drink/day 1–2 drinks/day 3–5 drinks/day >6 drinks/day	25 17 37 73 59 22 5	1.0 1.4 (0.7–2.7) 1.4 (0.8–2.3) 1.3 (0.8–2.2) 1.2 (0.7–2.1) 1.1 (0.6–2.0) 1.0 (0.4–2.8)	Age, smoking, race, education	No significant association between alcohol consumption and prostate cancer
Le Marchand *et al*. (1994), Hawaii, USA	Random 2% household surveys of the Hawaiian State Department of Health held since 1968 to collect demographic and health-related data; linked with Hawaiian Tumour Registry; final population, 41 400 persons (20 316 men); participation rate, 95%	Lifestyle questionnaire added to the survey during 1975–80 and addressed to all aged >18 years on height, weight, diet, alcohol use, smoking	*Alcohol intake (g/week)* 0–52 53–104 104–156 *Lifetime intake (g)* 0–1750 1751–3500 3501–5261	198 cases of invasive prostate cancer recorded through to 1989, all >45 years old at interview; no. of cases by alcohol intake not reported	 1.0 1.0 (0.7–1.6) 1.1 (0.7–1.6) *p*-trend=0.77 1.0 1.0 (0.6–1.5) 1.1 (0.7–1.7) *p*-trend=0.72	Age, ethnicity, income	Data recorded on current drinking status, age when drinking started, amount and frequency of intake of beer, wine, saké, and hard liquor.

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Cerhan *et al.* (1997), USA, 1982–93, Iowa 65+ Rural Health Study	3673 residents (1420 men), aged >65 years, from two rural counties in Iowa; 80% of the population (>65 years) were enrolled in 1982; data on prostate cancer obtained from 1050 men (mean age, 73.5 years) without registered cancer during 1972–82 and with no self-reported prior prostate cancer; cancer data obtained by linking with the Iowa State Health Registry	Interview on demographics, health and social characteristics, current alcohol use (beer, wine, liquor); annual follow-up by telephone or in-person interview	*Alcohol consumption* Never Former Current	 22 6 39	 1.0 0.6 (0.3–1.6) 1.0 (0.6–1.8)	Age	Number of prostate cancer cases through to 1993: 71 (histologically confirmed); mean age at diagnosis, 79.2 years

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Breslow *et al*. (1999), USA, NHANES I Epidemiological Follow-up Study	*Cohort I* (1971–75): 5766 men, aged 25–74 years; followed-up through to 1992; median follow-up, 17 years *Cohort II* (1982–84): 3868 men from Cohort I free of prostate cancer in 1982–84; followed-up through to 1992; median follow-up, 9 years; response rate in 1982–84 interview, 88%	Baseline (1972–74): questionnaire to assess 'usual consumption' (over the previous year); follow-up (1982–84): food-frequency questionnaire to assess current and 'distant past' alcohol intake at 25, 35, 45 and 55 years of age	*Alcohol intake (drinks/week)* 0 >0–1 2–7 8–14 15–21 >22 0 >0–1 2–7 8–14 15–21 >22	 96 41 65 25 8 17 59 19 29 16 9 2	*Cohort I* 1.0 1.0 (0.7–1.4) 0.9 (0.6–1.2) 1.0 (0.6–1.5) 0.9 (1.4–1.8) 1.4 (0.8–2.4) *Cohort II* 1.0 0.7 (0.4–1.3) 1.1 (0.7–1.8) 1.1 (0.6–1.9) 1.1 (0.6–2.3) 0.2 (0.06–0.95)	Race, design variables (age <65 versus ≥65 years, poverty census enumeration district, family income)	No association between alcohol consumption and prostate found; ICD 185, 233.4.

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Schuurman *et al*. (1999), Netherlands, Netherlands Cohort Study	58 279 men in 1986 followed up for prostate cancer incidence by computerized record linkage with all nine Dutch cancer registries and with the Dutch national database of pathology reports; follow-up, ≥96% complete; person–years at risk estimated using a random sample (subcohort) of 1688 men	Questionnaire completed in 1986 to assess consumption of food and drinks during the year prior to the start of the study	*Total alcohol (g)*			Age; multivariate-adjusted relative risks (age, socioeconomic status, family history of prostate cancer, total alcohol intake) not substantially different	Consumption of beer, red wine, white wine, sherry and other fortified wines, liquor (Dutch gin, brandy, whiskey) and liqueurs evaluated; alcohol content (in g/100 g): beer, 4; wine, 10; fortified wines, 14; liqueurs, 17; liquor, 29; relative risks for alcohol from beer, liquor, red wine and liqueur not different from unity; alcohol intake showed stronger association with localized than with advanced prostate tumours
			Non-drinkers	109	1.0		
			0.1–4	143	1.1 (0.8–1.5)		
			5–14	161	0.9 (0.7–1.3)		
			15–29	161	1.1 (0.8–1.4)		
			≥30	101	1.1 (0.8–1.6)		
					p-trend=0.74		
			Alcohol from wine (g)				
			No wine	219	1.1 (0.8–1.5)		
			0.1–4	198	1.1 (0.8–1.4)		
			5–14	90	0.9 (0.6–1.4)		
			15–29	39	1.1 (0.7–1.8)		
			≥30	20	2.3 (1.0–5.3)		
					p-trend=0.67		
			White wine (g)				
			0	359	1.1 (0.8–1.4)		
			0.1–4	180	1.0 (0.7–1.4)		
			5–14	19	1.2 (0.6–2.2)		
			≥15	8	3.3 (1.2–9.2)		
					p-trend=0.54		
			Fortified wines (g)				
			0	408	1.1 (0.8–1.5)		
			0.1–4	108	0.9 (0.6–1.3)		
			5–14	26	0.7 (0.4–1.1)		
			≥15–29	24	2.3 (1.2–4.7)		
					p-trend=0.77		

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Dennis (2000) Meta-analysis	Meta-analysis of six cohort studies of the association between prostate cancer and men	Articles published between January 1976 and July 1978	Ever versus never		1.0 (0.89–1.13)		
Ellison (2000), Canada, Nutrition Canada Survey Cohort	Population survey (1970–72) among 12 795 respondents (47%) and 3295 unsolicited volunteers, aged 50–84 years at interview or entering this age range during the follow-up period through to 1993; data from 3400 men used	Interviews on diet, 24-h food recall and 1-month food frequency	*Total intake (mL/day)* 0 >0–9.9 10.0–24.9 ≥25 Any	 38 54 22 25 101	 1.0 1.0 (0.6–1.5) 0.9 (0.5–1.5) 0.9 (0.6–1.6) 0.9 (0.6–1.4)	Tea and coffee consumption, serum level of vitamin A, 5-year age group	Alcohol content: beer, 5%; wine, 13.5%; spirits, 40%; consumption of wine (<10 g alcohol per day) versus none: relative risk, 1.5 (95% CI, 1.1–2.1) [no details given]

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Putnam *et al*. (2000), USA, 1986–95, Iowa Cohort	1601 (81%) men of 1989 from controls in a population-based case–control study of six cancer sites conducted 1986–89 in Iowa; data reported for 1572 men (mean age, 68.1 years; 99% white; 24% smokers; 57% drinkers); follow-up through to 1995.	Questionnaire (mailed) and interview by telephone on demographics, education, usual occupation, weight, height, family history of cancer, usual adult diet (55-item food list), usual intake of beer, wine, spirits, use of tobacco	*Any alcohol* No Yes *Wine (8-oz glasses/week)* None <0.2 0.2–0.9 >0.9 *Liquor (1-oz shots/week)* None <0.5 0.5–2.5 >2.5	 30 6 54 11 30 12 41 18	 1.0 1.7 (1.1–2.6) *p*-trend=0.02 1.0 1.2 (0.5–3.0) 1.5 (0.9–2.4) 1.9 (0.9–3.7) *p*-trend=0.02 1.0 1.6 (0.8–3.2) 1.5 (0.9–2.4) 1.7 (0.9–3.0) *p*-trend=0.05	Age (40–64, 65–69, 70–74, 75–79, >80 years)	

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Putnam *et al.* (2000) (contd)			*Beer (12-oz cans/week)*			Additional adjustment for body mass index, total energy, linoleic acid, lycopene, carbohydrates, retinal, red meat, history of prostate cancer	
			None	30	1.0		
			<1	22	2.4 (1.4–4.3)		
			1–3	15	1.3 (0.7–2.5)		
			>3	19	1.7 (0.9–3.0)		
					p-trend=0.08		
			Total alcohol intake (g/week)				
			None	30	1.0		
			<22	17	1.1 (0.6–2.1)		
			22–92	27	2.6 (1.4–4.6)		
			>92	18	3.1 (1.5–6.3)		
					p-trend=0.001		

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Lund Nilsen *et al*. (2000), Norway, 1984–95, Norwegian Cohort Study	77 310 residents (≥20 years of age by 31/12/1983) of the Norwegian county Nord-Trøndelag invited to participate in a health survey: in 1984–86l among these, 22 895 men (≥40 years) with no history of any cancer included; incident cases of prostate cancer identified through linkage with the Norwegian Cancer Registry; response rate, 90.8%	Questionnaire on tobacco and alcohol use, physical activity education level, occupation	*Alcohol consumption the past 2 weeks* None (not teetotaler) 1–4 times >4 times *Teetotaler* No Yes	 281 148 40 469 80	 1.0 1.2 (0.94–1.41) 0.9 (0.64–1.25) *p*-trend=0.862 1.0 1.22 (0.96–1.55)	Age	

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Sesso *et al.* (2001), USA, Harvard Alumni Health Study	7612 male Harvard alumni (mean age, 66.6 years) followed prospectively during 1988–93	Questionnaire in 1988 on alcohol use, smoking, use of 23 food items, parental cancer history, weight, height; response from 6686 alumni to a questionnaire sent in 1977 also available	**Servings** *Total alcohol* Almost never 1/month–3/ week 3/week–1/day 1–3/day ≥3/day *Liquor* Almost never 1/month–3/ week 3/week–1/day 1–3/day ≥3/day	 38 54 76 151 47 93 82 68 108 15	**Multivariate-adjusted** 1.0 1.3 (0.9–2.0) 1.7 (1.1–2.4) 1.9 (1.3–2.6) 1.3 (0.9–2.1) *p*-trend=0.35 1.0 1.2 (0.9–1.6) 1.7 (1.2–2.3) 1.6 (1.2–2.1) 1.1 (0.6–1.9) *p*-trend=0.10	Age, body-mass index, smoking (never/former/ current), physical activity, parental history of cancer	Mean total alcohol intake, 123.1 (SD, 136.3) g/ week; 28.6% from wine, 15.8% from beer and 55.6% from liquor (e.g. whiskey); significant increase in relative risk not seen for beer or wine; men who reduced alcohol intake in the period 1977–88 still at elevated risk compared with the ‘almost never’ group.

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Albertsen & Grønbaek (2002), Copenhagen, Denmark, three pooled studies	26 496 men, aged 20–98 years; data from 12 989 men used in the study (1976–94); follow-up time, 4.5–22.9 years (average, 12.3 years); mean participation rate, 80%	Multiple-choice questions on intake of wine, beer, spirits, tobacco, age, education, physical activity, body mass index	**Drinks/week**			Age, education, physical activity body mass index, smoking status, study of origin	Standard drink of wine, beer and spirits in Denmark considered to contain 12 g alcohol; ICD-7 177, ICD-10 DC619
			Total intake				
			<1	42	1.0		
			1–6	59	0.9 (0.6–1.3)		
			7–13	54	0.9 (0.6–1.3)		
			14–20	36	0.9 (0.6–1.4)		
			21–41	35	0.9 (0.6–1.5)		
			>41	7	0.7 (0.3–1.5)		
					p-trend=0.48		
			Beer				
			0	53	1.0		
			1–13	141	1.0 (0.7–1.5)		
			>13	39	1.0 (0.6–1.5)		
					p-trend=0.85		
			Wine				
			0	106	1.0		
			1–13	120	1.2 (0.9–1.6)		
			>13	7	0.9 (0.4–2.0)		
					p-trend=0.96		
			Spirits				
			0	101	1.0		
			1–13	122	1.0 (0.7–1.3)		
			>13	10	1.0 (0.5–2.0)		
					p-trend=0.90		

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Platz *et al.* (2004), USA, 1986–98, Health Professionals Follow-up Study	51 529 men, aged 40–75 years at enrolment in 1986; excluded: men diagnosed with cancer (except non-melanoma skin cancer) or returned incomplete questionnaire in 1986 (3.1%); 47 843 men, of whom 76.4% in 1986 reported drinking alcohol (2.9% consumed > 50 g/day); verification of cases via medical records and pathology reports; overall follow-up response, 94% at the end of 1998	Questionnaire, mailed and returned every 2 years, on diet, medical history, lifestyle factors; updated via the questionnaires mailed and returned in 1990 and 1994; deaths recorded via the National Death Index	*Intake (g/day)* 0 0.1–4.9 5.0–14.9 15.0–29.9 30.0–49.9 ≥50 0 0.1–4.9 5.0–14.9 15.0–29.9 30.0–49.9	 576 537 694 336 266 70 154 118 175 80 81	**Hazard ratios** *All cases* 1.0 1.0 (0.9–1.1) 1.1 (0.9–1.2) 1.1 (1.0–1.3) 1.1 (1.0–1.3) 1.0 (0.7–1.3) *p*-trend=0.20 *Advanced cases* 1.0 0.8 (0.7–1.1) 1.0 (0.8–1.3) 1.0 (0.8–1.4) 1.0 (0.7–1.3) *p*-trend=0.70	Current age, body mass index at 21 years, height, smoking (pack–years in past decade), family history of prostate cancer, major ancestry, vasectomy, high physical activity, diabetes, intake of: total energy, calcium, tomato sauce, fructose, red meat, fish, vitamin E, α-linolenic acid	Consumption over past year of beer, red wine, white wine and liquor (assumed to contain, resp., 12.8, 11.0, 11.0 and 14 g alcohol per serving); analysis of drinking pattern: for men who took ≥105 g alcohol on only 1 or 2 days of the week, hazard ratio was 1.64 (95% CI, 1.13–2.38); this group represented 1% of the cases in the cohort; advanced cases were Stage C or D or fatal.

Table 2.76 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Baglietto *et al.* (2006), Australia, Melbourne Collaborative Cohort Study	528 people (17 049 men), aged 27–75 years, recruited 1990–94 in the Melbourne metropolitan area via electoral rolls, advertisements and community announcements; data from 16 872 men, aged 27–70 years, used; follow-up through to 31 December 2003	Interview to collect data on age, country of birth, education, tobacco use, drinking habits, medical history; cases ascertained through the Victoria Cancer Registry		Not reported	**Hazard ratios** *All cases*	Co-variate: country of birth; adjustments for education, body mass index, smoking, total energy intake or medical history did not change risk ratios.	Lifetime abstainers never drank ≥12 drinks/ year; former drinkers did not drink alcohol at start of study; no difference in risk according to the type of alcohol consumed; 'aggressive' cancers defined as Gleason score >7 or advanced stage (T4 or N+ or M+)
			Lifetime abstainer		1.0		
			Former drinker		1.2 (0.8–1.6)		
			1–19 g alcohol/ day		1.0 (0.8–1.2)		
			20–39 g alcohol/day		1.0 (0.8–1.2)		
			40–59 g alcohol/day		1.0 (0.7–1.3)		
			≥60 g alcohol/ day		0.9 (0.7–1.3)		
					p-trend=0.62		
				Not reported	*Aggressive cases*		
			Lifetime abstainer		1.0		
			Former drinker		0.7 (0.3–1.7)		
			1–19 g alcohol/ day		0.7 (0.4–1.1)		
			20–39 g alcohol/day		0.7 (0.4–1.2)		
			40–59 g alcohol/day		0.7 (0.3–1.3)		
			≥60 g alcohol/ day		0.8 (0.4–1.5)		
					p-trend=0.58		

CI, confidence interval; ICD, International Classification of Diseases; NHANES, National Health and Nutrition Examination Survey; SD, standard deviation; SIR, standardized incidence ratio [a] Unless otherwise noted in the comments, the ICD code for prostate cancer is 185

Table 2.77 Case–control studies of alcoholic beverage consumption and cancer of the prostate[a]

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Schwartz *et al*. (1962), France, 1954–58	139 patients	139 age-matched non-cancer patients (accident victims)	Subjects interviewed in the hospital about alcohol drinking	Prostate cancer cases, average consumption of 11.0 cL pure alcohol per day; controls, same average daily alcohol intake	139	NR		Consumption according to age varied from 9.6 to 14.0 cL pure alcohol/ day; ICD 177
Wynder *et al*. (1971), New York, USA, 1965–67	217 patients (167 alcohol drinkers)	200 patients (163 drinkers)	Epidemiological questionnaire	*Alcohol consumed (units per day)* 1–2 3–6 >7 Binge	 106 36 22 3	NR		Unit/day = 1 oz spirits, 4 oz wine, 8 oz beer; a second study included 83 prostate cancer patients and 200 control patients
Williams & Horm (1977), USA, Third National Cancer Survey, 1969–71	465 patients	1323 patients with other cancers, not tobacco-related	Interview to collect data on the amount and the duration of alcohol and tobacco use	 <50 oz–years >50 oz–years	 62 127	**Odds ratio** 0.78 0.87	Age, race, smoking	Alcohol use expressed as ‘oz–years’ (units/ week × years drinking)

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Schuman *et al*. (1977), USA, Study period not reported	200 white patients from major hospitals in the Minneapolis-St Paul area	Patients in same hospital with non-genitourinary conditions; matched by age, race, date of admission; age- and race-matched neighbourhood controls (same street of residence)	Personal interview on history of residence, jobs, medication, hospitalization, smoking/ drinking habits, drugs, marital history	*Alcohol use* Yes No	 39 1	NR		Preliminary report
Niijima & Koiso (1980), Japan, 1963–78	187 patients diagnosed and treated at the Department of Urology, University of Tokyo; mean age, 68.7 years	200 patients without known prostatic disease: 106 cancers of the kidney, ureter, bladder or other organs; 94 diseases other than cancer	Not specified	About 56% of patients and 55% of controls were alcohol drinkers		NR	NR	NR
Jackson *et al*. (1981), USA, 1973–78	231 black patients with prostate carcinoma at Howard University and DC General Hospitals; data from 205 patients used; 100% histologically confirmed	205 age-matched patients free of neoplastic, urological and endocrine conditions	Interview using a pre-tested epidemiological questionnaire			NR	NR	A higher proportion of controls than of patients had a history of heavy alcohol use (beer, wine or liquor) in the 10 years before diagnosis [no data].

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Mishina *et al*. (1981), USA	100 prostatic cancer patients	100 matched for age (±1 year) and residence in the same prefecture	Questionnaire and interview on education, job history, income, religion, diet, marriage, sexual activity, physical condition	Rare No alcohol	61 39	1.73 CI not reported		
Talamini *et al*. (1986), northern Italy, 1980–83	166 patients recently diagnosed at the General Hospital of Pordenone (Friuli Venezia-Giulia), aged 48–79 years (median age, 66 years); 100% histologically confirmed; refusal rate, <2%	202 patients in the General Hospital of Pordenone admitted for acute conditions (no malignant, hormonal or urogenital disease) <1 year before interview, aged 50–79 years (median age, 63 years); refusal rate, <2%	Interview with questionnaire on general lifestyle habits, socio-demographic aspects, height, weight, frequency of food intake	Not specified		NR	NR	Risk for prostate cancer not related to wine drinking [data not shown]

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Ross *et al.* (1987), USA, 1977–80	316 black residents of Los Angeles County with prostate cancer (diag-nosed between January 1977 and August 1980), aged 60–75 years; a total of 179 were interviewed, 19 refused to participate; 190 white incident prostate cancer patients of a Los Angeles area retirement community (diagnosed 1972 through 1982), aged, 65–79 years; 142 patients interviewed, 48 refused to participate	142 neighbourhood controls; age-matched (±5 years) with cases 142 controls individually matched to cases on age (±1 year), length of residence in the community (±1 year)	Interview	Any alcohol use Any alcohol use	NR	*Blacks* 0.9 *Whites* 0.9	NR	No confidence intervals reported

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Yu *et al.* (1988), USA, 1969–84	1162 patients (14% blacks) in 20 hospitals across the USA, recently diagnosed and identified in the American Health Foundation registry; mean age, 62.9 years; verified through medical records and pathology reports	3124 patients (54% cancers, excluding cancers at 'alcohol-related' sites; 13% benign neoplasms, 33% non-neoplastic diseases; ~10% blacks) from the same hospitals; mean age, 62.2 years; 3:1 frequency-matched to cases by age at diagnosis (±2 years), race, year of interview, hospital	Interviews at time of admission or diagnosis on race, education, marital status, years of education, height, weight, religion, occupation, smoking, alcohol use	*Intake* 0 1 oz/day 3 oz/day 0 1 oz/day 3 oz/day	 436 321 211 74 46 37	*Whites* 1.0 1.0 (0.6–1.7) 1.2 (0.9–1.5) *Blacks* 1.0 1.4 (0.8–2.3) 1.3 (0.7–2.3)	Age at diagnosis	Consumption of alcohol expressed as whiskey equivalent, (beer amount/8) + (wine amount/4) + whiskey amount in oz/day
Mettlin *et al*. (1989), Roswell Park Memorial Institute, USA, 1957–65	371 patients, 55–85 years of age (mean age, 68.3 years); 2.2% non-white; 100% histologically confirmed	371 patients (4.0% non-white) without diagnosis or history of cancer (12.1% benign prostatic hyperplasia), aged 55–85 years (mean age, 68.1 years)	Questionnaire with 45-item food-frequency check-list; weekly frequency of consumption of beer, wine or liquor			NR		No significant increase or reduction in risk was found for beer, wine or liquor [no details were reported].

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Fincham *et al*. (1990), Canada, 1981–83	382 identified via the Alberta Cancer Registry (April 1981–September 1983), aged ≥45 years	625 age group-matched to cases, chosen from the roster of the Alberta Health Care Insurance Plan	Interview with questionnaire on ethnicity, marital status, job history personal/family medical history, tobacco/alcohol use, puberty age, physical status; diet history over 2-month periods with 6-month interval	NR				Cases consumed somewhat more alcohol (mean, 127 oz/month) than controls (mean, 120 oz/month)
Walker *et al*. (1992), South Africa	166 black hospitalized patients (90% advanced-stage D), residents of Soweto; mean age, 69.2 years (range, 48–84 years); 100% histologically confirmed	166 black age-matched selected from immediate neighbours of patients; mean age, 69.6 years (range, 52–85 years)	Patients questioned as to their diet before they became ill	Non-drinker Occasional drinker Regular drinker	20 35 45	No data		Differences between patients and controls not significant
Nakata *et al*. (1993), Japan	294 patients	294 general population controls chosen from 13 areas in Gunma Prefecture; age-matched (±2 years)	Questionnaire or interview	History of drinking: yes/ no		*Odds ratio* 0.93 (0.62–1.39)	Age	Prostate cancer risk not statistically different between cases and controls

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Slattery & West (1993), Utah, USA, 1983–86	362 white men living in 4 counties in Utah, diagnosed between 1 January 1984 and 15 November 1985 with first-primary prostate cancer, aged 45–74 years; 100% histologically confirmed; completion rate, 77.4%	685 matched to cases by 5-year age group, selected by random-digit dialling (<65 years) or from Social Security records (≥65 years); completion rate, 76.9%	Quantitative food-frequency questionnaire to assess use of alcohol, coffee, tea	*Total alcohol* None Any *Beer* None Any *Wine* None Any *Spirits* None Any	 90 89 114 65 130 49 105 74	 1.0 1.2 (0.9–1.6) 1.0 1.2 (0.9–1.7) 1.0 0.8 (0.6–1.1) 1.0 1.1 (0.8–1.5)	Crude odds ratio values given; adjustment for dietary intake, body size, age within strata, demographic features did not change the results.	Data are shown for all prostate tumour types, and for cases/controls ≤67 years; results for 'aggressive tumours' or for subjects >67 years did not change the outcome.
van der Gulden *et al*. (1994), Netherlands 1988–90	345 prostate cancer cases from the Comprehensive Cancer Centre IKO diagnosed January 1988 until April 1990; mean age, 72 years; 100% histologically confirmed; response rate, 84%	1346 patients treated in the IKOregion for prostate hyperplasia, but without histological signs of malignancy; mean age, 69 years	Questionnaire (mailed) on smoking/ drinking habits, work history, socio-economic status; response rate, 78%	*Alcohol use* Never <1 day/week 1–4 days/week 5–7 days/week All drinkers	 21 324 90 176 58	 1.0 1.2 (0.7–2.0) 1.4 (0.8–2.3) 1.4 (0.8–2.5) 1.4 (0.8–2.2)	Age	Age at which drinking began or duration of drinking not related to risk for prostate cancer

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Tavani *et al*. (1994b), northern Italy, 1985–92	Histologically confirmed, incident prostate cancer cases (*n*=281; median age, 67 years; range 25–79 years) diagnosed during the year before interview, admitted to cancer institutes and major hospitals	Patients (*n*=599; median age, 63 years; range 27–79 years) admitted to the same network of hospitals as the cases for acute, non-neoplastic conditions	Interviews with questionnaire on age, education, height, weight, marital status, smoking and drinking habits, intake of several indicator foods	*Total alcohol intake (drinks/ day)*			Age, study centre; estimates from multiple logistic regression with age, centre, education, marital status, body mass index and smoking status gave comparable results.	Average number of drinks/day (a drink defined as 150 mL wine, 330 mL beer, or 30 mL spirits, each with 12–15 g ethanol); separate analyses for wine (0,<5, ≥5 per day), beer (no/yes), spirits (no/ yes) or duration of use (0, <40, ≥40 years) did not substantially change the results.
				0	22	1		
				<3	63	1.3 (0.7–2.4)		
				3–<5	55	1.9 (0.5–1.6)		
				5–<8	63	1.2 (0.6–2.3)		
				≥8	78	1.1 (0.6–2.1)		
				Wine (drinks/ day)				
				0	26	1		
				<5	152	1.2 (0.7–2.0)		
				≥5	103	0.9 (0.5–1.7)		
				Beer (drinks/ day)				
				No	197	1		
				Yes	84	1.1 (0.8–1.6)		
				Spirits (drinks/ day)				
				No	184	1		
				Yes	97	0.8 (0.5–1.1)		
				Duration of use/years				
				0	22	1		
				>0–<40	92	1.1 (0.6–2.1)		
				≥40	167	1.3 (0.7–2.3)		
Wei *et al*. (1994), China	27 admitted to the hospital of West-China University of Medical Sciences	27 patients with malignant, non-urological tumours, 27 with urological (non-malignant) disease	Questionnaire to assess lifestyle, diet, marital status, history of prostate disease	Not specified		1.0 (0.4–2.5)	Age, sex, race, day of admission	Ten drinkers among cases and 21 drinkers among controls

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
De Stefani *et al*. (1995), Uruguay, 1988–94	156 adenocarcinoma of the prostate admitted (1988 through 1994) at the Instituto Nacional de Oncologia; 100% histologically confirmed; no refusals recorded	302 patients admitted to the same institute, with diagnoses not related to alcohol, tobacco or diet, aged 40–89 years	Interview by 3 social workers; routine questionnaire given to all patients admitted.			**Odds ratios***	Age, residence, level of education, cigarette smoking, dietary items (meat, milk, fruits)	* Odds ratio versus lifelong abstainers; daily alcohol intake expressed as mL pure ethanol, using 60, 120 and 460 mL/L for beer, wine and hard liquor, respectively; odds ratios for beer drinkers versus lifelong abstainers (intake in mL pure ethanol/day): 1–30, 1.2 (0.5–2.8); ≥31, 3.2 (1.2–8.1)
				Beer				
				Non-drinkers	134			
				1–9 mL/day	5	0.7 (0.2–2.1)		
				10–60 mL/day	9	1.7 (0.7–4.3)		
				≥61 mL/day	8	3.2 (1.0–9.6)		
						p=0.04		
				Wine				
				Non-drinkers	67			
				1–30 mL/day	42	1.3 (0.7–2.1)		
				31–60 mL/day	17	0.8 (1.4–1.5)		
				≥61 mL/day	30	1.4 (0.8–2.6)		
						p=0.35		
				Liquor				
				Non-drinkers	103			
				1–45 mL/day	37	0.7 (0.3–1.3)		
				46–69 mL/day	29	1.1 (0.6–2.1)		
				≥70 mL/day	38	1.2 (0.6–2.3)		
						p=0.62		
				Total alcohol				
				Non-drinkers	52			
				1–45 mL/day	37	1.4 (0.8–2.4)		
				46–120 mL/day	29	0.9 (0.5–1.7)		
				≥121 mL/day	38	1.8 (0.9–3.1)		
						p=0.18		
Andersson *et al*. (1996), Sweden, 1989–91	256 eligible prostate cancer patients (aged <80 years) from Orebro county, January 1989–September 1991; response rate, 74.6%	252 age-matched screened for prostate cancer with negative results; response rate, 76.6%	Interviewer-administered standardized food-frequency questionnaire; clinical data	Non-drinker	106	1.0	Age	Adjustment for smoking reduced alcohol estimates modestly [data not given]
				<24.4 g/week	18	0.9 (0.4–1.7)		
				24.4–48.5 g/week	23	1.1 (0.6–2.1)		
				48.6–96 g/week	29	1.4 (0.8–2.6)		
				>96 g/week	31	1.5 (0.8–2.8)		
						p for trend=0.11		

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Ewings & Bowie, (1996), United Kingdom, 1989–91	159 newly diagnosed prostatic cancer patients in three hospitals; patients interviewed between May 1989 and October 1991; 100% histologically confirmed	2 controls for each case; frequency-matched (5-year age groups), selected from the same hospital: one with benign prostate enlargement, one with non-urological condition (avoiding alcohol- and diet-related disorders)	Questionnaires completed	*Ever use of alcohol*	134	**Odds ratio** 0.6 (0.4–1.2)	NR	
Grönberg *et al*. (1996), Sweden 1959–89	Link between Swedish Twin Registry and Swedish Cancer Registry yielded 406 cases of prostate cancer; mean age at diagnosis, 72.6 years (range, 47–91 years).	1218 3:1 age-matched, unrelated	Questionnaire mailed in 1967 to all same-sex, male twin pairs born in 1886–1925 on food intake and use of beer, wine spirits; 19 (4.7%) cases diagnosed	Non-users Former versus non-user Current versus non-user	64 25 275	**Odds ratio** 1 0.8 (0.5–1.4) 0.9 (0.6–1.3) *p*-trend=0.54	Age	Non-users, former users (did not drink during the last year), current users; beer, wine or spirits: non-users, <1 time/week, 1–2 times per week, almost daily; no increased risk found for total alcohol consumption, nor for beer, wine or spirits

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Hayes *et al.* (1996), USA, 1986–89	479 black, 502 white patients diagnosed 1 August 1986–30 April 1989, aged 40–79 years; 100% pathologically confirmed; response rate, 76%	594 black, 721 white residents of Atlanta, Detroit and 10 counties in New Jersey, covered by three cancer registries; response rate, 71%	In-person interviews (1986–89) on alcohol intake, duration of use, age when started, age when stopped	*Drinks per week* Never used Any ≤7 8–21 22–56 ≥57 *Recent drinker* Never used ≤7 8–21 22–56 ≥57 *Former drinker* Never used ≤7 8–21 22–56 ≥57 *Regional/ distant* None ≤7 8–21 22–56 ≥57	 94 385 96 113 119 54 94 57 64 67 28 94 36 45 48 24 56 65 84 63 36	 1 1.2 (1.0– 1.5) 1.1 (0.9–1.4) 1.1 (0.9–1.4) 1.4 (1.0–1.8) 1.9 (1.3–2.7) *p*-trend<0.001 1 1.1 (0.8–1.5) 1.1 (0.8–1.5) 1.2 (0.9–1.7) 1.7 (1.1–2.6) 1 1.2 (0.8–1.8) 1.3 (0.9–1.9) 1.6 (1.1–2.4) 2.0 (1.2–3.4) 1 1.0 (0.7–1.5) 1.1 (0.8–1.7) 1.3 (0.9–1.9) 2.1 (1.3–3.5)	Age, ethnicity, study site	Drinkers: >1 drink per month for at least 6 months; increased risk with higher consumption apparent for beer and liquor, not for wine; elevated risks also reported for those with poorly or undifferentiated tumours

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Guess *et al.* (1997), USA, nested case–control study 1964–71	106 incident cases selected from >125 000 members of the Kaiser Permanente Medical Care Program with health examination data and serum samples available (1964–71); diagnosis between September 1970 and November 1987	106 pair-matched to each case on age, date of serum sampling, location of clinic.	Multi-phasic health examination; bioassay	Non-drinker ≤2 drinks/day ≥3 drinks/day	17 46 28	NR		Alcohol consumption was examined as a confounder.

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Jain *et al.* (1998), Canada	*Ontario*: 187 patients listed in Ontario Cancer Registry between April 1990 and April 1992 and living in or around Toronto; refusal rate for interview, 20.2% *Quebec*: 229 patients admitted to five Montreal hospitals between 1989 and 1993; refusal rate, 15.5% *British Columbia*: 201 patients (random sample from 6183) in the British Columbia Cancer Registry, in the years 1989–1991; refusal rate, 7%; all histologically confirmed prostate adenocarcinoma	*Ontario*: 207 chosen at random from lists of the Ministry of Finance; matched with cases by geographic area, 5-year age group; refusal rate, 37% *Quebec*: 230 chosen via a modified random-digit dialling method, with the same first three phone digits as the cases *British Columbia*: 199 selected at random from Medical Services Plan rosters; refusal rate, 15%	Questionnaires:, weight, physical activity, personal and medical history (e.g, rectal examinations), smoking habits, frequency of use of medical system and demographic data, amount and frequency of food intake in the year before the diagnosis (cases) or before the date of the interview (controls)	*Total alcohol intake* 0 >0–<10 g/day 10–<20 g/day 20–<30 g/day ≥30 g/day *Beer* 0 >0–9 g/day ≥10 g/day *Wine* 0 >0–9 g/day ≥10 g/day *Liquor* 0 >0–15 g/day ≥16 g/day	 175 168 82 57 135 333 189 95 323 193 101 331 190 96	**Odds ratio** 1.0 0.8 (0.6–1.1) 0.8 (0.6–1.2) 0.8 (0.5–1.1) 0.9 (0.6–1.3) *p* for trend=0.51 1.0 0.8 (0.6–1.1) 0.7 (0.5–0.9) *p* for trend=0.01 1 0.8 (0.6–1.0) 1.12 (0.8–1.55) *p* for trend=0.8 1 0.9 (0.7–1.2) 0.9 (0.6–1.2)	Age (continuous), total energy intake	Percentage alcohol in beer, 3.6%; wines and sherry, 11.5%; liquor/ spirits, 37.9%; amount of alcohol in 350mL beer, 12.6 g; in 120mL wine, 13.8 g; in 45mL whiskey, 17.1 g; odds ratios for combined data for all 3 centres; odds ratios for individual centres and for different types of beverage not significantly different from unity; additional adjustment for smoking (ever versus never), educational level, family history of prostate cancer, history of benign prostate hypertrophy, Quetelet index, energy intake and retinol intake had little impact on the results.

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Lumey *et al*. (1998), USA, 1977–91	699 identified in computerized registry of the American Health Foundation (1977–1991) in 20 US hospitals; mean age, 62.6 years; 100% histologically confirmed; response rate, 94%	2041 hospital patients without tobacco- or alcohol-related disease and without benign prostatic hypertrophy; mean age, 61.1 years; 3:1 matched with cases by age at diagnosis (within 5 years), year of diagnosis, hospital, race; response rate, 94%	Interview at the time of admission to the hospital, with a structured questionnaire on demographic, socioeconomic and behavioural aspects, smoking, drinking	*Drinks/week* Never Any ≤7 8–21 22–56 ≥57	 106 593 235 160 123 62	**Odds ratios** 1.0 1.2 (0.9–1.5) 1.2 (0.9–1.6) 1.1 (0.8–1.5) 1.3 (1.0–1.8) 1.1 (0.7–1.5)	Age at diagnosis, study site	Odds ratios for current and former drinkers similar; adjustment for marital status, occupation, religion, education, smoking habits did not change the results; separate analyses for beer, wine and liquor, or for different age groups (≤64 or ≥65 years) did not influence the results; one drink defined as a glass of whisky, a glass of wine or a glass of beer.
Hsieh *et al*. (1999), Greece, 1994–97	320 patients (95% aged >60 years) with prostate carcinoma from six hospitals in the Greater Athens area between 1994 and 1997; 100% histologically confirmed	246 (90% aged >60 years) non-cancer patients in the same hospitals as the cases	Interviews from February 1994 to January 1997 at the hospital, with questions about demographic, socioeconomic, reproductive, biomedical, dietary variables	*Alcohol drinking (glasses/day)* None <1 1–<2 2–<3 3–<4 ≥4	 101 43 38 32 29 61	NR	Age, body mass index, height, years of schooling	

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Dennis (2000)	Meta-analysis of 27 case–control studies examining the association between alcohol use and prostate cancer		Articles published between January 1976 and July 1978	Ever versus never		1.1 (0.98–1.13)		
Sharpe & Siemiatycki (2001), Montreal, Canada, 1979–85	Interview data obtained from 449 of 557 (80.6%) eligible incident cases, histologically confirmed, in Montreal; reliable alcohol consumption data obtained from 399 cases	541 chosen from electoral lists 1979–82 and 1984–85, 199 by random digit dialling; 533 responded (rate, 72%), of whom 512 were interviewed; data from 476 were used	Interviews on use of beer, wine and spirits, frequency of use, time when drinking started; data expressed as 'drink–years'	Never drank daily	69	1.0	Age, ethnicity, respondent status, family income, body mass index, cigarette smoking	A drink of beer, wine or spirits was estimated to contain 13.6 g alcohol; the study was primarily designed to study occupational causes of cancer;
				Drank weekly, never daily	133	1.6 (1.1–2.4)		
				Drank daily				
				Age at starting daily drinking (years)				
				<15	17	3.8 (1.6–9.3)		
				15–19	51	1.4 (0.8–2.4)		
				20–24	49	1.6 (0.9–2.7)		
				≥25	68	1.2 (0.8–2.0)		
						p-trend=0.009		
				Duration of drinking (years)				
				<20	32	1.3 (0.7–2.4)		
				20–39	64	1.1 (0.7–1.8)		
				>39	88	2.0 (1.2–3.1)		
						p-trend=0.01		

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Sharpe & Siemiatycki (2001) (contd)				*Cumulative consumption (daily drinkers)*				647 cancer controls selected from other, not alcohol-related cancer cases (response rates, 78–85%) also included; findings similar when using cancer controls
				<58 drink–years	54	1.4 (0.9–2.3)		
				58–125 drink–years	44	1.1 (0.7–1.9)		
				>125 drink–years	99	2.1 (1.3–3.3)		
						p-trend=0.003		
				Combined use				
				Beer only	57	1.6 (0.9–2.5)		
				Wine only	16	1.4 (0.7–2.9)		
				Spirits only	12	1.9 (0.4–1.9)		
				Beer and wine	17	1.2 (0.6–2.4)		
				Beer and spirits	78	1.9 (1.2–3.1)		
				Wine and spirits	20	1.1 (0.6–2.2)		
				Beer, wine and spirits	130	1.8 (1.2–2.7)		

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Crispo *et al.* (2004), Italy 1991–2002	1294 patients with prostate carcinoma; median age, 66 years (range, 46–74 years); 100% histologically confirmed;. refusal rate, <5%; 1369 patients with benign prostatic hyperplasia; median age, 65 years (range, 46–74 years); refusal rate, <5%	1451 patients admitted to the same hospitals for non-neoplastic disorders; median age, 63 years (range, 46–74 years); refusal rate, <5%	Personal interviews with questionnaire on alcohol drinking: number of days per week, number of drinks per week, duration (up to 1 year prior to diagnosis or admission)			*Prostate cancer patients*	Age, study centre, education, body mass index, physical activity, history of prostate cancer in first-degree relatives	Abstainers never consumed alcohol; former drinkers had abstained ≥1 year; one drink: 125 mL wine, 330 mL beer, 30 mL hard liquor (12–15 g alcohol); analysis by different types of beverage (beer, wine, spirits) did not show any significant association with risk for prostate cancer; some evidence for an inverse relationship with the risk for benign prostatic hyperplasia.
				Abstainer	71	1.0		
				Former drinker	93	0.8 (0.5–1.3)		
				Current drinkers	1130	0.9 (0.6–1.3)		
				<3 drinks/ week	496	0.9 (0.6–1.3)		
				3–4 drinks/ week	355	0.9 (0.6–1.3)		
				5–6 drinks/ week	177	1.1 (0.7–1.7)		
				7–8 drinks/ week	107	1.0 (0.6–1.5)		
				≥9 drinks/ week	88	0.9 (0.5–1.4)		
Hodge *et al.* (2004), Melbourne, Perth, Sidney, Australia, 1994–97	858 patients diagnosed 1994–97 with 'clinically important' prostate cancer (Gleason score ≥5), aged <70 years; registered to vote; 100% histologically confirmed; response rate, 65%	905 randomly selected from State Electoral Rolls; age-matched; response rate, 50%	Personal interviews, dietary habit questions and a 121-item food frequency questionnaire; men with energy intake from food >3 SD above the mean not included; alcohol intakes from beer, wine, spirits and total use recorded	*Total alcohol intake (g/day)*	NR		State, age group, year, country of birth, socio-economic group, family history of prostate cancer	Analysis by different types of beverage (beer, wine, spirits) did not show any association with prostate cancer risk.
				<20		1.0		
				20–39		1.0 (0.8–1.3)		
				40–59		1.0 (0.7–1.3)		
				≥60		1.0 (0.7–1.4)		

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Chang *et al*. (2005), Sweden, 2001–02	1499 incident prostate cancers identified from Swedish regional cancer registries; mean age, 66.4 years; histologically confirmed as adenocarcinoma; response rate, 79%	1130 identified from the Swedish Population Registry database; mean age, 67.3 years; response rate, 67%	Self-administered questionnaire to assess known and potential risk factors for prostate cancer	Non-drinker Former drinker Current drinker *Ethanol (g/ week)* 0.0 0.1–45 45.1–90.0 90.1–135.0 >135.1 *Localised disease* 0.0 0.1–45 45.1–90.0 90.1–135.0 >135.1 *Advanced disease* 0.0 0.1–45 45.1–90.0 90.1–135.0 >135.1	122 112 1259 218 379 311 202 359 NR NR 	1.0 2.1 (1.4–3.3) 1.6 (1.2–2.1) 1.0 1.1 (0.8–1.4) 1.2 (0.9–1.5) 1.3 (0.9–1.7) 1.3 (1.0–1.7) *p*-trend=0.06 1.0 1.5 (1.1–2.1) 1.4 (1.0–2.0) 1.4 (1.0–2.1) 1.4 (1.0–2.0) *p*-trend=0.27 1.0 0.8 (0.6–1.0) 0.9 (0.7–1.2) 1.1 (0.8–1.5) 0.9 (0.7–1.2) *p*-trend=0.50	Age (5-year categories), smoking history (ever, never), current body mass index, family history of prostate cancer, intake of other alcohol types, dairy products, red meat, fruit, vegetables	Light, medium and strong beers (33 cL) contain 6, 9.1 and 14.6 g ethanol; light and strong wines (15 cL) contain 14.2 and 20.7 g ethanol; a shot of liquor (4 cL) contains 12.6 g ethanol; light beers were not counted in number of drinks per week; non-drinkers included consumers of only light beer; former drinkers were those who stopped ≥18 months before; current drinkers included those who stopped <18 months before.

Table 2.77 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Schoonen *et al.* (2005), USA, 1993–96	753 Caucasian and African-American men living in King County (Washington State, USA), newly diagnosed with prostate cancer in 1993–96, aged, 40–64 years; 100% histologically confirmed; participation rate, 82.1%; participant refusal, 12.5%	941 identified using random-digit dialling; frequency-matched to cases by 5-year age group; 703 interviewed; participation rate, 75%; participant refusal, 24%.	Histological and clinical details on case subjects from the Seattle-SEER cancer registry; interview with food-frequency questionnaire and data on medical history, prostate-cancer screening history, family history of cancer, demographics, height, weight, lifetime alcohol use, smoking habits, marital and sexual history, lifestyle and occupational factors			**Odds ratio**	Age, use of prostate screening, lifetime number of female sexual partners, smoking status Odds ratio values for red wine also adjusted for intake of other types of alcohol	One bottle of beer (12 oz), one glass of wine (4 oz), one shot of liquor (1.5 oz) contain 13, 11 and 14 g ethanol, respectively; analyses by age at first alcohol use, lifetime duration of use, or by heavy drinking period (yes/no) did not affect the outcome; associations were similar for less and more aggressive cancers; subjects consuming <1 drink/week were included in the reference group; non-drinkers had ≤12 drinks during life.
				Ever use	681	1.1 (0.7–1.5)		
				Lifetime alcohol (g)				
				0	72	1.0		
				>0–6000	186	1.1 (0.8–1.7)		
				>6000–12 000	122	0.9 (0.6–1.4)		
				>12 000–24 000	138	1.0 (1.6–1.5)		
				>24 000	235	1.3 (0.8–2.0) *p*-trend=0.33		
				Drinks per week				
				None or <1	126	1.0		
				1–7	266	0.9 (0.7–1.3)		
				8–14	166	1.0 (0.7–1.5)		
				≥15	195	1.1 (0.7–1.6) *p*-trend=0.32		
				Red wine (drinks/week)				
				Non-drinker	134	1.0		
				1–3	121	0.8 (0.5–1.3)		
				4–7	66	0.5 (0.3–0.9)		
				≥8	27	0.5 (0.2–0.9) *p*-trend=0.02		

CI, confidence interval; ICD, International Classification of Diseases; NR, not reported; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Result

[a] Unless otherwise noted in the comments, the ICD code for prostate cancer is 185

2.15.3 *Meta-analysis*

A meta-analysis that included six cohort and 27 case–control studies that were reported before July 1998 resulted in an estimate of 1.05 (95% CI, 0.98–1.11) for ever consumption of alcoholic beverages (Dennis, 2000). There was a suggestion of a weak dose–response relationship for increasing levels of alcoholic beverage consumption (relative risk, 1.21; 95% CI, 1.05–1.39 for four drinks/day) when data from 15 of the studies were used. [Results for the six cohort studies and the 27 case–control studies are presented in Tables 2.76 and 2.77, respectively.]

2.16 Cancer of the kidney

Twenty cohort studies that assessed the relationship between alcoholic beverage intake and kidney cancer were identified; six of these were in special populations of heavy alcoholic beverage consumers whose rates of kidney cancer were compared with those of other populations, one was a mortality follow-up of a Japanese population, one was a study among cirrhotic patients and twelve were part of a pooled analysis. Twenty-one case–control studies that included information on alcoholic beverages and kidney cancer were identified.

2.16.1 *Cohort studies (Tables 2.78 and 2.79)*

Several of the five follow-up studies of heavy alcoholic beverage consumers (Pell & D'Alonzo, 1973; Jensen, 1979; Robinette *et al*., 1979; Adami *et al*., 1992a; Tønnesen *et al*., 1994; Table 2.78) were seriously limited by very small numbers of renal-cell cancer and an inability to control for confounding by smoking. Two of these had approximately 40 cases (Jensen, 1979; Tønnesen *et al*., 1994); the SIRs were 1.0 and 1.4, respectively.

Recently, a pooled analysis that was part of the Pooling Project of Prospective Studies of Diet and Cancer (Lee *et al*., 2007; Table 2.79) included 12 cohorts that found at least 25 incident cases of renal-cell carcinoma and consisted of 530 469 women and 229 575 men, with a maximum follow-up time of 7–20 years. Only four of these studies (Nicodemus *et al*. 2004; Mahabir *et al*., 2005; Rashidkhani *et al*., 2005; Lee *et al*., 2006) had previously published findings, which tended to show inverse or null associations between alcoholic beverage intake and the incidence of renal-cell cancer. In most of the other cohorts, the numbers of renal-cell cancers were relatively small and the results may have not been published. A total of 1430 incident cases of renal-cell cancer were identified. Alcoholic beverage consumption was inversely related to risk; compared with non-drinkers, the relative risk was 0.72 (95% CI, 0.60–0.86) for consumption of ≥15 g alcohol per day (p for trend <0.001). Although there was significant heterogeneity among studies, the inverse trends were similar and statistically significant in both men and women.

Table 2.78 Cohort studies of alcoholic beverage consumption and cancer of the kidney in special populations

Reference, location, name of study	Cohort description	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Follow-up studies of heavy drinkers							
Pell & D'Alonzo (1973), USA	Employees of a chemical company: 899 alcoholics identified through company physicians, 921 controls; matched for age, sex, payroll class, geographical location; follow-up, 1965–69; 88.1% of alcoholics and 96.3% of controls still alive in 1969	Kidney (189)	Alcoholics Controls	26 deaths (2 renal) 7 deaths (1 renal)			

Table 2.78 (continued)

Reference, location, name of study	Cohort description	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Jensen (1979), Denmark, Danish Brewery Cohort	14 313 Danish brewery workers employed at least 6 months in 1939–63; followed for cancer incidence and mortality in 1943–73; age not given; workers allowed 2.1 L of free beer/day (77.7 g pure alcohol).	Kidney (189); cases and deaths identified through Cancer Registry, classified with 4-digit code of ICD-7			**SIR**	Age, sex, area, time trends	Cancer morbidity and mortality compared with those of the general population
			All cancers	1303	1.1 (1.0–1.2)		
			Kidney cancer	38	1.0 (0.7–1.4)		
Robinette *et al*. (1979), USA, World War II Veterans Study	4401 US Army service men, hospitalized for chronic alcoholism 1944–45; 4401 service men treated for nasopharyngitis matched to alcoholic subjects by age; follow-up through to 1974	Deaths; kidney (ICD-8, 189)	**In 1974**	Deaths	**Mortality rate ratio**		[a] Based on age- and time-specific US death rates in the USA [b] Ratio of observed/ person–years for alcoholism over nasopharyngitis
			Alcoholics				
			All causes	1438	1.78 (1.74–2.00)		
			All cancers	166	1.08 (0.96–1.38)[a]		
			Cancer of kidney, ureter and other	1	0.27 (0.01–2.09)[b]		

Table 2.78 (continued)

Reference, location, name of study	Cohort description	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Adami *et al.* (1992a), Sweden	9353 individuals (8340 men) with a discharge diagnosis of alcoholism in 1965–83; mean age at entry, 49.4 years; at diagnosis, 60.0–68.1 years; follow-up for through to 1984 (maximum, 19 years; mean, 7.7 years); first year of follow-up excluded	Ascertained through National Swedish Cancer Registry; 94% microscopically confirmed; cases occurring in the first year after entry into the cohort excluded			**SIR**		No data on individual alcohol or tobacco use
			All cancers	491 deaths	1.4 (1.3–1.6)		
			Kidney cancer				
			Men	20	1.3 (0.8–2.1)		
			Women	2	2.0 (0.2–7.1)		
Tønnesen *et al.* (1994), Denmark	15 214 male and 3093 female alcohol abusers who entered an outpatient clinic in Copenhagen during 1954–87; average follow-up, 12.9 years for men and 9.4 years for women	Cases identified by record linkage with the Danish Cancer Registry (95% complete)	All cancers	1623 deaths	1.6 (1.5–1.7)		Most subjects consumed about 200 g alcohol daily; cancer morbidity compared with total Danish population
			Kidney cancer				
			Men	42	1.4 (1.0–1.9)		
			Women	4	1.7 (0.5–4.4)		
			Total		1.4 (1.0–1.9)		

Table 2.78 (continued)

Reference, location, name of study	Cohort description	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Sigvardsson *et al*. (1996), Sweden, Cohort of Alcoholic Women	15 508 alcoholic women identified from the Temperance Board records; comparison group of 15 508 women individually matched on day of birth, region; follow-up, [1947–77]; case ascertainment, Swedish Cancer Registry	Identified through Cancer Registry (ICD-7)	Alcoholics	20	1.2 (0.6–2.3)	Age, region	Estimates not adjusted for smoking

Table 2.78 (continued)

Reference, location, name of study	Cohort description	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Sørensen *et al.* (1998), Denmark, Cohort of 1-year Survivors of Cirrhosis	11 605 1-year survivors of cirrhosis identified from Danish National Registry of patients that covered all hospital admissions in Denmark; follow-up, 1977–93; 7165 alcoholic cirrhosis (5079 men, 2086 men); case ascertainment, Danish Cancer Registry (100%)	Identified by linkage with Danish Cancer Registry (almost complete average of country); reports from pathology department and autopsy	Alcoholic cirrosis Total Men Women	 45 27 18	**SIR** 2.2 (1.6–3.0) 2.1 (p>0.05) 2.5 (p>0.05)	Age, sex, calendar period	Estimate not adjusted for smoking; reference, national incidence rates

CI, confidence interval; ICD, International Classification of Diseases; SIR, standardized incidence ratio

2.16.2 *Case–control studies (Table 2.80)*

The 21 case–control studies generally showed no or inverse associations (some of which were statistically significant), and no significantly positive associations. Four relatively recent, large case–control studies of renal-cell cancer are particularly informative. A multicentre case–control study conducted in Australia, Denmark, Sweden and the USA is notable because of the large number of cases (1185 of renal-cell cancer) and the detailed data collected on potentially confounding factors (Wolk *et al*., 1996). The relative risk in men for consumption of ≥15 drinks per week was 1.0 (95% CI, 0.70–1.4) and that in women for consumption of ≥10 drinks per week was 0.5 (95% CI, 0.3–0.8). In a large Italian case–control study of 348 cases, the relative risk was 0.8 (95% CI, 0.5–1.3) for six or more drinks per day (Pelucchi *et al*., 2002b) and, in a large case–control study from Canada conducted by mailed questionnaire (1279 cases), the relative risks for 18 or more servings of alcoholic beverage per week were 0.7 (95% CI, 0.5–0.9) for men and 0.6 (95% CI, 0.4–1.1) for women with significant inverse trends in both sexes (Hu *et al*., 2003). A multicentre hospital-based case–control study in eastern Europe (1065 cases) calculated average lifetime alcoholic beverage consumption (Hsu *et al*., 2007); the relative risk for those who drank more than 137.5 g alcohol per week was 0.83 (95% CI, 0.61–1.12) and that for the top decile of intake was 0.39 (95% CI, 0.24–0.66).

All the large case–control studies and the pooled analysis of cohort studies were limited to renal-cell carcinomas. No studies of alcoholic beverage consumption in relation to cancer of the renal pelvis were identified.

2.16.3 *Evidence of a dose–response*

The best available evidence on dose–response comes from the pooled analysis of cohort studies (Lee *et al*., 2007). Relative risks were 0.97 (95% CI, 0.85–1.11) for 0.1–4.9 g/day, 0.82 (95% CI, 0.69–0.96) for 5.0–14.9 g/day and 0.72 (95% CI, 0.60–0.86) for 15 or more g/day (p for trend <0.001). A non-parametric regression curve was fit to the continuous data from these studies, and significant departure from linearity was suggested (P=0.02) with flattening of the curve above approximately 30 g/day.

The participating cohort studies had validated data for alcoholic beverage consumption; therefore, regression calibration was used to correct the observed associations for measurement error in alcoholic beverage intake, and limited this correction to the range of 0–30 g/day (94% of the data) because the relation appeared to be close to linear within this range. The uncorrected relative risk was 0.79 (95% CI, 0.70–0.89) for a 10-g/day increment within this range; after correction for measurement error, the relative risk was 0.81 (95% CI, 0.74–0.90).

The large case–control studies all found relative risks of 1.0 or below for the highest category of alcoholic beverage consumption and were generally consistent with

Table 2.79 Cohort studies of alcoholic beverage consumption and cancer of the kidney in the general population

Reference, location, name of study	Cohort description	Exposure assessment	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Nicodemus *et al*. (2004), USA, Iowa Women's Health Study Cohort [included in Lee *et al*. (2007)]	99 826 randomly selected women, aged 55–69 years, from Iowa driver's licence list, sent a questionnaire in January 1986; 41 836 (42%) women responded, 34 637 (98% white) included; follow-up, 15 years	Questionnaire on lifestyle, medical history, reproductive history, food intake, drinking habits, physical activity	Incident primary renal-cell carcinoma ascertained via the State Health Registry of Iowa; all cases histologically confirmed (ICD-9, 189.0)	*Alcohol intake (g/day)*	117 cases		Age, physical activity, high blood pressure, diuretic use, insulin use, hormone replacement therapy, regularity of menstrual cycles, parity	
				0	79	1.0		
				0.1–2.9	31	1.0 (0.7–1.6)		
				≥3	14	0.4 (0.2–0.8)		
				Beer use				
				No	110	1.0		
				Yes	14	0.6 (0.4–1.1)		
				Red wine				
				No	110	1.0		
				Yes	14	0.5 (0.3–0.8)		
				White wine				
				No	106	1.0		
				Yes	18	0.6 (0.4–1.0)		

Table 2.79 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Mahabir *et al.* (2005), Finland, 1985–99, Finnish Smokers Cohort Study [included in Lee *et al.* (2007)]	27 111 men in the α-Tocopherol, β-Carotene Cancer Prevention Study cohort for whom data on alcohol consumption and diet were available	Questionnaire: height, weight, blood pressure, medical history, food frequency during past year, alcohol intake	Incident cases identified via the Finnish Cancer Registry and confirmed with hospital records and reports from pathology; response rate, 93%	*Total alcohol (g/day) [median]* 0–2.5 [0.4] 2.6–11.0 [6.2] 11.1–24.0 [17.3] 24.1–278.5 [39.1] *Spirits (g alcohol/day) [median]* 0–0.4 [0] 0.5–5.3 [1.7] 5.4–15.9 16.0–160 [22.8] *Beer (g alcohol/day) [median]* 0 [0] 0.01–1.9 [1.2] 2.0–7.4 [4.0] 7.5–242.6 [14.8]	195 cases 56 52 53 34 62 42 56 35 65 53 45 32	*Multivariate-adjusted* 1.0 0.91 (0.6–1.3) 0.94 (0.6–1.4) 0.53 (0.3–0.8) *p*-trend=0.005 1.0 0.9 (0.6–1.4) 0.8 (1.6–1.2) 0.6 (0.4–0.9) *p*-trend=0.02 1.0 1.2 (0.9–1.8) 0.8 (0.6–1.2) 0.6 (0.4–0.9) *p*-trend=0.002	Age, body mass index, supplement group, calories (excluding alcohol sources), blood pressure, years of regular smoking, total number of cigarettes smoked per day, smoking inhalation, and fruits and vegetables	Alcohol use given in quartile groups, with 6774–6782 subjects per group

Table 2.79 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Rashidkhani *et al*. (2005), Sweden, Swedish Mammography Cohort [included in Lee *et al*. (2007)]	66 561 Swedish women, aged 40–76 years, living in the counties of Västmanland and Uppsala, who responded to a questionnaire in 1987–90 (participation rate, 74%), with follow-up questions in 1997 (rate of response, 70%); average follow-up, 14.2 years	Questionnaire in 1997 on diet (67 food items) during past 6 months, alcohol and tobacco use, education, weight, height, history of hypertension, diabetes	Incident cases of renal-cell carcinoma (ICD-9, 189.0); recorded by matching with Regional Cancer Register, between the return of the questionnaire (1987–90) and 30/06/2004	*Alcohol intake (g/day)*	132 cases	**Rate ratio** *All women*	Age, body mass index	* Includes strong (4.5%) and medium-strong (2.8%) but not light beer
				<2.5 (median 1.1)	94	1.0		
				2.5–4.3 (median 3.3)	19	0.66 (0.40–1.09)		
				>4.3 (median 6.0)	19	0.7 (0.42–1.19)		
				All alcoholic beverages (servings/week)				
				<1	94	1.0		
				≥1	38	0.6 (0.4–0.9)		
				Wine (servings/week)				
				<1	120	1.0		
				≥1	12	0.6 (0.3–1.1)		
				Beer (servings/month)*				
				<1	116	1.0		
				≥1	16	0.7 (0.4–1.2)		
				Hard liquor (servings/week)				
				<1	107	1.0		
				≥1	25	0.8 (0.5–1.3)		

Table 2.79 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Rashidkhani *et al*. (2005) (contd)				*Alcohol intake (g/day)*		*Aged ≥55 years*		
				<2.5 (median 1.1)	65	1.0		
				2.5–4.3 (median 3.3)	10	0.8 (0.4–1.5)		
				>4.3 (median 6.0)	3	0.3 (0.1–1.1)		
				All alcoholic beverages (servings/week)				
				<1	69	1.0		
				≥1	9	0.44 (0.22–0.88)		
				Wine (servings/week)				
				<1	76	1.0		
				≥1	2	0.23 (0.06–0.95)		
				Beer (servings/month)*				
				<1	73	1.0		
				≥1	5	0.7 (0.3–1.6)		
				Hard liquor (servings/week)				
				<1	71	1.0		
				≥1	7	0.48 (0.22–1.04)		

Table 2.79 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Lee *et al*. (2006), USA, Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) [included in Lee *et al*. (2007)]	NHS: 121 700 female registered nurses, aged 30–55 years, returning a mailed questionnaire in 1976; HPFS: 51 529 health professionals (all men), aged 40–75 years, responding to a mailed questionnaire in 1986; follow-up of 88 759 women (NHS) from 1980, 47 828 men (HPFS) from 1986 with follow-up rate >90%; follow-up ended in 2000, on 31/05 for NHS, on 31/01 for HPFS	Semiquantitative food-frequency questionnaires sent in 1980 and 1984 to NHS participants, and in 1986 and every 4 years after to both cohorts; questions on extent and frequency of alcohol use and total intake of fluids (including water)	Renal-cell carcinoma self-reported and then verified by histological data	NHS	132 cases	**Pooled multivariate**	NHS: body mass index, history of hypertension (yes/no), history of diabetes (yes/no), parity, smoking status, total energy intake; HPFS: body mass index, history of hypertension (yes/no), smoking status, multi-vitamin use, total energy intake *Additionally adjusted for the two other alcoholic beverages	Alcohol use divided into quartile groups
				HPFS	116 cases			
				Total alcohol (g/day)				
				0	58	1.0		
				0.1–4.9	88	1.0 (0.7–1.3)		
				5.0–14.9	61	0.9 (0.5–1.6)		
				≥15	41	0.7 (0.4–1.0)		
						p-trend=0.07		
				Beer				
				No beer	164	1.0*		
				Beer drinkers	82	0.7* (0.4–1.2)		
				Wine (servings)				
				<1/month	93	1.0*		
				1/month–<2/ week	96	1.2* (0.9–1.6)		
				≥2/week	59	1.1* (0.7–1.8)		
				Liquor (servings)				
				<1/month	129	1.0*		
				1/month–<2/ week	58	0.9* (0.7–1.2)		
				≥2/week	60	0.9 (0.6–1.2)		

Table 2.79 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Case definition (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Lee *et al*. (2007), Pooled analysis including 12 cohorts; includes four previously published studies (Nicodemus *et al*., 2004; Mahabir *et al*., 2005; Rashidkhani *et al*., 2005; Lee *et al*., 2006)	530 469 women and 229 575 men with maximum follow-up of 7–20 years	Self-administered questionnaires	Cases ascertained by follow-up questionnaires and subsequent review of medical records, linkage to cancer registries, or both; histologically confirmed renal-cell cancer (ICD-0-2, C64.9); 61% renal-cell carcinoma, not otherwise specified (code 8312)	*Total alcohol (g/day)* 0 0.1–4.9 5.0–14.9 ≥15 *Beer(g/day)* 0 1.0–4.9 ≥5.0 *Wine(g/day)* 0 0.1–1.49 ≥5.0 *Liquor(g/day)* 0 1.0–4.9 ≥5.0	1430 cases (711 women, 719 men)	 1.0 0.97 (0.85–1.11) 0.82 (0.69–0.96) 0.72 (0.60–0.86) *p*-trend<0.001 1.0 0.98 (0.85–1.12) 0.87 (0.68–1.11) 1.0 0.93 (0.79–1.08) 0.72 (0.59–0.87) 1.0 1.02 (0.88–1.17) 0.88 (0.75–1.03)	Age, hypertension, body mass index, smoking, parity, age at first birth, energy intake	Relative risks similar for men and women with significant inverse trends in both sexes

CI, confidence interval; ICD, International Classification of Diseases

Table 2.80 Case–control studies of alcoholic beverage consumption and cancer of the kidney

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Schwartz *et al.* (1962), France, 1954–58	69 cases of rena-cell cancer	69 accident victims); age-matched in 5-year age groups	Interviewed in the hospital on alcohol drinking	Cases, 10.8 cL/day Controls, 12.6 cL/day	NR			Average consumption according to age (5-year age groups) varied from 9.6 to 14.0 cL pure alcohol/day
Williams & Horm (1977), USA, Third National Cancer Survey, 1969–71	101 kidney cancer cases (53 men, 48 women) among 7518 cancer patients		Interviewed to collect data on the amount and the duration of alcohol and tobacco use	*Men* <50 oz–years >50 oz–years *Women* <50 oz–years >50 oz–years	 11 14 6 3	 1.07 0.76 0.80 0.76	Age, race, smoking	Oz–years = units/week × years drinking

Table 2.80 (continued)

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Goodman *et al*. (1986), USA, 1977–83	267 patients (189 men, 78 women) with newly diagnosed primary adenocarcinoma of the kidney in 18 hospitals in 6 cities, aged 20–80 years; 100% histologically confirmed; refusal rate, 11%	267 patients (189 men, 78 women) with diseases not tobacco-/obesity-related, diagnosed and interviewed ≤1 year after the case interview; matched 1:1 on age, sex, race, hospital, time of admission; refusal rate, 12%	Standardized interview on medical history, life-style drinking/ smoking habits, demographic information, job history, leisure time and worksite energy expenditure	**Men and women** *Alcohol use* Never Ever *Alcohol score** 1–9 10 *Beer* Never Ever *Wine* Never Ever *Hard liquor* Never Ever **Men only** *Former use of beer* Never 1–3 years >4 years	 65 193 60 69 134 133 129 138 122 144 89 8 5	 1.0 0.6 (0.4–1.0) 0.5 (0.3–0.8) 0.9 (0.5–1.7) 1.0 0.8 (0.5–1.1) 1.0 0.7 (0.5–0.96) 1.0 0.7 (0.5–1.01) 1.0 0.3 (0.0–1.1) 0.2 (0.0–0.5)		* Alcohol score: years of drinking × average daily consumption (in alcohol equivalents)
Yu *et al*. (1986), USA	6 renal-cell carcinoma; aged <55 years; 100% histologically confirmed	160 population-based; matched by age, sex	Personal interviews using questionnaire					Cases and controls did not differ significantly by consumption of alcoholic beverages (no data given)

Table 2.80 (continued)

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Asal *et al.* (1988), USA, 1981–84	315 (209 men, 106 women; 34 non-white) incident renal-cell carcinomas in 29 Oklahoma hospitals; 300 histologically confirmed, 15 radiologically confirmed	313 (208 men, 105 women) patients; psychiatric illnesses or kidney disease excluded; 12% had cancer; matched by age (within 5 years), sex, race, hospital, time of interview; 336 (195 men, 141 women) selected by random-digit dialling from the Oklahoma population; frequency-matched by age (within 10 years), sex	Interviews in hospital, at home or at work on medication, medical history, radiation therapy, main occupation, tobacco/alcohol use, height and weight, family history of disease	**Wine (glass/week)** *Ever* Men Women *Men* Never <1 1–4 >4 *Women* Never <0.5 0.5–3 >3	 85 30 124 48 15 16 76 15 5 10	 0.5 (0.4–0.8) 0.5 (0.3–0.9) 1.0 0.4 (0.3–0.7) 0.7 (0.3–1.9) 0.7 (0.3–1.6) 1.0 0.5 (0.2–1.0) 0.6 (0.2–1.5) 1.1 (0.4–3.0)	 Age, weight, smoking Age, weight	One alcohol unit = 1 oz (28.4 g) hard liquor, 4 oz (113 g) wine, 8 oz (227 g) beer; 'ever' drinkers included subjects who drank unknown amounts (6 cases, 3 controls)
Brownson (1988), USA, 1984–86	326 (205 men, 121 women; all white) Missouri residents with primary adenocarcinoma of the kidney, identified via the Missouri Cancer Registry, aged ≥20 years; 100% histologically confirmed	978 (615 men, 363 women) patients in the Registry with cancers of the small intestine colon, rectum, prostate, skin, nervous, reticulo-endothelial and haematopoietic systems and lymph nodes	Information on smoking, alcohol use, job history recorded at the time of diagnosis	*Men* Never drank Ever drank Unknown *Women* Never drank Ever drank Unknown *Both sexes* Never drank Ever drank Unknown	NR	 1.0 0.9 (0.6–1.3) 1.1 (0.6–2.1) 1.0 1.1 (0.6–2.0) 0.8 (0.3–2.0) 1.0 1.0 (0.7–1.4) 1.0 (0.6–1.7)	Age, smoking Age, smoking, sex	

Table 2.80 (continued)

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Kadamani *et al.* (1989), USA, 1981–83	210 (142 men, 68 women; 90% white) newly diagnosed renal-cell carcinomas in 23 Oklahoma hospitals, aged ≥20 years;197 histologically confirmed, 13 radiologically confirmed	210 (142 men, 68 women) selected by random-digit dialling from the Oklahoma population; frequency-matched by age (within 5 years), sex; refusal rate, 45%	Interviews on demographics, job history, use of tobacco/ alcohol; exposure to hydrocarbons (HC) estimated from job history by industrial hygienists	No HC exposure *Never wine use* *Ever wine use* Low HC exposure *Never wine use* *Ever wine use* Moderate HC exposure *Never wine use* *Ever wine use* High HC exposure *Never wine use* *Ever wine use*	NR	**Odds ratio** *Men (women)* 1.0 (1.0) 1.3 (0.8) 2.3 (0.5) 0.56 (1.00) 4.3 (3.2) 0.4 (0.8) 3.1 (0.9) 0.4 (0.6)	Men: weight, education; women: weight	No CIs given; this study focused primarily on effects of occupational exposure to hydrocarbons on the risk for renal-cell carcinoma.
Maclure & Willett (1990), Massachusetts, USA	203 incident renal adeno-carcinomas diagnosed in 37 hospitals in the Boston area, aged ≥30 years; 100% histologically confirmed	605 neighbourhood controls; not matched	Questionnaire administered by interviewer on diet, medication, smoking and alcohol, occupational history, physical activity	*Wine* Low Moderate High *Beer* Low Moderate High *Spirits* Low Moderate High		 1.0 0.7 (0.4–1.2) 1.0 (0.3–3.0) 1.0 1.1 (0.7–1.7) 1.4 (0.8–2.5) 1.0 1.1 (0.7–1.6) 1.1 (0.6–1.9)	Age, sex, drinking	

Table 2.80 (continued)

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Talamini *et al.* (1990b), Italy, 1986–89	240 (150 men, 90 women) renal-cell cancers in hospitals in northern Italy (Veneto, Pordenone, Milan area), aged 20–74 years; 100% histologically confirmed; renal pelvis cancers excluded; refusal rate for interview, 3%	665 (445 men, 220 women) patients in the same hospitals for acute conditions not related to alcohol, tobacco or hormones; matched 3:1 on sex, age (± 5 years), area of residence; refusal rate, 4%	Interviews on lifestyle, occupation, medical history (urologic, hormone-related, infectious diseases), socio-demographic factors, smoking, alcohol drinking	*Highest category of intake per day*: Alcohol, ≥100 g Wine, ≥4 drinks Beer, ≥1 drink Spirits, ≥1 drink	 18 98 53 77	 0.7 (0.4–1.3) 0.9 (0.6–1.3) 1.0 (0.7–1.5) 1.2 (0.8–1.7)	Age, sex, education, body mass index, area of residence	
Benhamou *et al*. (1993), France, 1987–91	196 (138 men, 58 women) renal-cell cancers in 10 French hospitals; mean age, 61.7 and 61.3 years, respectively; 100% histologically confirmed after nephrectomy; refusal rate, 0.5%	347 (235 men, 112 women) hospital patients; mean age, 62.8 and 62.5 years; matched on sex, age at interview (within 5 years), hospital, interviewer; 107 men and 54 women had non-alcohol-related malignancies; refusal rate, 0.5%	Questionnaire and interview on smoking, use of alcohol, coffee drinking, height, weight.	Men Women	NR	0.9 (0.5–1.6) 1.1 (0.5–2.1)		Exposure categories not defined; no trend in association of daily consumption of alcoholic beverages with cancer

Table 2.80 (continued)

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Kreiger *et al.* (1993), Canada, 1986–87	513 (312 men, 201 women) newly diagnosed renal-cell carcinomas resident in the province of Ontario, aged 25–69 years; 100% histologically confirmed; response rate, 81%	1369 (664 men, 705 women) selected from the 1986–87 Enumeration Composite Records of the Ministry of Revenue; matched 1:1 (men) or 2:1 (women) on age, sex, place of residence; response rate, 72%	Questionnaire on diet habits, socio-demographic data, smoking habits, medical history, job exposures and history, diuretic or analgesic use, hormonal and reproductive information (women only)	**Alcohol intake** *Men* None Moderate High* *Women* None Moderate High*	 43 173 36 65 84 18	 1.0 0.9 (0.6–1.3) 1.3 (0.7–2.4) 1.0 0.7 (0.5–1.0) 0.7 (0.4–1.4)	Age, active cigarette smoking, Quetelet index (combined for two time points: at 25 years of age, and at 5 years prior to the study)	*High = top 10% of the distribution
Mellemgaard *et al.* (1994), Denmark, 1989–91	368 (226 men, 142 women) renal-cell carcinomas of 482 diagnosed, born and living in Denmark, identified via the Danish Cancer Registry, aged 20–79 years; 100% histologically confirmed; refusal rate, 6.8%	396 (237 men, 159 women) of 500 identified from Central Population Register via the personal identification number, born and living in Denmark, aged 20–79 years; refusal rate, 14.4%	Questionnaire on education, jobs, height, weight, medical history, family history of cancer, smoking, alcohol use and diet; data recorded for the period ≥1 year prior to interview	**Weekly intake** *Men* Not regularly <75 mL 75–300 mL >300 mL *Women* Not regularly <40 mL 40–100 mL >100 mL	 43 68 68 45 89 31 12 9	 1.0 1.0 (0.6–1.8) 0.8 (0.5–1.5) 0.8 (0.4–1.6) 1.0 1.0 (0.5–1.8) 0.5 (0.2–1.2) 0.4 (0.2–0.9)	Age, socioeconomic status, body mass index, cigarette pack–years	

Table 2.80 (continued)

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Muscat *et al*. (1995), USA, 1977–93	788 (543 men, 245 women; >90% white) newly diagnosed renal-cell cancers in 7 hospitals; 100% histologically confirmed; mean age, 58.7 years for men, 59.3 years for women	779 (529 men, 250 women; >90% white) patients hospitalized for non-tobacco-related conditions: 52% histologically confirmed cancers (excluding kidney, lung, upper aerodigestive tract, stomach, bladder and pancreas), 7% benign prostatic hypertrophy; excluding emphysema, hepatitis, cirrhosis, bronchitis, stroke and heart disease patients; frequency-matched by age (± 5 years), race, year of diagnosis	Interview with questionnaire on demographics, tobacco/alcohol consumption, medical history, occupational exposures	*Wine (oz/day)**		*Men*	Age, education, years of smoking	*Alcohol intake expressed in oz of whisky equivalents: 8 oz beer = 4 oz wine = 1 oz hard liquor
				Never/occasionally	510	1.0		
				1–<4	27	0.9 (0.5–1.7)		
				>4	6	0.9 (0.8–1.0)		
				Beer (oz/day)				
				Never/occasionally	409	1.0		
				1–<4	87	0.9 (0.6–1.2)		
				4–7	19	0.8 (0.4–1.5)		
				>7	27	1.1 (0.6–2.0)		
				Hard liquor (oz/day)				
				Never/occasionally	428	1.0		
				1–<4	73	1.0 (0.7–1.4)		
				4–7	22	1.9 (0.9–4.3)		
				>7	20	0.6 (0.3–1.1)		
				Wine (oz/day)		*Women*		
				Never/occasionally	219	1.0		
				1–<4	23	1.2 (0.6–2.3)		
				Beer (oz/day)				
				Never/occasionally	237	1.0		
				1–<4	8	0.6 (0.2–1.4)		
				Hard liquor (oz/day)				
				Never/occasionally	227	1.0		
				1–<4	18	1.1 (0.6–2.2)		

Table 2.80 (continued)

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Wolk *et al*. (1996), multi-centre, Australia, Denmark, Sweden, USA, 1989–91	1185 incident renal-cell adeno-carcinomas newly diagnosed identified in cancer registries in Sidney, Denmark, Uppsala and Minnesota; mean age, 62 years (men), 63 years (women); 100% histologically confirmed	1526 selected from population registers (Denmark, Uppsala), electoral rolls (Sidney), Health Care beneficiary lists (Minnesota, 65–79-year age group) or by random-digit dialling (Minnesota, 20–64-year age group) chosen from the same area as cases; mean age, 62 years (men), 63 years (women); frequency-matched on sex, 5-year age group	Personal interview on use of tobacco, diuretics analgesics, diet pills, anti-hypertension drugs, hormones and alcohol, height, weight, physical activity, reproductive and medical history, family history of cancer, job history; dietary intake assessed in a questionnaire (part of interview in Uppsala)	**Total alcohol (drinks/week)** *Men* <1 1–3 4–7 8–14 ≥15 *Women* <1 1–2 2–4 5–9 ≥10 **Wine (glass/ week)*** *Men* 0 <0.5 0.5–0.6 0.7–1.2 ≥1.3 *Women* 0 <0.5 0.5–0.6 0.7–2.9 ≥3.0	NR	 1.0 1.1 (0.8–1.5) 1.0 (0.7–1.3) 0.9 (0.6–1.3) 1.0 (0.7–1.4) 1.0 0.8 (0.5–1.4) 0.6 (0.4–0.9) 0.5 (0.3–0.9) 0.5 (0.3–0.8) 1.0 0.7 (0.5–1.2) 0.8 (0.6–1.1) 0.5 (0.3–1.0) 0.8 (0.5–1.3) 1.0 0.5 (0.3–0.8) 0.7 (0.5–1.1) 0.3 (0.1–0.6) 0.2 (0.1–0.4)	Age, sex, study centre, body-mass index, smoking, total calories	* Sweden not included due to lack of data on specific alcoholic beverages; data for beer, port/sherry and spirit included

Table 2.80 (continued)

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Lindblad *et al*. (1997), Sweden, 1989–91	379 of 542 eligible newly diagnosed renal-cell cancers among individuals born in Sweden and residing in any of eight counties in central Sweden between 1/6/89 and 31/12/91, identified via Regional Cancer Registries, aged, 20–79 years; mean age, 63.6 years (men), 64.4 years (women); 100% histologically confirmed; refusal rate, 12%	353 of 493 selected from the register of the same population; mean age, 62.7 years (men), 63.4 years (women); frequency-matched by sex, age (within 5 years); refusal rate, 26%	Interview with questionnaire on usual diet (63 items) prior to 1987, alcohol use, demographics, height, weight, physical activity, medical history, reproductive history, occupation and smoking; specific data collected on dietary habits 20 years ago	*Alcohol intake (g/day)**			Age, sex, body mass index, smoking, level of education, total energy intake	*Alcohol intake defined in quartiles
				<0.23	84	1.0		
				0.23	117	1.4 (0.8–2.3)		
				1.60	90	1.1 (0.6–2.0)		
				2.75	87	1.0 (0.6–1.7)		

Table 2.80 (continued)

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Mattioli *et al*. (2002), Italy, 1986–94	219 renal-cell carcinomas, registered in 1987–94 at the University Hospital of Bologna; 100% histologically confirmed; response rate, 67.6%	219 patients in the same hospital, admitted in 1991 with any disease but renal-cell carcinoma; matched on sex, age (within 5 years), birthplace, residence area; response rate, 67.6%	Questionnaire interview by telephone on height, weight, lifelong use of tobacco, alcohol, coffee and meat; job history	**Alcohol intake (g/day)** *Men* 0 1–12 13–24 25–36 37–48 >48 *Women* 0 1–12 >12	 22 43 56 19 9 16 20 17 15	 1.0 4.0 (1.1–14.8) 3.4 (1.1–10.3) 7.3 (1.2–44.6) 0.5 (0.1–2.5) 1.0 (0.3–4.0) 1.0 2.2 (0.3–16.1) 4.2 (0.3–53.5)	Age, gender, birthplace, residence	

Table 2.80 (continued)

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Parker *et al*. (2002), Iowa, USA	406 of 463 (261 men, 145 women) residents of Iowa with incident renal-cell carcinoma identified via the Iowa Cancer Registry, aged 40–85 years; 100% histo-logically confirmed; response rate, 88%	2429 controls (1598 men, 831 women); aged <65 years selected from Iowa driver's licence records; aged ≥65 years randomly selected from listings of Health Care Financing; matched by sex, 5-year age group; those with a history of cancer excluded; response rates, 82% (<65 years) and 79% (≥65 years)	Mailed questionnaire followed by telephone inter-view on demo-graphics, height and weight at various times in life, smoking history and status, medical history, job history, physical activity, family history of cancer; usual use of alcohol over all adult years ascertained in a food-frequency questionnaire	*Alcohol intake* Never Ever *Servings/week* 0 ≤3 >3 *Ethanol (g/week)* 0 ≤35 >35 *Wine (units/week)* 0 ≤0.5 >0.5 *Beer(units/week)* 0 ≤1 >1 *Liquor (units/week)* 0 ≤1 >1	 98 163 98 80 83 98 77 86 197 32 32 127 56 78 153 57 51	*Men* 1.0 1.0 (0.7–1.5) 1.0 1.2 (0.8–1.8) 0.9 (0.6–1.3) 1.0 1.3 (0.9–1.9) 0.9 (0.6–1.3) 1.0 0.8 (0.5–1.3) 1.2 (0.7–2.0) 1.0 1.4 (0.9–2.0) 1.0 (0.7–1.4) 1.0 1.4 (1.0–2.1) 1.1 (0.7–1.6)	Men: age, pack–years of smoking, family history of kidney cancer, history of hypertension, history of bladder infection, exercise, intake of red meat and fruit; women: age, pack–years of smoking, family history of kidney cancer, body mass index, history of hypertension, intake of red meat, vegetables and fruit	[Results for women shown only when *p* for trend was significant] 1 unit = 8-oz wine glass or 12-oz beer can or 1-oz liquor shot; 1 oz = 29.57 mL

Table 2.80 (continued)

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Parker *et al.* (2002) (contd)				*Alcohol intake*		*Women*		
				Never	93	1.0		
				Ever	52	0.8 (0.5–1.2)		
				Servings/week				
				0	93	1.0		
				≤3	43	1.0 (0.6–1.5)		
				>3	9	0.4 (0.2–1.0)		
						p for trend 0.04		
				Ethanol (g/week)				
				0	93	1.0		
				≤35	41	1.0 (0.6–1.5)		
				>35	11	0.4 (0.2–0.9)		
						p for trend 0.04		
Pelucchi *et al.* (2002b), Italy, 1985–92	348 (236 men, 112 women) renal-cell cancers in general hospitals and university clinics in Milan and the Pordenone province, aged 25–77 years (median, 60 years); 100% histologically confirmed; refusal rate for interview, 4%	1048 (753 men, 295 women) patients admitted to the same hospitals and clinics for acute, non-neoplastic, non-urological and non-genital problems, aged 23–79 years (median, 60 years); refusal rate for interview, 4%	Questionnaire on personal characteristics, socio-demographic and lifestyle details (smoking, coffee drinking), intake of selected food items, medical history, alcohol intake	*Alcohol (drinks/day)*			Age, sex, study centre, education, body mass index, history of bladder infection, cigarette smoking, intake of vegetables, meat and fruit	Among women, 69% of the cases and 72% of the controls were drinkers; among men, these percentages were 88% and 91%, respectively.
				Never	64	1.0		
				Ever	284	0.8 (0.6–1.2)		
				<3	101	0.8 (0.5–1.1)		
				3–5	98	1.0 (0.6–1.5)		
				≥6	85	0.8 (0.5–1.3)		
				Duration (years)				
				<30	53	0.5 (0.3–0.7)		
				≥30	229	1.0 (0.7–1.5)		
				Wine (drinks/day)				
				0	68	1.0		
				<3	109	0.9 (0.6–1.3)		
				3–5	105	0.9 (0.6–1.4)		
				≥6	66	0.9 (0.6–1.5)		
				Beer				
				Never	270	1.0		
				Ever	99	1.0 (0.7–1.4)		
				Spirits				
				Never	249	1.0		
				Ever	99	1.1 (0.8–1.4)		

Table 2.80 (continued)

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Hu *et al.* (2003), Canada, 1994–97	1279 (691 men, 588 women) incident renal-cell cancers in 8 provinces; 100% histologically confirmed; response rate, 79.9% of those contacted	5370 population, age-stratified; response rate, 71.3% of those contacted	Mailed questionnaire on socio-economic status, job history, residential history, height, weight, smoking history, physical activity, alcohol use, dietary history, food-frequency questionnaire	*Alcohol (servings/week)*		*Men*	Age, province, education, smoking (not body mass index)	
				Never	217	1.0		
				1–6	253	0.8 (0.6–1.0)		
				7–17	116	0.7 (0.5–0.9)		
				≥18	104	0.7 (0.5–0.9)		
						p-trend=0.006		
						Women		
				Never	342	1.0		
				1–6	191	0.7 (0.6–0.9)		
				7–17	36	0.6 (0.4–0.8)		
				≥18	19	0.6 (0.4–1.1)		
						p-trend=0.0003		

Table 2.80 (continued)

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Bravi *et al*. (2007), Italy, 1992–2004	767 (494 men, 273 women) renal-cell carcinomas admitted to major hospitals, aged 24–79 years; median age, 62 years; 100% histologically confirmed; cancers of renal pelvis and ureter not included; refusal rate, <5%	1534 (988 men, 546 women) patients admitted to the same hospitals for acute non-neoplastic conditions, aged 22–79 years; (median age, 62 years; matched 2:1 by study centre, sex, age (5-year groups); refusal rate, <5%	Hospital-based interview with questionnaire on anthropometric measures, socio-demographic and lifestyle details, use of alcohol, tobacco, coffee, medical history, family history of cancer in first-degree relatives; food-frequency questionnaire on 78 items	*Drinks per week* Never <21 ≥21 Former drinkers*	 131 361 212 63	 1.0 0.88 0.80 0.97	None	*Former drinkers had not had a drink for ≥1 year

Table 2.80 (continued)

Reference, tudy location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Hsu *et al*. (2007), multicentre, eastern Europe, 1999–2003	1065 newly diagnosed renal-cell cancers, aged, 20–79 years; 100% histologically confirmed; response rate, 90–98.6% across centres	1509 patients admitted to the same hospitals as cases with diagnoses unrelated to smoking or genitourinary disorders; frequency-matched on age, response rate, 90.3–96.1% across centres	In-person interview on usual weekly alcohol consumption during five periods of life; average lifetime consumption was calculated	*Intake (g/alcohol/week)* None <36.5 36.5–137.5 137.5 Top decile of alcohol intake	 274 310 290 191 27	 1.0 1.18 (0.93–1.49) 1.15 (0.88–1.48) 0.83 (0.61–1.12) 0.39 (0.24–0.66)	Age, country, gender, tobacco use, education, body mass index, hypertension, medication, consumption of vegetables, white meat, red meat	Data for wine, beer and liquor separately also presented in article

CI, confidence interval; NR, not reported

the results of the pooled analysis, although no formal meta-analysis of these studies is available.

2.16.4 *Type of alcohol*

In the Pooling Project of cohort studies (Lee *et al*., 2007), inverse trends were seen for beer, wine and liquor, but only the trend for wine was statistically significant. However, the relative risks for different beverages did not differ significantly from each other.

The data from the case–control studies also did not provide clear evidence that the inverse association with kidney cancer was limited to a specific beverage.

2.16.5 *Interactions*

The associations between alcoholic beverage intake and kidney cancer did not vary appreciably by body mass index, history of hypertension, smoking status or age at diagnosis.

2.17 Cancers of the lymphatic and haematopoietic system

Lymphomas and haematopoietic malignancies comprise a heterogeneous group of malignancies and their etiology is not fully understood. There is a growing number of epidemiological studies that have examined the associations of alcoholic beverage consumption with the risk for these cancers.

2.17.1 *Cohort studies*

(a) Special populations (Table 2.81)

Five studies among heavy alcoholic beverage users or brewery workers have investigated the risk for lymphatic and/or haematopoietic cancers (Hakulinen *et al*., 1974; Jensen, 1979; Robinette *et al*., 1979; Schmidt & Popham, 1981; Carstensen *et al*., 1990). Among the three studies that examined lymphatic/haematopoietic cancers combined, one showed no significant differences between the observed number of cases among Danish brewery workers, compared with the expected number of cases computed from age-, sex- and area-specific rates (Jensen, 1979); one showed a slightly increased risk for these cancers among Swedish brewery workers compared with the expected number of cases calculated using age-, follow-up time- and area-standardized rates for the Swedish male population (Carstensen *et al*., 1990); and another showed a non-significant decreased risk among chronic alcoholic male US veterans compared with expected numbers computed from age- and time-specific rates for US men (Robinette *et al*., 1979).

Table 2.81 Cohort studies of alcoholic beverage consumption and cancers of the lymphatic and haematopoietic system in special populations

Reference, location	Cohort description	Organ site (ICD code)	No. of cases/ deaths Obs (Exp)	SIR/SMR (95% CI)	Adjustment factors	Comments
Hakulinen *et al*. (1974), Helsinki, Finland	Approximately 205 000 male alcohol misusers and a mean of 4370 male chronic alcoholics, aged >30 years, registered as chronic alcoholics between 1967 and 1970; morbidity during same period determined from Finnish Cancer Registry	Lymphoma, Hodgkin disease Leukaemia	1 (1.67) 1 (1.22)	[0.60 (0.02–3.34)] [0.82 (0.02–4.57)]	None	The expected numbers of cases were calculated from data from the Finnish Cancer Registry (1965–68). The exact amount of alcohol consumed by these men was unknown.
Jensen (1979), Denmark	14 313 Danish brewery workers employed at least 6 months in 1939–63; followed for cancer incidence and mortality in 1943–73; age not given; workers were allowed 2.1 L of free beer/day (77.7 g pure alcohol).	Lymphatic and haematopoietic Leukaemia	68 (65.98) 25 (26.33)	**SIR** 1.03 (0.80–1.31) **SMR** 0.95 (0.61–1.40)	Age, sex, area (capital/ provincial towns)	Expected numbers were computed from age-, sex- and area-specific rates and corresponding perso–years at risk.

Table 2.81 (continued)

Reference, location	Cohort description	Organ site (ICD code)	No. of cases/ deaths Obs (Exp)	SIR/SMR (95% CI)	Adjustment factors	Comments
Robinette *et al*. (1979), USA	4401 chronic alcoholic male veterans, hospitalized in 1944–45 and followed in 1946–74 for mortality; 29 years follow-up, age not given	Lymphatic and haematopoietic (ICD-8 200–209)	13 (17.3)	[0.75 (0.40–1.28)]	Age	Expected mortality was computed from age- and time-specific rates for US males that were applied to the actual numbers of person–years at risk at each age and in each calendar year.
		Leukaemia (ICD-8 204–207)	3 (6.4)	[0.47 (0.10–1.37)]		
		Haemato-poietic (ICD-8 200–203, 208–209)	10 (10.9)	[0.92 (0.44–1.69)]		
Schmidt & Popham (1981), Ontario, Canada	9889 alcoholic men, aged ≥15 years, admitted to the clinical service of the Addiction Research Foundation of Ontario between 1951 and 1970; maximum 21 years of follow-up	Malignant lymphoma (ICD-7 200, 201, 203)	5 (10.67)	0.47 [0.15–1.09]	Age	Expected deaths were calculated using the age-specific death rates for the general male population.
		Leukaemia (ICD- 7 204)	3 (6.94)	0.43 [0.09–1.26]		

Table 2.81 (continued)

Reference, location	Cohort description	Organ site (ICD code)	No. of cases/ deaths Obs (Exp)	SIR/SMR (95% CI)	Adjustment factors	Comments
Carstensen *et al*. (1990), Sweden	6230 men occupied in the Swedish brewery industry at the time of the 1960 census and followed between 1961 and 1979, aged 20–69 years	Lymphatic and haematopoetic (ICD-7 200–205)	60 (46.9)	1.28 (0.98–1.65)	Age, follow-up period, region	Expected numbers of cases were calculated using the total male population as a reference and with standardization for year of birth, follow-up period and region of residence in 1960.
		Leukaemias (ICD-7 204)	30 (19.1)	1.57 (1.06–2.24)		

CI, confidence interval; ICD, International Classification of Diseases; Obs (Exp), observed (expected); SIR, standardized incidence ratio; SMR, standardized mortality ratio

In two studies, the observed number of cases of lymphoma among alcoholics was lower than that expected based on rates for the general population (Hakulinen *et al*., 1974; Schmidt & Popham, 1981).

In studies among alcoholics, the observed number of cases of leukaemia did not differ significantly from those expected in one study (Hakulinen *et al*., 1974), and was non-significantly lower in two other studies (Robinette *et al*., 1979; Schmidt & Popham, 1981). Among brewery workers, a Danish study found no significant difference between the observed and expected number of leukaemia deaths (Jensen, 1979), while a Swedish study found a 1.6-fold higher risk of mortality among brewery workers compared with that expected from the local population (Carstensen *et al*., 1990).

(b) General population (Table 2.82)

Four prospective cohort studies examined associations between alcohol intake and the risk for the lymphatic and/or haematopoietic cancers (Boffetta *et al*., 1989; Kato *et al.,* 1992c; Chiu *et al.,* 1999; Lim *et al*., 2006).

For non-Hodgkin lymphoma specifically, Chiu *et al*. (1999) found a non-significant inverse association with alcoholic beverage intake among postmenopausal women in the USA. This relationship persisted after adjustment for several potential confounding factors including age, total energy intake, residence (farm, no farm), education, marital status, history of transfusion and diabetes, and intake of red meat and fruit. [The Working Group noted that the level of alcohol intake was very low in this study.] In the only other cohort study of non-Hodgkin lymphoma and alcoholic beverage consumption, Lim *et al*. (2006) found weak evidence of an inverse association among male Finnish smokers in a multivariate analysis.

In a study among American men of Japanese ancestry that also considered several potential lifestyle, medical and dietary confounding factors, results were presented for lymphoma and leukaemia combined. A threefold higher risk for lymphoma/leukaemia was associated with consumption of ≥30 mL alcohol per day compared with non-drinkers (Kato *et al*., 1992c).

In the two prospective cohort studies that assessed the association between alcoholic beverage intake and the risk for multiple myeloma, one study found no association (Lim *et al*., 2006) and one found a lower risk among ever regular drinkers compared with never regular drinkers (Boffetta *et al*., 1989).

2.17.2 *Case–control studies*

(a) Lymphoma (Hodgkin disease, non-Hodgkin lymphoma and other lymphomas) (Table 2.83)

Sixteen published case–control studies examined associations between alcoholic beverage intake and the risk for lymphomas (Williams & Horm 1977; Cartwright *et al*., 1988; Brown *et al*., 1992; Nelson *et al*., 1997; Tavani *et al.,* 1997; De Stefani *et al.,*

Table 2.82 Cohort studies of alcoholic beverage consumption and cancers of the lymphatic and haematopoietic system in general populations

Reference, ocation, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Boffetta *et al.* (1989), USA, American Cancer Society (ACS) Cancer Prevention Study II	Case–control study nested within a prospective cohort of 508 637 men and 676 613 women, aged ≥30 years, who completed a questionnaire in 1982 and were followed up for mortality for 4 years; cause of death determined from the death certificate; 282 multiple myeloma cases (128 incident, 154 prevalent) matched 1:4 to controls on sex, ACS division, year of birth, ethnic group	Self-administered questionnaire that asked about drinking history	Multiple myeloma (incident)	Ever regular drinker	20	0.6 (0.3–1.0)	Age, sex, ethnic group	Analyses were presented using incident cases only.

Table 2.82 (continued)

Reference, ocation, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Kato *et al*. (1992c), Oahu, Hawaii, USA, Honolulu Heart Study	6701 American men of Japanese ancestry, born in 1900–19, residents of Oahu with no personal history of cancer at baseline who were identified by the Selective Service draft file of 1942; interviewed in 1965–68; 19-year follow-up for cancer incidence using SEER Registry	24-h diet recall during in-person interview to obtain usual monthly and actual intake of beer, spirits and wine (including sake)	Lymphoma, leukaemia (ICD-8 200–202, 204–207)	*Ethanol (mL/day)* 0 <30 ≥30 *Beer (mL/day)* 0 <500 ≥500	 19 25 21 20 26 19	 1.0 1.0 (0.6–1.9) 3.1 (1.6–5.9) *p*-trend<0.01 1.0 1.5 (0.9–2.8) 2.8 (1.5–5.3) *p*-trend<0.01	Age, cigarette smoking	Of the total alcohol consumed by participants, 69% was beer, 24% spirits, 7% wine.

Table 2.82 (continued)

Reference, ocation, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Chiu *et al.* (1999), Iowa, USA, Iowa Women's Health Study	35 156 postmenopausal women, aged 55–69 years, who completed a mailed questionnaire in 1986, had no personal history of cancer and a total calorie intake of 600–5000 Kcal; followed through 1994 for cancer incidence using Iowa SEER data; 143 incident NHL cases developed	Mailed food-frequency questionnaire including usual intake of beer, wine and spirits over the last year	NHL (ICD-O 9590, 9670–3, 9675, 9680–2, 9684–6, 9690–3, 9695–6, 9698, 9700)	*Ethanol (g/day)* 0 ≤3.4 >3.4	 96 27 20	 1.0 0.78 (0.51–1.21) 0.59 (0.36–0.97) *p*-trend=0.03	Total energy, age, residence, education, marital status, transfusion history, diabetes history, intake of red meat, fruit	Inverse associations also seen for wine, liquor intake and beer intake

Table 2.82 (continued)

Reference, ocation, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Lim *et al.* (2006), Finland, α-Tocopherol β Carotene Cancer Prevention (ATBC) Study	27 111 healthy Finnish male smokers (≥5 cigarettes per day), aged 50–69 years, with no personal history of cancer who completed a baseline dietary questionnaire, randomized to a supplement that contained α-tocopherol, β-carotene, both or placebo; followed up to 16.4 years for cancer incidence using the Finnish Cancer Registry; 195 NHL, 11 HL and 32 MM cases developed	Self-administered dietary questionnaire to assess intake over the previous 12 months	NHL (ICD-O2 9590-9595, 9670–9677, 9680–9688, 9690–9698, 9700–9715, 9823), MM (9732), HL (9650, 9652–9655, 9657–9667)	**Ethanol (g/day)** *NHL* 0 0.04–5.2 5.3–13.3 13.4–27.6 27.7–278.5	 19 55 43 46 32	 0.67 (0.40–1.14) 1.0 (reference) 0.83 (0.56–1.24) 0.97 (0.65–1.45) 0.76 (0.49–1.20)	Age, calories, education, smoking history, serum high-density lipoprotein	Alcohol non-significantly inversely associated with DL, FL, TCL and non-significantly positively associated with CLL, SLL; No association between alcohol intake and MM (data not shown)

CI, confidence interval; CLL, chronic lymphocytic leukemia; DL, diffuse lymphoma; FL, Follicular lymphoma; HL, Hodgkin lymphoma; ICD, International Classification of Diseases; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; SEER, Surveillance, Epidemiology, and End Results; SLL, small lymphocytic lymphoma; TCL, T-cell lymphoma

Table 2.83 Case–control studies of alcoholic beverage consumption and lymphomas

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD-9 code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounding factors	Comments
Williams & Horm (1977), Multicentre, USA	42 exposed men, 54 exposed women; 46 exposed men, 23 exposed women with incident, invasive cancer from the Third National Cancer Survey	1746 men, 3134 other cancers; 1742 men, 3165 other cancers; from the Third National Cancer Survey; excluding cancers of the lung, larynx, mouth, oesophagus, bladder	Interviewer-administered standardized questionnaire	Lympho-sarcoma; HD	**Lymphosarcoma** *Men* None <51 oz/years ≥51 oz/years *Women* None <51 oz/years ≥51 oz/years **Hodgkin disease** *Men* None <51 oz/years ≥51 oz/years *Women* None <51 oz/years ≥51 oz/years **Other lymphomas** *Men* None <51 oz/years ≥51 oz/years *Women* None <51 oz/years ≥51 oz/years	 5 8 8 3 7 7 4 0 4 1 1 0	 1.0 0.40 0.53 1.0 0.94 0.75 1.0 0.45 0.82 1.0 0.87 – 1.0 0.19 0.74 1.0 0.50 –	Age, race, smoking	Controls excluded cancers of the lung, larynx, mouth, oesophagus, urinary bladder; for other lymphomas, fewer than 11 cases for women and fewer than 18 for men; results presented only for lymphosarcoma and Hodgkin disease

Table 2.83 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD-9 code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounding factors	Comments
Cartwright *et al*. (1988), Yorkshire, United Kingdom, 1979–84	437 cases (244 men, 193 women) from hospitals in Yorkshire, aged ≥15 years; 100% histologically confirmed; response rate, 31%	724 hospital-based with diseases unrelated to smoking; matched 2:1 by sex, age (± 3 years), residential district; response rate not given	Interviewer-administered standardized questionnaire	NHL	Wine drinker	50	<2.0 (p>0.05)	Not given	27 cases and 22 controls had had a previous non-skin cancer.
Brown *et al*. (1992), Iowa, Minnesota, USA, 1981–84	622 white men (438 living, 184 deceased) from Iowa Health Registry and Minnesota surveillance network, aged ≥30 years; 100% histologically confirmed; response, 89%	1245 white male population-based (820 alive, 425 deceased) selected by RDD (alive and <65 years), HCFA (≥65 years) or death certificate (deceased); frequency-matched to cases on age (±5 years), vital status at time of interview, state; response rate, 78%	Interviewer-administered standardized questionnaire	NHL	Drinker versus non-drinker *Drinks/week* Non-drinker <5 5–11 12–23 >23	461 357 117 120 121 103	0.9 (0.7–1.1) 1.0 0.7 (0.5–1.0) 1.0 (0.7–1.4) 0.9 (0.6–1.2) 0.9 (0.7–1.3)	Age, state, tobacco use	Drinkers were subjects who had ever consumed any alcoholic beverage at least weekly; no significant associations with lymphoma subtype (follicular, diffuse, small lymphocyte) or with intake of liquor only or beer or wine only; farming, education, family history of cancer and exposure to high-risk jobs or chemicals did not confound results; population overlaps with Chiu *et al*. (2002).

Table 2.83 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD-9 code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounding factors	Comments
Nelson *et al*. (1997), Los Angeles County, USA, 1989–92	378 (185 men, 193 women) from a population-based cancer registry in Los Angeles, CA, aged 18–75 years; 100% histologically confirmed; response rate, 35%	378 population-based controls (185 men, 193 women); matched 1:1 on sex, age (±3 years), race/ethnicity, language of interview, neighbourhood; response rate not given	Interviewer-administered standardized questionnaire that asked about weekly alcohol use before the reference date	NHL	**Men** *Drinks/week* Non-drinker Current drinker 0.1–4 5–11 ≥12 **Women** *Drinks/week* Non-drinker Current drinker 0.1–4 5–11 ≥12	 69 46 37 29 50 122 71 45 13 13	 1.0 0.68 (0.43–1.08) 0.61 (0.34–1.12) 0.45 (0.24–0.84) 1.09 (0.60–1.98) *p*-trend=0.82 1.0 0.63 (0.40-1.00) 0.74 (0.43–1.27) 0.51 (0.24–1.06) 0.50 (0.23–1.09) *p*-trend=0.03	Matching factors adjusted for using conditional logistic regression	All cases and controls HIV negative; no significant differences in associations according to alcoholic beverage type
Tavani *et al*. (1997), Milan and Pordenone, Italy, 1983–92	829 cases (158 HD, 429 NHL, 141 MM, 101 STS); aged 17–79 years; 100% histologically confirmed; response rate, >97%	1157 hospital-based, aged 17–79 years; response rate, >97%	Interviewer-administered structured questionnaire	HD, NHL	Alcohol drinking HD Tertile 1 Tertile 2 Tertile 3 NHL Tertile 1 Tertile 2 Tertile 3	 33 68 57 67 172 190	 1.0 1.1 (p>0.05) 0.9 (p>0.05) 1.0 0.8 (p>0.05) 0.8 (p>0.05)	Centre, age, sex	This study partially overlaps with Tavani *et al*. (2001b)
De Stefani *et al*. (1998b), Uruguay, 1988–95	160 (85 men, 75 women) from a single oncology institution in Uruguay, aged 20–84 years; histological confirmation not given; response rate, 36.7%	163 hospital-based (86 men, 77 women); frequency-matched to cases on sex, age (±10 years), residence, urban/rural status	Interviewer-administered standardized questionnaire	NHL	*Men* Never drinker 1–60 mL alcohol/day ≥61 mL alcohol/day	30 20 35	1.0 1.4 (0.5–3.9) 1.1 (0.5–2.5)	Age, year of diagnosis, residence, urban/rural status, ‘mate’/ years, salted meat intake, type of tobacco	No significant association with wine or liquor intake, but a positive association with ≥61 mL/day beer intake (odds ratio, 5.5; 95% CI, 1.1–26.7)

Table 2.83 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD-9 code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounding factors	Comments
Matsuo *et al*. (2001), Nagoya, Japan, 1988–97	333 (202 men, 131 women) adults from a single cancer centre hospital; 100% histologically confirmed; response rate, 98.6%	55 904 non-cancer hospital outpatients (15 811 men, 40 093 women); response rate, 98.6%	Self-administered standardized questionnaire	Malignant lymphoma: HD + NHL + TCL (ICD-10, C81-85)	Never drinker Former drinker <1.5 drinks/day ≥1.5 drinks/day Current drinker <1.5 drinks/day ≥1.5 drinks/day	183 14 13 1 136 87 49	1.00 1.01 (0.85–1.77) 1.57 (0.87–2.82) 0.18 (0.02–1.28) 0.67 (0.52–0.85) 0.63 (0.48–0.83) 0.74 (0.52–1.04)	Age, sex	
Tavani *et al*. (2001b), Milan and Pordenone, Italy, 1981–94	446 cases (256 men, 190 women) from hospitals in Pordeno, aged 17–79 years; 100% histologically confirmed; response rate, 97%	1295 hospital-based (791 men, 504 women), aged 17–79 years; 97% response rate	Interviewer-administered standardized questionnaire	Incident NHL (200, 202)	*Total alcohol (drinks/day)* Non-drinker <3 3–6 ≥7	 68 155 135 86	 1.0 0.92 (0.65–1.30) 0.98 (0.66–1.45) 1.02 (0.64–1.63) *p* trend=0.84	Age, sex, centre, education, marital status, blood transfusions, diabetes, intake of milk, meat, green vegetables and fruit	Test for trend for spirit intake (p=0.08); no significant associations for total alcohol, wine, beer or spirit intake; beer and spirit intake were associated with a borderline significantly increased risk.
Briggs *et al.* (2002),USA, 1984–88	960 living men identified from eight US population-based cancer registries, aged 32–60 years; 100% histologically confirmed; response rate, 88%	1717 male population-based (living) selected by RDD; frequency-matched to cases on date of birth (± 5 years), geographical region; response rate, 83%	Interviewer-administered standardized questionnaire	NHL (ICD-O 9591, 9600, 9602, 9611–13, 9621, 9630, 9640, 9642, 9691, 9694, 9696, 9750)	Never drinkers All drinkers Current drinker Former drinker Wine drinker 1–6 drinks/week ≥1 drink/day	300 660 490 170 178 46	1.0 0.9 (0.8–1.1) 0.9 (0.8–1.1) 1.0 (0.8–1.3) 0.8 (0.5-1.3) 0.4 (0.2-0.9) *p*-trend = 0.02	Age, race/ ethni-city, cancer registry, smoking history, education	No associations with beer or spirit intake; an inverse dose–response association of wine intake with risk for NHL (p=0.02), particularly for those who started drinking wine at age ≤16 years (p-trend= 0.004)

Table 2.83 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD-9 code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounding factors	Comments
Chiu *et al.* (2002), pooled analysis USA, Kansas, 1979–81; Iowa, Minnesota, USA, 1980–83	170 white men (79 living, 91 deceased) from Kansas statewide tumour registry, aged ≥ 21 years; 100% histologically confirmed; 622 white men (429 living, 193 deceased) from Iowa Health Registry and Minnesota surveillance network; aged ≥30 years; 100% histologically confirmed; response rate, 89%–96%	2193 white population-based men (1278 living, 915 deceased) selected by RDD (<65 years), HCFA ≥65 years), or death certificate (deceased); frequency-matched to cases on age (±5 years), vital status at time of interview, state; response rate, 77–93%	Interviewer-administered standardized questionnaire	NHL	*Ethanol (g/week)* Non-drinker Tertile 1 Tertile 2 Tertile 3	 364 121 152 152	 1.0 0.8 (0.6–1.0) 0.9 (0.7–1.1) 0.8 (0.7–1.1) *p*-trend=0.25	Age, state, marital status, type of respondent, first degree relative with HLPC, use of herbicides, tobacco use	Significant interaction of alcohol intake with family history of HLPC: positive association of alcohol with risk for NHL in those with a family history; no association in those with no family history

Table 2.83 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD-9 code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounding factors	Comments
Morton *et al*. (2003), Connecticut, USA, 1995–2001	601 living women identified from the Connecticut Tumor Registry, aged 21–84 years; 100% histologically confirmed; 72% response rate	718 female population-based (living) selected by RDD (<65 years), HCFA (≥65 years); frequency-matched to cases on age (± 5 years); response rate, 69% (RDD), 47% (HCFA)	Interviewer-administered standardized questionnaire	NHL (ICD–O 9590–9642, 9690–9701, 9740–9750)	Never drinker Ever drinker *Ethanol (g/month)* <70 70–300 >300 *Duration (years)* 1–24 25–40 >40	230 371 124 126 121 138 122 111	1.0 0.82 (0.65-1.04) 0.82 (0.61–1.10) 0.83 (0.62–1.13) 0.82 (0.60–1.10) *p*-trend=0.79 1.05 (0.76–1.43) 0.89 (0.65–1.22) 0.62 (0.46–0.85) *p*-trend=0.01	Age, education	Race, family history of cancer, body mass index, smoking, menopausal status, daily fruit, fat, protein and animal protein intake did not confound results; no significant associations with beer or liquor consumption; significantly reduced risk for NHL associated with >40 years of wine drinking (*p*-trend=0.02) and ≥25 years at initiation of wine drinking.

Table 2.83 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD-9 code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounding factors	Comments
Chang *et al*. (2004), Sweden, 2000–02	613 living (364 men, 249 women) identified from a network of physicians and the regional cancer registries, aged 18–74 years; 99% histologically confirmed; response rate, 75.5%	480 living (279 men, 201 women) identified using population registries, aged 18–74 years; frequency-matched to cases on sex, age (±10 years); response rate, 66.8%	Self-administered standardized questionnaire	NHL (ICD-10 C82–85, 88.0, 91.3–5, 91.7), CLL (91.1)	**Men**			Age, smoking status	All subjects HIV-free; body mass index, height, education, history of rheumatoid arthritis, blood transfusion or skin cancer, occupational exposure to pesticides, dietary intake of dairy products, fried red meat and vegetables did not confound results; for all NHL, no associations for any specific type of alcohol; significant positive association of CLL (a subtype of NHL) with two highest categories of wine intake (p-trend=0.03)
					Never drinker	15	1.0		
					Current drinker	329	1.1 (0.5–2.4)		
					Total alcohol(g/day)				
					0–2.2	43	1.0		
					>2.2–8.4	61	1.5 (0.8–2.5)		
					>8.4–19.1	108	1.7 (1.0–2.9)		
					>19.1	147	1.8 (1.1–2.9)		
							p-trend=0.06		
					Women				
					Never drinker	26	1.0		
					Current drinker	213	1.0 (0.6–2.0)		
					Total alcohol(g/day)				
					0–2.2	103	1.0		
					>2.2–8.4	66	0.8 (0.5–1.3)		
					>8.4–19.1	57	0.8 (0.5–1.4)		
					>19.1	22	0.7 (0.3–1.4)		
							p-trend=0.33		
					Current versus never drinker			Sex, age, smoking status	
					Diffuse B-cell	NR	0.7 (0.3–1.4)		
					CLL	NR	2.4 (0.9–6.5)		
					Follicular	NR	1.0 (0.4–2.3)		
					T-cell	NR	0.3 (0.1–0.9)		

Table 2.83 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD-9 code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounding factors	Comments
Willett *et al*. (2004), United Kingdom, 1988–2001	700 Caucasians (362 men, 338 women) identified through the Leeds General Infirmary or haematological departments in other hospitals, aged 18–64 years; 100% histologically confirmed; response rate, 75%	915 living (495 men, 420 women) identified from the same general practice as the case, aged 18–64 years; individually matched on sex, date of birth, residence; response rate, 71%	Interviewer-administered standardized questionnaire	NHL (ICD03 9679–84, 9690–98, 9689, 9699, 9673, 9700–19, 9827, 9659)	*Drinks/day* Never >0–1 >1–2 >2–4 >4–6 >6	 34 315 198 85 33 35	 0.91 (0.57–1.47) 1.0 0.79 (0.62–1.02) 0.89 (0.64–1.25) 0.81 (0.50–1.31) 0.84 (0.52–1.35)	Sex, age, region	Alcohol consumption defined as ever drinking wine, spirits, beer or lager ≥once a year in the 20 years preceding diagnosis/ pseudo-diagnosis; no evidence of an interaction between smoking status and alcohol intake; no associations for any specific beverage type or NHL subtype.
Morton *et al*. (2005), pooled analysis of nine case–control studies, Italy, Sweden, United Kingdom, USA, 1988–2002	6492 completed a questionnaire between 1990 and 2004, with electronic data available, data for alcohol intake, age 17–84 years; 100% histologically confirmed; participation rates, 68%–>97%	8683 RDD-, hospital-, population-based; participation rates, 47%–>97%	Standardized questionnaires	NHL	Non-drinker Ever drinker 1–6 drinks/week 7–13 drinks/ week 14–27 drinks/ week ≥28 drinks/week	1804 4688 2027 958 951 745	1.0 0.83 (0.76–0.89) 0.81 (0.74–0.88) 0.83 (0.74–0.92) 0.85 (0.76–0.95) 0.87 (0.76–0.99) *p*-trend=0.97	Sex, age, ethnic origin, socioeco-nomic status	Associations did not differ by beverage type: significant or borderline significantly decreased risks; lowest risk observed for Burkitt lymphoma

Table 2.83 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD-9 code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounding factors	Comments
Besson *et al.* (2006a), Czech Republic, France, Germany, Ireland, Italy, Spain, 1998–2004	1742; 100% histologically confirmed; response rate, 82.1–91%	2465 hospital-based and population-based; matched by sex, age, residence/ region; response rate, 44.4%–96.4%	In-person interview using standardized questionnaires	NHL (NR)	Regular drinking Never Ever *Ethanol (g/week)* ≤194 >194–≤730 >730	 584 627 79 225 219	 1.0 0.99 (0.84–1.18) 0.84 (0.62–1.15) 1.19 (0.94–1.49) 0.90 (0.71–1.15) *p*-trend=0.90	Sex, age, educational level, smoking status, centre	No association with any specific alcoholic beverage type; no significant differences in associations by histological subtype; generally lower risk of NHL for men but not for women; no interaction between alcohol drinking status and smoking status
Besson *et al*. (2006b), Czech Republic, France, Germany, Ireland, Italy, Spain, 1998–2004	340 (185 men, 155 women); aged ≥17 years, 100% histologically confirmed; response rate, 87.7%	2465 population- or hospital-based (1322 men, 1143 women); matched on sex, age (±5 years of birth), study region; response rates, 81.2% for hospital controls, 51.5% for population controls	Interviewer-administered standardized questionnaire	Hodgkin lymphoma	Regular drinking Never Ever	 876 866	 1.0 0.61 (0.43–0.87)	Sex, age, education, smoking status, centre	Stronger inverse association in older (≥35 years) versus younger (<35 years) individuals; inverse asssociation strongest for wine for subjects <35 years; no interaction between alcohol and smoking for younger or older groups

Table 2.83 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD-9 code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounding factors	Comments
Nieters *et al*. (2006), Germany, 1999–2002	710 (390 men, 320 women) recruited from physician offices and hospitals in six regions of Germany; aged 18–80 years; 46% histologically confirmed; response rate, 87.4%	710 population-based (390 men, 320 women); matched 1:1 on sex, age (±1 years of birth), study region; response rate, 44.3%	Interviewer-administered standardized questionnaire	Lymphoma	**Men** Non-drinker Drinker *Ethanol (g/day)* 2–<10 10–<40 ≥40 **Women** Non-drinker Drinker *Ethanol (g/day)* 0.5–<2 2–<10 ≥10	 101 287 117 129 41 85 233 87 93 53	 1.0 0.47 (0.31–0.71) 0.52 (0.33–0.81) 0.41 (0.26–0.65) 0.50 (0.28–0.91) 1.0 0.68 (0.45–1.03) 0.67 (0.42–1.07) 0.66 (0.41–1.08) 0.73 (0.42–1.27)	Education, pack–years of smoking	Non-drinker defined as <2 g ethanol/day for men and <0.5 g ethanol/day for women; alcohol intake assessed for 5–10 years prior to diagnosis; among men, significant inverse associations observed for all beverage types and for follicular, B-cell and Hodgkin lymphoma; among women, significant inverse associations observed for Hodgkin lymphoma.

CI, confidence interval; CLL, chronic lymphocytic leukaemia; HCFA, Health Care Financing Administration; HD, Hodgkin disease; HIV, human immunodeficiency virus; HLPC, haematolymphoproliferative cancer; ICD, International Classification of Diseases; MM, multiple myeloma; NR, not reported; RDD, random-digit dialling; NHL, non-Hodgkin lymphoma; STS, soft tissue sarcoma; TCL, T-cell lymphoma

1998b; Matsuo *et al.,* 2001; Tavani *et al.,* 2001b; Briggs *et al*., 2002; Chiu *et al*., 2002; Morton *et al*., 2003; Chang *et al*., 2004; Willett *et al*., 2004; Besson *et al*., 2006a,b; Nieters *et al*., 2006).

Most case–control studies of alcoholic beverage consumption and lymphoma focused specifically on non-Hodgkin lymphoma and/or its histological subtypes. In the study of Chang *et al*. (2004), a positive association was observed only for men and only for the histological subtype chronic lymphocytic leukaemia. In that study, all cases and controls were free of human immunodeficiency viral infection and careful consideration was given to several potential confounding factors including age, tobacco smoking and occupational exposure to pesticides. Most other studies of non-Hodgkin lymphoma observed an inverse association with alcoholic beverage intake. The largest of these studies (Briggs *et al*., 2002) included 960 male (living only) cases and more than 1700 population-based controls and found no difference in the risk for non-Hodgkin lymphoma between drinkers and non-drinkers after adjustment of age, ethnicity and smoking status.

Most individual studies of non-Hodgkin lymphoma had limited power to conduct detailed analyses of alcoholic beverages and risk for this disease, particularly for specific beverage types and histological subtypes. Therefore, data from nine case–control studies conducted in Italy, Sweden, the United Kingdom and the USA were pooled to include 6492 cases of non-Hodgkin lymphoma and 8683 controls (Morton *et al*., 2005). Results of that analysis showed a significantly lower risk for non-Hodgkin lymphoma for ever drinkers compared with non-drinkers; however, there was no consistent dose–response relationship between frequency of alcoholic beverage intake and risk for the disease. There was also no consistent evidence of an association with duration of alcoholic beverage drinking or with the age at starting drinking; moreover, the risk for non-Hodgkin lymphoma for current drinkers was lower than that for former drinkers in a subset of the pooled data. No difference in the association by alcoholic beverage type or a combination of beverage types consumed was observed. For specific subtypes of non-Hodgkin lymphoma, no significantly elevated risks were found. The lowest risk associated with ever drinking was that for Burkitt lymphoma (odds ratio, 0.51; 95% CI, 0.33–0.77 for ever versus non-drinker). Lower risks for diffuse B-cell, follicular and T-cell lymphomas were also associated with ever drinking. The authors noted that all disease misclassification was probably non-differential and therefore unlikely to explain a significant inverse association; findings were similar when analyses were restricted to studies that had a high response rate.

A multicentre case–control study of non-Hodgkin lymphoma and alcoholic beverage intake included data from five European countries and comprised 1742 cases and 2465 controls (Besson *et al.,* 2006a). Overall, there were no associations observed for ever drinking, age at starting drinking, duration of drinking or monthly consumption with risk for all non-Hodgkin lymphomas or with any histological subtype; similarly, no associations with risk for non-Hodgkin lymphoma were found for any specific type of alcoholic beverage. However, a lower risk associated with regular alcoholic beverage

intake was observed for men (odds ratio, 0.76; 95% CI, 0.62–0.93; 691 exposed cases) and for non-Mediterranean countries (odds ratio, 0.7; 95% CI, 0.6–0.9).

Among the four studies that examined Hodgkin lymphoma specifically (Williams & Horm, 1977; Tavani *et al*., 1997; Besson *et al*., 2006b; Nieters *et al*., 2006), there was a consistent inverse association. For example, in the large multicentre European study, the odds ratio for Hodgkin lymphoma associated with ever regular drinking compared with never regular drinking was 0.61 (95% CI, 0.43–0.87; 81 exposed cases); this association was consistent for younger and older adults (Besson *et al*., 2006b).

(b) Leukaemia (Table 2.84)

The association of alcoholic beverage intake with risk for adult leukaemia was examined in six epidemiological case–control studies (Williams & Horm, 1977; Brown *et al*., 1992; Wakabayashi *et al*., 1994; Pogoda *et al*., 2004; Rauscher *et al*., 2004; Gorini *et al*., 2007). No consistent patterns of association between total alcoholic beverage intake and risk for all leukaemias combined were observed. Two studies showed a non-significant two- to threefold higher risk for acute lymphocytic leukaemia associated with heavy drinking (Wakabayashi *et al*., 1994) or with any drinking (Brown *et al*., 1992), a third found no association of drinking with risk for this type of leukaemia (Gorini *et al*., 2007). Similarly, there was no consistent evidence of associations with acute non-lymphocytic, chronic lymphocytic or chronic myeloid leukaemias among studies. The available evidence also did not support an association for any specific alcoholic beverage type.

(c) Multiple myeloma (Table 2.85)

Five case–control studies (four in the USA and one in Canada) examined associations between alcoholic beverage intake and the risk for multiple myeloma (Williams & Horm, 1977; Gallagher *et al*., 1983; Linet *et al*., 1987; Brown *et al*., 1992, 1997). In the largest study, there was a lower risk for multiple myeloma among drinkers compared with non-drinkers in white men and to a lesser extent in black men and white women (Brown *et al*., 1997). There was a non-significant 2.8-fold higher risk for multiple myeloma for white women who consumed ≥22 drinks per week (Brown *et al*., 1997). Among the other case–control studies, no consistent patterns of association were observed. It should be noted that most studies collected data on alcoholic beverage consumption from proxy respondents, and that some included prevalent cases. In addition, not all studies controlled for the potential confounding effects of tobacco smoking, and only one controlled for other factors such as farming, family history of cancer and occupational exposure to high-risk chemicals (Brown *et al*., 1992).

2.17.3 *Parental exposure and childhood cancers (Table 2.86)*

Six case–control studies in Australia, Canada, Europe and the USA examined associations of paternal alcoholic beverage intake before pregnancy and/or maternal

Table 2.84 Case–control studies of alcoholic beverage consumption and leukaemia

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Williams & Horm (1977), Multicentre, USA	33 exposed men, 29 exposed women with incident, invasive cancer from the Third National Cancer Survey	1755 men, 3159 women with other cancers (excluding lung, larynx, mouth, oesophagus, urinary bladder) from the Third National Cancer Survey	Interviewer-administered standardized questionnaire	CLL	*Men* None <51 oz/year ≥51 oz/year *Women* None <51 oz/year ≥51 oz/year	 9 8 3 2	 1.0 2.0 (NR) 1.10 (NR) 1.0 0.71 (NR) 1.20 (NR)	Age, race, smoking	For other histological subtypes, fewer than 16 cases for women, and less than 17 cases for men; results are presented only for CLL.

Table 2.84 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Brown *et al.* (1992), Iowa, Minnesota, USA, 1981–84	578 white men (340 living, 238 deceased) from Iowa Health Registry and Minnesota surveillance network, aged ≥30 years; 100% histologically confirmed; response rate, 86%	820 white population-based men selected by RDD (alive and <65 years), HCFA (≥65 years) or death certificate (deceased); frequency-matched to cases on age (± 5 years), vital status at time of interview, state; response rate, 78%	Interviewer-administered standardized questionnaire	Leukaemia	*Drinker versus non-drinker* All leukaemia ANLL CML CLL ALL Myelodysplasia Other	 333 72 31 138 12 41 39	 1.3 (0.8–1.3) 0.8 (0.5–1.1) 1.0 (0.6–1.9) 1.0 (0.7–1.3) 3.0 (0.9–9.9) 1.6 (0.9–2.7) 1.5 (0.8–2.6)	Age, state, tobacco use	Drinkers were subjects who had ever consumed any alcoholic beverage at least weekly; farming, education, family history of cancer and exposure to high-risk jobs or chemicals did not confound results; no meaningful associations with any specific beverage type.

Table 2.84 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Wakabayashi *et al.* (1994), Hyogo, Japan, 1981–90	142 (87 men, 55 women) ALL, ANL or CLL treated at a single institution in Hyogo, Japan, aged ≥18 years; histological confirmation not given; response rate not given	284 hospital-based (174 men, 110 women) from the Department of Ophthalmo–logy; matched 2:1 on sex, age; response rate not given	Clinical chart abstraction	Leukaemia	**Ethanol (g/day)**			None	
					ANLL				
					0	48	1.0		
					1–21	18	2.52 (1.08–5.89)		
					22–43	3	2.52 (0.35–18.36)		
					≥44	6	1.89 (0.52–6.91)		
					ALL				
					0	65	1.0		
					1–21	22	2.44 (1.14–5.25)		
					22–43	4	1.09 (0.28–4.27)		
					≥44	8	2.44 (0.72–8.32)		
					CLL				
					0	35	1.0		
					1–21	6	2.87 (0.56–14.7)		
					22–43	2	0.38 (0.07–2.04)		
					≥44	–	–		
Pogoda *et al.* (2004), Los Angeles County, CA, USA, 1992–94	164 (88 men, 76 women) from a population-based cancer registry in Los Angeles, CA, aged 25–75 years; histological confirmation not given; response rate, 57%	164 population-based (88 men, 76 women); matched 1:1 on sex, birth (± 5 years), race/ethnicity, neighbourhood; response rate not given	Interviewer-administered standardized questionnaire	AML (ICD-O 9861, 9864, 9866, 9867, 9891)	*Ethanol (g/day)*			Education, pack–years of smoking	
					0	24	1.0		
					1–3	9	0.7 (0.3–1.5)		
					4–10	10	0.7 (0.3–1.4)		
					>10	6	0.8 (0.4–1.6)		
							p-trend=0.2		

Table 2.84 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Rauscher *et al.* (2004), Multicentre, USA, 1986–89	765 incident from clinical sites throughout the USA; median age, 48 years; histological confirmation not given; response rate, 84%	618 population-based identified by RDD; frequency-matched by sex, age (± 10 years), race, region of residence; response rate, 66%	Interviewer-administered questionnaire	Acute leukaemia	Regular versus non-regular drinker *Drinks/week* <1 1–5 6–8 >8	NR 383 148 62 172	0.75 (0.60–93) 1.0 0.69 (0.52–0.92) 0.59 (0.40–0.87) 0.88 (0.66–1.2)	Age, race, sex, region, education	524 cases and 540 controls were self-respondents; smoking, solvent and exposure to ionizing radiation exposure did not confound results; significant inverse associations for light and moderate beer intake.

Table 2.84 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Gorini *et al.* (2007), Italy, 1990–93	649 (381 men, 268 women) from population-based cancer registries and clinical, pathology records in 11 areas; aged 20–74 years; 100% histologically confirmed; response rate, 88%	1771 population-based (913 men, 858 women) randomly selected through computerized demographic files or from National Health Service files, aged 20–74 years; frequency-matched to cases on sex, age, area of residence; response rate, 81%	Interviewer-administered standardized questionnaire	Leukaemia (ICD-O 204–208)	**Ethanol (g/day)** *All leukaemias* Ever versus never Non-drinker <9.0 9.1–7.9 18.0–1.7 >1.7 *ALL* Ever versus never *CLL* Ever versus never	 519 119 83 152 126 158 37 168	 0.97 (0.74–1.26) 1.0 0.73 (0.51–1.03) 1.05 (0.77–1.43) 1.03 (0.74–1.45) 1.15 (0.82–1.63) *p*-trend=0.007 0.88 (0.40–1.93) 0.86 (0.58–1.28)	Age, gender, smoking status, area of residence, educational level, type of interview	No associations between total alcohol intake and risk for ALL or CLL; no significant associations with beer or liquor consumption; wine consumption associated with a borderline significantly increased risk for all leukaemias, ALL and CLL (tests for trend, *p*=0.001, *p* = 0.004, *p*=0.01, respectively).

ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; ANLL, acute non-lymphocytic leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; HCFA, Health Care Financial Administration; ICD, International Classification of Diseases; NR, not reported; RDD, random-digit dialling

Table 2.85 Case–control studies of alcoholic beverage consumption and multiple myeloma

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Williams & Horm (1977), Multicentre, USA	37 exposed men, 34 exposed women with incident invasive cancer from the Third National Cancer Survey	1751 men, 3154 women with other cancers (excluding lung, larynx, mouth, oesophagus, bladder) from the Third National Cancer Survey	Interviewer-administered standardized questionnaire	Multiple myeloma	*Men* None <51 oz/years ≥51 oz/years *Women* None <51 oz/years ≥51 oz/years	 1 10 2 3	 1.0 0.19 (NR) 0.74 (NR) 1.0 0.42 (NR) 0.93 (NR)	Age, race, smoking	
Gallagher *et al*. (1983). Vancouver, Canada, 1972–81	84 living (49 men, 35 women) incident and prevalent from a single clinic, aged 34–83 years; histological confirmation not given; response rate, 100%	84 patients with non-head and neck cancers (26 gastrointestinal, 10 basal-cell carcinoma, 27 breast/female genital, 7 male genital, 1 brain, 12 haematopoietic); diagnosed in 1977–80; matched 1:1 on sex, age (±5 years), year of diagnosis (±5 years); response rate, 100%	Interviewer-administered standardized questionnaire	Multiple myeloma	NR	NR	No association (data not shown)	Matching factors adjusted for using conditional logistic regression	

Table 2.85 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Linet *et al*. (1987), Baltimore, MD, USA, 1975–82	100 (19 direct, 81 proxy) ascertained from seven Baltimore area hospitals; whites who were residents of the area; 100% histologically confirmed; response rate, 83%	100 hospital-based randomly selected from non-cancer patients (53 direct, 47 proxy); matched (1:1) on sex, age (±5 years), year of diagnosis; response rate, 68%	Interviewer-administered standardized questionnaires by telephone	Multiple myeloma (ICD-8/9 203)	Ever beer drinker versus non-drinker	NR	0.8 (0.4–1.6)	Matched pair analysis used with no adjustment for other covariates	
					Ever hard liquor drinker versus non-drinker	NR	1.7 (0.9–3.3)		

Table 2.85 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Brown *et al.* (1992), Iowa, USA, 1980–83	173 white men (101 living, 72 deceased) from Iowa Health Registry, aged ≥30 years; 100% histologically confirmed; response rate, 84%	452 living white population-based men selected by RDD (alive and <65 years) or HCFA (≥65 years); frequency-matched to cases on age (± 5 years), vital status at time of interview; response rate, 78%	Interviewer-administered standardized questionnaire	Multiple myeloma	Non-drinker Drinker *Drinks/week* <5 5–11 12–23 >23 *Beverage type* Beer or wine only Hard liquor Other combinations	76 97 23 36 20 17 38 17 42	1.0 1.3 (0.9–1.9) 1.0 (0.6–1.8) 1.8 (1.1–3.1) 1.0 (0.6–1.8) 1.4 (0.7–2.6) 1.1 (0.7–1.7) 1.2 (0.6–2.3) 1.7 (1.0–2.7)	Age	Drinkers were subjects who had ever consumed any alcoholic beverage at least weekly; farming, education, family history of cancer and exposure to high-risk jobs or chemicals did not confound results.

Table 2.85 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Brown *et al*. (1997), Georgia, Michigan, New Jersey, USA, 1986–89	365 white (192 men, 173 women) and 206 black (91 men, 115 women) (101 living, 72 deceased) from the regional tumour registry rapid case-ascertainment system, aged 30–79 years; histological confirmation not given; response rate, 63% for whites and 67% for blacks	1155 white (736 men, 419 women), 967 black (614 men, 353 women) selected by RDD (<65 years), HCFA (≥65 years); frequency matched to cases on sex, race, age, area; response rate, 75% for HCFA and 78% for RDD	Interviewer-administered standardized questionnaire	Multiple myeloma	*White men* Never drinker Ever drinker *Drinks/week* <8 8–21 22–56 ≥57 *Years drinking* <30 30–39 ≥40 *Beverage type* Liquor Beer Wine *Black men* Never drinker Ever drinker *Drinks/week* <8 8–21 22–56 ≥57	 55 137 55 42 31 9 26 43 65 96 110 58 24 67 18 22 21 6	 1.0 0.6 (0.4–0.9) 0.7 (0.5–1.1) 0.6 (0.3–0.9) 0.6 (0.4–1.1) 0.6 (0.3–1.3) 0.6 (0.4–1.1) 0.9 (0.5–1.4) 0.5 (0.3–0.8) 0.7 (0.4–1.0) 0.6 (0.4–0.9) 0.6 (0.4–1.0) 1.0 0.8 (0.5–1.3) 0.8 (0.4–1.5) 0.7 (0.4–1.3) 0.9 (0.5–1.8) 0.7 (0.3–1.8)	Age, education, study area	Duration (years) of alcohol drinking was associated with a non-significant decreased risk in black men and white women and had no association in black women; beverage type was not associated with risk.

Table 2.85 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Brown *et al.* (1997) (contd)					*White women*				
					Never drinker	112	1.0		
					Ever drinker	61	0.7 (0.5–1.0)		
					Drinks/week				
					<8	38	0.6 (0.4–1.0)		
					8–21	14	0.6 (0.3–1.2)		
					≥22	8	2.8 (0.9–8.2)		
					Black women				
					Never drinker	75	1.0		
					Ever drinker	40	1.0 (0.6–1.6)		
					Drinks/week				
					<8	23	1.0 (0.6–1.8)		
					8–21	12	1.1 (0.5–2.2)		
					≥2	4	0.6 (0.2–2.0)		

CI, confidence interval; HCFA, Health Care Financial Administration; ICD, International Classification of Diseases; RDD, random-digit dialling

Table 2.86 Case–control studies of parental alcoholic beverage consumption and childhood haematopoietic cancer

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
McKinney *et al.* (1987), United Kingdom, 1980–83	234 (139 boys, 95 girls; 171 leukaemia, 63 lymphoma) in three regions from a single clinic, aged <15 years; 100% histologically confirmed; response rate not given	468 hospital-based; matched (2:1) on age, sex, hospital; response rate not given	Interviewer-administered standardized questionnaire for alcohol intake during pregnancy	Leukaemia or lymphoma	NR	NR	No association (data not shown)	None	
van Duijn *et al*., (1994), Netherlands, 1981–82	80 ANLL (47 boys, 33 girls) and 517 ALL cases (288 boys, 229 girls), ascertained from Dutch Childhood Leukaemia Group, aged <15 years, 100% histologically confirmed; response rate for ALL and ANLL, 86%	240 population-based (141 boys, 99 girls) randomly selected from census lists; matched (3:1) on sex, age (±3 months), residence; response rate, 67%	Mailed standardized questionnaires for frequency of parental alcohol intake before or during pregnancy	ANLL, ALL	**Maternal alcohol intake during pregnancy (yes versus no)** *ANLL* Age at diagnosis 0–4 years 5–9 years 10–14 years *ALL* Age at diagnosis 0–4 years 5–9 years 10–14 years	 42 21 15 6 115 51 22	 2.6 (1.4–4.6) 2.8 (1.2–6.5) 3.0 (1.1–8.4) 0.8 (0.3–2.3) 1.1 (0.8–1.9) 0.8 (0.5–1.5) 1.0 (0.4–2.1)	Age, gender, social class, maternal smoking, prescription drug use, ultrasound, exposure to radiation or viral infection during pregnancy, occupational exposure to hydrocarbons	No associations for parental alcohol intake 1 year before pregnancy

Table 2.86 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Severson *et al.* (1993), Canada, USA, 1980–84	187 (94 boys, 93 girls) identified through the Children's Cancer Group, aged ≤17 years; 100% histologically confirmed; response rate, 78%	187 (97 boys, 90 girls) population-based selected by RDD; matched (2:1) to cases on date of birth (±6 months–2 years), race, telephone area code, exchange; response rate, 78.5%	Interviewer-administered standardized questionnaire to assess parental intake before or during pregnancy	AML	**Maternal alcohol intake**			Unclear	Maternal age at birth of child, education, use of mind altering drugs, sex of child and race of the child did not confound the results; paternal alcohol intake 1 month before conception was not associated with risk for AML.
					Current drinker	41	1.02 (0.65–1.63)		
					Ever drank	32	1.07 (0.63–1.82)		
					Drank during pregnancy	51	1.42 (0.91–2.23)		
					Age at diagnosis				
					0–2 years	21	3.00 (1.23–8.35)		
					3–10 years	13	0.81 (0.36–1.80)		
					11–17 years	17	1.13 (0.53–2.44)		

Table 2.86 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Shu *et al.* (1996), Australia, Canada, USA, 1983–88	302 infant leukaemia (203 ALL, 88 AML, 11 other) identified through the Children's Cancer Group, aged ≤18 months; 100% histologically confirmed; response rate, 79%	558 population-based selected by RDD; matched 1–4:1 on year of birth, telephone area code, exchange; response rate, 75%	Interviewer-administered (by telephone) standardized questionnaire to assess parental alcohol intake before, during or after pregnancy	AML, ALL	**Maternal intake during pregnancy** *ALL* Ever versus never 2nd and/or 3rd trimester None 1–20 drinks >20 drinks *AML* Ever versus never 2nd and/or 3rd trimester None 1–20 drinks >20	 NR NR NR NR NR NR NR NR	 1.43 (1.00–2.04) 2.28 (1.26–4.13) 1.0 1.76 (1.14–2.72) 0.93 (0.53–1.62) *p*-trend=0.40 2.64 (1.36–5.06) 10.48 (2.79–39.33) 1.0 2.36 (1.11–5.03) 3.13 (1.20–8.06) *p*-trend<0.01	Sex, maternal age, education, maternal smoking during pregnancy	Maternal alcohol intake during pregnancy: no specific associations for drinking during nursing period or by beverage type except for AML associated with 1-4 drinks/month of liquor (odds ratio, 6.37; 95% CI, 1.95–20.80; *p*<0.01); paternal alcohol intake 1 month before pregnancy: no associations with total alcohol or with specific beverage types for ALL or AML

Table 2.86 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Infante-Rivard *et al.*, (2002) Québec, Canada, 1980–93	491 incident (275 boys, 216 girls) identified from tertiary care centres; aged 0–9 years; histological confirmation not given; response rate, 96%	491 (275 boys, 216 girls) selected from family allowance files (government files); matched to cases (1:1) on age, sex, region of residence at the time of diagnosis; response rate, 84%	Interviewer-administered (by telephone) standardized questionnaire that referred to maternal alcohol intake 1 month prior to pregnancy through to the nursing period and paternal intake 1 month prior to pregnancy	ALL	*Maternal intake* None 1 month before pregnancy During pregnancy <1.0 drink/day ≥1 drink/day Nursing period *Paternal intake 1 month before pregnancy* None Any <1.0 drink/day 1–2 drinks/day ≥3 drink/day	 NR 254 180 151 20 46 NR 420 189 143 79	 1.0 0.8 (0.6–1.1) 0.7 (0.5–0.9) 0.7 (0.5–1.0) 0.8 (0.5–1.6) 0.5 (0.3–0.8) 1.0 1.4 (1.0–2.0) 1.4 (1.0–2.0) 1.6 (1.1–2.5) 1.7 (1.1–2.7) *p*-trend=0.01	Mother's age, education	For maternal alcohol intake, patterns of association similar across alcohol type; appeared to be potential interactions of maternal alcohol intake with the *GSTM1* null genotype and with *CYP2E1*5* allele

Table 2.86 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Menegaux *et al.* (2005), France, 1995–99	280 (166 boys, 114 girls) newly diagnosed with acute leukaemia, aged <15 years; response rate, 95%	288 (168 men, 120 women) hospitalized for conditions other than cancer or birth defects; frequency-matched on age, gender, hospital, ethnic origin; response rate, 99%	Interviewer-administered standardized questionnaire assessed maternal alcohol intake during pregnancy and breastfeeding	ANLL, ALL	**Maternal intake during pregnancy** *ALL* Never Ever 1 glass/week 2 glasses/week ≥3 glasses/week *ANLL* Never Ever 1 glass/week 2 glasses/week ≥3 glasses/week	 87 153 103 25 25 12 28 21 – 7	 1.0 2.0 (1.4–3.0) 2.0 (1.3–3.0) 2.8 (1.3–6.0) 1.9 (0.9–3.5) 1.0 2.6 (1.2–5.8) 2.8 (1.2–6.6) – 2.4 (0.8–7.1)	Age, gender, hospital, ethnic origin	No differences in associations according to beverage type; wine and spirits significantly increased the risk of ALL but was not significantly associated with ANLL.

ALL, acute lumphocytic leukaemia; AML, acute myeloid leukaemia; ANLL, acute non-lymphocytic leukaemia; CI, confidence interval; CYP, cytochrome P-450; GST, glutathione *S*-transferase; ICD, International Classification of Diseases; NR, not reported; RDD, random-digit dialling

alcoholic beverage intake during pregnancy with risk for haematopoietic cancers in children (McKinney *et al*., 1987; van Duijn *et al*., 1994; Severson *et al*., 1993; Shu *et al*., 1996; Infante-Rivard *et al*., 2002; Menegaux *et al*., 2005). Three of four studies reported no association between paternal alcoholic beverage intake 1 month or 1 year before pregnancy and risk of any childhood leukaemia or lymphoma (van Duijn *et al*., 1994; Severson *et al*., 1993; Shu *et al*., 1996), whereas a positive association between a higher number of drinks per day and the risk for acute lymphocytic leukaemia was observed in the fourth study (Infante-Rivard *et al*., 2002). For maternal alcoholic beverage intake during pregnancy, one study showed no association with leukaemia or lymphoma (McKinney *et al*.,1987), while another showed a reduced risk for acute lymphocytic leukaemia when comparing any intake with no intake (Infante-Rivard *et al*., 2002). Statistically significant two- to 2.4-fold higher risks for acute non-lymphocytic leukaemia were associated with any maternal alcoholic beverage intake during pregnancy in two studies (van Duijn *et al*., 1994; Menegaux *et al*., 2005). Similarly, statistically significant positive associations between maternal alcoholic beverage intake and risk for acute lymphocytic (Shu *et al*., 1996; Menegaux *et al*., 2005) and acute myeloid (Severson *et al*., 1993; Shu *et al*., 1996) leukaemias were observed. The strongest associations observed in the studies of alcoholic beverages and acute myeloid leukaemia were for children diagnosed at 10 years of age or younger (Severson *et al*., 1993; Shu *et al*., 1996). Overall, there was no consistent evidence of dose–response relationships for maternal or paternal alcoholic beverage intake or for intake of any specific type of alcohol beverage and risk for any childhood haematopoietic cancer. Most studies adjusted for potential confounding factors including maternal age, maternal smoking and child's gender. Importantly, it is unclear whether any of the observed associations between maternal or paternal alcoholic beverage intake and risk for childhood haematopoietic cancers are attributed to recall bias.

2.18 *Cancer at other sites*

2.18.1 *Testis (Table 2.87)*

(a) Parental exposure

Among two cohort (Robinette *et al.,* 1979; Jensen, 1980) and three case–control studies (Schwartz *et al.,* 1962; Brown *et al.,* 1986; Weir *et al*., 2000) conducted in the general population, only one case–control study suggested a possible association between testicular cancer in adults and maternal drinking during pregnancy (Brown *et al*., 1986). The association was of borderline significance for the consumption of more than one drink per week relative to no drinking (odds ratio, 2.3; 95% CI, 1.0–5.2), but no association was observed for one drink (odds ratio, 1.1; 95% CI, 0.6–2.2), and no clear trend was apparent with the amount of alcohol consumed.

Table 2.87 Case–control studies of alcoholic beverage consumption and testicular cancer

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Parental exposure								
Brown *et al.* (1986), USA, 1979–81	225 mothers (pre- and perinatal cancer); response rate, 88%	213 mothers; response rate, 90%	Standardized telephone questionnaire	Never drinker		1.0	Tobacco smoking	
				1 drink/ week		1.1 (0.6–2.2)		
				>1 drink/ week		2.3 (1.0–5.2)		
						p-trend=0.14		
Weir *et al.* (2000), Ontario, Canada, 1987–89	346 case mothers/502 cases, aged 16–59 years; response rate, 80.8%	522 control mothers/ 975 controls; aged 16–59 years; response rate, 67.8%	Self-administered questionnaire	*Drinks/ week during pregnancy*			Age (5-year age group)	
				0	232	1.0		
				<2	83	1.2 (0.9–1.7)		
				≥2	24	0.8 (0.5–1.3)		
Chen *et al.* (2005b), USA, 1993–2001	278 incident childhood germ-cell; response rate, 80.8%	422; response rate, 66.6%; 1:2 match	Telephone interview; self-administered questionnaire	*Ever drank ≥6 months*			Gender of children, age, maternal education, race, family income	
				Never	182	1.0		
				Yes	92	0.9 (0.7–1.2)		
				Ever drank during 1 month before pregnancy to nursing				
				Never	126	1.0		
				Yes	148	0.9 (0.7–1.2)		

Table 2.87 (continued)

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Adult exposure								
Swerdlow *et al.* (1989), Oxford and West Midlands, United Kingdom 1977–81	259 cases of histologically confirmed testis cancer, aged ≥10 years	2 sets of controls: 238 radiotherapy controls treated in the same centres as cases; 251 non-radiotherapy controls who were general surgical, orthopaedic ENT and dental in-patients	Interview	Ever drank *Alcohol regularly?* Wine No Yes	NR	 1.0 1.7 (1.21–2.43)	Social class	There was no dose–response relationship between risk for the tumour in relation to mean or to maximal wine consumption
UK Testicular Cancer Study Group (1994), United Kingdom, 1984–86	794, aged 15–49 years; response rate, 92%	609; 1:2 match (case/controls); response rate, 83.1%	Face-to-face interview	*Alcohol (g/week)* None <68.8 68.8–124.6 124.6–<211.2 211.2–<364.7 ≥364.7	 92 150 147 130 135 140	 1.0 1.26 (0.86–1.83) 1.23 (0.85–1.79) 0.87 (0.60–1.28) 1.06 (0.72–1.56) 1.13 (0.97–1.66) *p*-trend=0.41	Cryptorchidism, inguinal hernia at age <15 years	No evidence of an effect of testicular temperature on cancer risk

CI, confidence interval

One additional cohort study conducted among male and female cirrhotics in Denmark found a slightly increased risk for testicular cancer of all histological types (SIR, 2.3; 95% CI, 1.0–4.5) that varied little with type of cirrhosis and disappeared after 10 years of follow-up (Sørensen *et al.*, 1998).

One case–control study investigated the association of childhood germ-cell tumours (seminoma, embryonal carcinoma, yolk-sac tumour, choriocarcinoma, immature teratoma and mixed germ-cell tumours) and parental alcohol drinking (Chen *et al.*, 2005b). Results showed no association between germ-cell cancer overall and alcoholic beverage drinking by either parent before pregnancy, or during pregnancy or nursing; odds ratios were 0.9 (95% CI, 0.7–1.2) and 1.0 (95% CI, 0.8–1.3) for ever drinking, for mothers and fathers, respectively. Additional stratified analyses by sex, histological type and anatomical site did not show any association.

(b) Adult exposure

Two case–control studies in the United Kingdom investigated the association between alcoholic beverage drinking and testicular cancer. Swerdlow *et al.* (1989) found no association for regular alcoholic beverage drinking, duration of drinking or consumption of beer, cider or spirits; however, a significant association was found with regular consumption of wine, with an odds ratio of 1.71 (95% CI, 1.21–2.43), but no dose–response relation. The other case–control study found no association with alcohol intake at the time of diagnosis or at age 20 years (UK Testicular Cancer Study Group, 1994).

2.18.2 *Cancer of the brain*

(a) Parental exposure and childhood brain cancer (Table 2.88)

Only one cohort study found an association between alcoholic beverage consumption and brain cancer (Robinette *et al.*, 1979). Three additional studies with suboptimal methodology did not provide evidence of an association between increased alcoholic beverage consumption and brain cancer (IARC, 1988). However, a descriptive study based on cancer registries and national mortality data in France (Remontet *et al.*, 2003) showed a large increase in the incidence of and mortality from brain cancer between 1980 and 2000, during which time alcohol consumption decreased markedly.

Five case–control studies have assessed the association between alcoholic beverage consumption of parents and childhood brain cancer. Two of the studies were conducted in the USA and Canada (Bunin *et al.*, 1994; Yang *et al.*, 2000), one in China (Hu *et al.*, 2000), one in Germany (Schüz *et al.*, 2001) and one in the USA (Kramer *et al.*, 1987). Three of the studies examined the association between neuroblastoma and parental alcoholic beverage consumption (Kramer *et al.*, 1987; Yang *et al.*, 2000; Schüz *et al.*, 2001). Kramer *et al.* (1987) found a weak, non-significant association for any maternal alcoholic beverage drinking during pregnancy, with a suggestive increase

Table 2.88 Case–control studies of parental alcoholic beverage consumption and childhood brain tumours

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Kramer *et al.* (1987), Great Delaware Valley, USA, 1970–79	104 incident from the Great Delaware Valley Pediatric Tumor registry and the Cancer Research Center between 1970 and 1979; response rate, 74.8%	101; selection through RDD; response rate, 57.1%	Telephone interview	*Maternal drinking during pregnancy*			Not specified	90% CI reported; 1 drink=1 serving of beer, wine or liquor
				Any drinking	36	1.44 (0.94–2.21)		
				≥1 drink/day (frequent)	9	9.0 (2.16–37.56)		
				≥3 drinks/day (binge)	6	6.0 (1.26–28.54)		
				≥1 drink/day or ≥3 drinks occasionally	12	12.0 (3.14–45.82)		
Bunin *et al.* (1994), Canada, USA, 1986–89	322 diagnosed before 6 years of age in 1986–89; identified through the Children's Cancer Group; response rate, 65%	321; selected through RDD; 1:1 match; response rate, 74%	Telephone interview of the mother or father	*Maternal exposure to beer during pregnancy*			Income	*Crude odds ratio reported
				Astrocytoma	10	1.4 (0.5–3.7)		
				Primitive neurecto-derma tumour	12	4.0 (1.1–22.1)*		

Table 2.88 (continued)

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Hu *et al*. (2000), Northeast, Heilongjiang Province, China, 1991–96	82 consecutive incident (43 boys, 39 girls) intracranial primary brain tumours, ≤18 years of age; 100%; residing in Heilongjiang Province at the time of diagnosis; 100% histologically confirmed; participation rate	3 individually matched per case; participation rate, 100%	Structured questionnaire (interview) administered to parents of all study subjects; history of parental liquor drinking obtained	*Lifetime paternal liquor consumption (L)* Never ≤200 ≥201	 41 20 21	 1.00 3.21 (1.43–7.22) 4.43 (1.94–10.14) *p* for trend=0.0001	Family income, mother's education, father's education	Similar associations for paternal age when started to drink liquor and numbers of years of drinking liquor; only one mother in the case group and two mothers in the control group reported drinking hard liquor.

Table 2.88 (continued)

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Yang *et al.* (2000), Canada, USA, 1992–94	538 children newly diagnosed with neuroblastoma in 1992–94, ≤19 years old; 100% histologically confirmed; response rate, 73%	504 mothers selected by RDD; 304 fathers directly interviewed; proxy interviews obtained for 142 (28%); 1:1 match; response rate, 72%	Structured telephone questionnaire to parents	*Maternal drinking*			Child's gender, mother's race and education, household income in the birth year	No association for paternal lifetime alcohol consumption, or before mother's pregnancy
				Lifetime	253	0.9 (0.7–1.1)		
				Around pregnancy[a]	235	1.1 (0.8–1.4)		
				1 month before conception	205	1.1 (0.8–1.4)		
				1st trimester	96	1.2 (0.9–1.7)		
				2nd trimester	60	1.6 (1.0–2.4)		
				3rd trimester	58	1.4 (0.9–2.1)		
				Breastfeeding	54	1.0 (0.5–2.0)		

Table 2.88 (continued)

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Schüz *et al.*, (2001), Germany, 1988–94	Pooled analysis of 2 case–control studies (1988–93; 1992–94); total of 192; children; response rate, 83.1%	2537; 2:1 match by gender and date of birth within 1 year; response rate, 71%	Questionnaire and telephone interview; same exposure assessment in both studies	**Maternal alcohol consumption**			Socioeconomic status, degree of urbanization	Odds ratio from a matched logistic regression on age, gender, birth year
				Overall				
				Never	140	1.0		
				1–7 glasses/ week	38	0.84 (0.56–1.26)		
				>7 glasses/ week	3	3.04 (0.75–12.2)		
				Stage I/II				
				Never	73	1.0		
				1–7 glasses/ week	12	0.90 (0.45–1.80)		
				>7 glasses/ week	0	–		
				Stage III/VI				
				Never	39	1.0		
				1–7 glasses/ week	23	0.88 (0.53–1.45)		
				>7 glasses/ week	3	5.23 (1.33–20.6)		

CI, confidence interval; RDD, random-digit dialling

[a] Exposure category includes drinking 1 month before pregnancy, during pregnancy and during breastfeeding

in risk with amount and frequency. However, these results were based on very small numbers of controls. A case–control study based on the Children's Cancer Group and Paediatric Oncology Group institutions in the USA and Canada (Yang *et al*., 2000) found no associations between the risk for neuroblastoma and either maternal or paternal alcoholic beverage consumption, while the combined analysis of two case–control studies used in the German study observed no overall association between maternal alcoholic beverage consumption during pregnancy and neuroblastoma or stage I/II neuroblastoma. However, an association was observed between advanced stage (III/IV) neuroblastoma and high alcoholic beverage consumption either during lifetime or around the time of pregnancy (Schüz *et al*., 2001).

One study conducted in the USA and Canada found that maternal beer consumption during pregnancy was associated with primitive neuroectoderma tumours, but no association was found between alcoholic beverage consumption and astrocytoma (Bunin *et al*., 1994), while the Chinese study reported that paternal hard liquor consumption before the pregnancy was associated with brain cancer (Hu *et al*., 2000). [The Working Group considered that there was a possibility of recall bias in this study.]

(b) Adult brain cancers (Table 2.89)

One cohort study (Efird *et al*., 2004) assessed associations between cigarette smoking and other lifestyle factors, including alcohol, and the occurrence of glioma in adults. There was no association with consumption of alcoholic beverages, beer or wine in the past year, although a slight non-significant association was observed for liquor consumption in the past year.

Nine case–control studies assessed the association between alcoholic beverage consumption and brain cancer in adults (Table 2.89). In studies conducted in Australia (Ryan *et al*., 1992; Hurley *et al*., 1996), Germany (Boeing *et al*., 1993) and the USA (Preston-Martin *et al*., 1989; Hochberg *et. al*., 1990; Lee *et al*., 1997), no significant associations or trends were observed with the consumption of alcoholic beverages and the occurrence of glioma or meningioma. However, three studies, one conducted in Canada and two conducted in China, did find an association between the consumption of alcoholic beverages and brain cancer. The Canadian study found an elevated risk for 'ever use' of wine, but not of beer or spirits (Burch *et al.,* 1987) and one Chinese study (Hu *et al*., 1998) found that consumption of liquor was associated with the occurrence of glioma in men with significant trends for the number of years of drinking, lifetime consumption and average consumption. However, no associations were seen for beer in adjusted analyses. In a separate report of the same study (Hu *et al*., 1999), higher levels of consumption of beer, liquor and total alcohol were all associated with brain cancer, with respective adjusted odds ratios of 2.9 (95% CI, 1.1–7.6), 3.8 (95% CI, 1.6–9.2) and 3.2 (95% CI, 1.5–7.0) in the third tertile of consumption.

Table 2.89 Case–control studies of alcoholic beverage consumption and adult brain cancer

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Choi *et al.* (1970), Minneapolis-St Paul Metropolitan area, USA, 1963–64	All (157) histologically proven primary tumours diagnosed in 4 hospitals between June and January 1963, and from June 1963 to June 1964; 126 histologically confirmed	157 patients admitted with conditions other than tumour of any site, neurological, psychiatric, ophthalmological or lymphatic disorders; matched on hospital of admission, sex, age, race, geographic area of residence, location of residence	Questionnaire interview	Central nervous system	*Verified tumours* Never Ever *Gliomas* Never Ever *Astrocytoma* Never Ever *Glioblastoma* Never Ever *Meningioma* Never Ever	 39 65 20 35 14 10 5 23 10 14	 p=0.008 p=0.007	Age	Odds ratios and confidence intervals not presented; for subjects <20 years of age, his/her mother was approached for an interview; a proxy was interviewed when a subject could not provide proper responses.

Table 2.89 (continued)

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Musicco *et al.* (1982); Milan, Italy, 1979–80	51 patients hospitalized with gliomas, >20 years of age; mean age, 47 years; 15 astrocytomas, grades I and II; 10 oligodendrogliomas; and 26 astrocytomas, grades III and IV, and/or glioblastoma multiforme	201 admitted to the same hospital for meningioma, intervertebral disc prolapse or radiculitis, neuraxitis or multiple sclerosis, epilepsy, cerebrovascular disease, other neurological diseases; mean age 49 years; 2:1 matched for age, sex, place of residence	Interview	Central nervous system	Drinkers	24	1.0 p=1.000		Analyses based on 42 case–control pairs; patients who drank alcoholic beverages daily were considered drinkers; some diseases included in the control group may be linked to alcoholic beverage consumption; CI not reported.

Table 2.89 (continued)

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Burch *et al.* (1987), southern Ontario, Canada, 1979–82	247 astrocytomas and glioblastomas (no meningiomas), aged 25–80 years; residents of metropolitan Toronto and southern Ontario; histologically confirmed through medical records; response rate, 75%	228 hospital-based, free of cancer; patients admitted to any hospital in the study area and who had a condition other than cancer at any site; response rate, 56%	Interviewer-administered questionnaire at home	Brain	*Beer* Never Low Medium High *Spirits* Never Low Medium High *Wine* Never Low Medium High		 1.0 2.68 (1.18–6.07) 0.49 (0.23–1.05) 1.47 (0.71–3.03) 1.0 1.29 (0.74–2.25) 1.35 (0.50–3.65) 0.83 (0.41–1.71) 1.0 1.06 (0.46–2.43) 2.07 (0.91–4.73) 2.92 (1.20–7.07)	Age, sex, proxy status, residence	Matched pair analysis
Preston-Martin *et al.* (1989), Los Angeles, USA, 1980–84	277 black and white men residing in Los Angeles County in 1980–1984, aged 25–49 years; first diagnosed with glioma or meningioma; response rate, 74%	272 neighbourhood; response rate, 98.2%	Face-to-face or telephone	Brain	*Glioma* Beer at least once a month Wine at least once a month Liquor at least once a month *Meningioma* Beer at least once a month Wine at least once a month Liquor at least once a month	 32 39 55 7 14 15	 0.7 (0.5–1.2) 0.7 (0.5–1.1) 1.3 (0.8–1.9) 0.4 (0.1–0.9) 0.7 (0.3–1.4) 0.7 (0.3–1.4)	No adjustment specified	

Table 2.89 (continued)

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Hochberg *et al.* (1990), USA, 1977–81	160 newly diagnosed glioblastoma or astrocytoma identified in collaborating hospitals in Boston, Providence and Baltimore	128 friends of cases, excluding blood relatives; matched for sex, age (±5 years), place of residence	Self-administered questionnaire, with telephone follow-up	Brain	Regular consumption of beer	67	0.7 (0.4–1.1)	Age, sex, socioeconomic status	Proxy interviews for 20% of cases and 2% of controls
Ryan *et al.* (1992), Adelaide, Australia, 1987–90	190 incident gliomas or meningiomas in 1987–90, aged 25–74 years; identified through the South Australian Central Cancer Registry; response rate, 90.5%	419 selected from the Australian electoral poll; 2:1 match; response rate, 63.3%	Face-to-face questionnaire at home or at work	Brain (191, 192)	*Glioma* Non-drinkers All sources 0–6.9 g/day 7–19.9 g/day ≥20 g/day *Meningioma* Non-drinkers All sources 0–6.9 g/day 7–19.9 g/day ≥20 g/day		 1.0 0.94 (0.57–1.55) 0.86 (0.47–1.60) 0.74 (0.39–1.40) 1.00 (0.53–1.91) 1.0 0.59 (0.33–1.05) 0.63 (0.31–1.30) 0.49 (0.22–1.09) 0.58 (0.22–1.49)	Sex, age	Never drinkers were subjects who never drank at least once a month for a year; similar associations for beer, wine and spirit consumption.

Table 2.89 (continued)

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Boeing *et al.* (1993), Southwest Germany, 1987–88	115 gliomas, 81 meningiomas and 30 acoustic neuromas, aged 25–75 years; 100% histopathologically confirmed; participation rate, 97.8%	418 randomly selected from the residential registries of the study area; participation rate, 72%	Standardized interview	Brain (191.0, 192.0, 192.1)	Consumption of alcoholic beverages assessed by lifelong history				No numerical data on alcohol presented; alcohol consumption was assessed by lifelong history; no significant association of risk for glioma or meningioma with lifelong consumption of a single alcoholic beverage or total alcohol.

Table 2.89 (continued)

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Hurley *et al.* (1996), Australia (state of Victoria), 1987–91	416 incident (250 men, 166 women) primary gliomas, aged 20–70 years; identified through medical records from 14 Melbourne hospitals; 100% histologically confirmed; participation rate, 66% of eligible and 86% of the contacted cases	Selected from the electoral roll; 422 interviewed (252 men, 170 women); participation rate, 43.5% of those identified as eligible and 64.7% of the contacted controls	Structured questionnaire (interview); subjects sent a section of the questionnaire on details of some other variables	Brain (ICD-0 938–946)	**Drank any alcoholic beverages** *All* Never Ever *Men* Never Ever *Women* Never Ever	318	 1.00 0.96 (0.67–1.37) 1.00 1.40 (0.81–2.43) 1.00 0.62 (0.42–1.15)	 Age, gender, reference date Age, reference date Age, reference date	No increase in risk when average daily alcohol consumption considered
Lee *et al.* (1997), California, USA 1991–1994	494 incident gliomas from 1991 to 1994, aged ≥20 years; identified through hospital records in the San Francisco Bay area; response rate, 82%	462 (random-digit dialling telephone number); frequency matched by age, gender, race/ethnicity; response rate, 63%	Structured questionnaire face-to-face	Brain (glioma) (ICD-0-2 9380–9481)	Mean consumption levels		No levels presented	Age, education, income	Only mean consumption levels of cases and controls presented; no significant differences noted

Table 2.89 (continued)

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Hu *et al.* (1998), China (Northeast, Heilongjiang Province), 1989–95	218 incident primary gliomas (139 astrocytomas and 79 other brain gliomas) identified from the Department of Neurosurgery of 6 major hospitals, aged 20–74 years; 100% histologically confirmed; participation rate, 100%	436 subjects with non-neoplastic, non-neurological diseases; 2:1 matched for sex, age, area of residence; participation rate, 100%.	Structured questionnaire (interview)	Brain	**Liquor** *Age started to drink* Never ≤20 ≥21 *Average oz/ day* Never ≤2 >2	 55 54 31 55 38 47	 1.00 1.98 (1.05–3.72) 1.40 (0.70–2.78) *p* for trend=0.28 1.00 1.54 (0.77–3.06) 1.87 (0.98–3.58)	Income, education, occupational exposure, consumption of vegetables and fruit; liquor also controlled for number of years of beer drinking, and beer controlled for number of years of liquor consumption	Only subjects directly interviewed included; associations for liquor similar for numbers of years drinking and lifetime liquor consumption; no associations noted for similar measures of beer consumption in the Hu *et al.* (1998) analysis, but were seen in an expanded analysis (Hu *et al.*, 1999, see text).

CI, confidence interval; ICD, International Classification of Diseases

2.18.3 *Cancer of the thyroid*

The association of alcoholic beverage consumption and thyroid cancer was examined in four cohort (Table 2.90) and six case–control (Tables 2.91). studies.

One cohort study among alcoholics in Sweden reported no signfiicant excess risk for thyroid cancer compared with the general population (Adami *et al*., 1992a). Two cohort studies conducted in the general population also reported no significant association of increasing alcohol consumption with risk for thyroid cancer (Iribarren *et al*., 2001; Navarro Silvera *et al*., 2005).

A pooled analysis of the case–control studies (Table 2.91), based on 1732 cases, found no association with increasing intake of beer and wine (relative risk, 0.9 (95% CI, 0.7–1.1) for more than 14 drinks per week) (Mack *et al*., 2003). No difference was found for wine or beer separately or between men or women.

No data were available on the effect of duration of alcoholic beverage drinking or cessation of drinking on the risk for thyroid cancer.

2.18.4 *Melanoma*

(a) Cohort studies (Table 2.92)

Two cohort studies, one in a group of radiological technologists exposed to ionizing radiation in the USA (Freedman *et al*., 2003) and one in alcoholic women in Sweden (Sigvardsson *et al*., 1996), found no significant associations between the risk for melanoma and alcoholic beverage intake.

(b) Case–control studies (Table 2.93)

Six of nine case–control studies reported no significant association between alcoholic beverage intake and the risk for melanoma (Østerlind *et al*., 1988; Bain *et al*., 1993; Kirkpatrick *et al*., 1994; Westerdahl *et al*., 1996; Naldi *et al*., 2004; Vinceti *et al*., 2005). These studies were conducted in Australia, Italy, Denmark, Sweden and the USA.

Three case–control studies in the USA reported some increase in risk for melanoma associated with alcoholic beverage intake (Stryker *et al*., 1990; Millen *et al*., 2004; Le Marchand *et al*., 2006). None of these were adjusted for exposure to ultraviolet light and thus the possibility of confounding can not be excluded.

2.18.5 *Other female cancers (vulva and vagina)*

(a) Cohort studies (Table 2.94)

Two cohort studies have examined the association between alcoholic beverage intake and risk for other female cancers. These studies were carried out in special populations, namely women being treated for alcohol abuse or alcoholism in Sweden (Sigvardsson *et al*., 1996; Weiderpass *et al*., 2001b). One study indicated an elevated

Table 2.90 Cohort studies of alcoholic beverage consumption and thyroid cancer

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Special populations								
Hakulinen *et al*. (1974), Finland	Chronic alcoholic men (mean annual number in registry, 4370), aged >30 years, registered in 1967–70 when under custody of alcohol-misuse supervision, or when sent to a labour institute because of the vagrant law		Thyroid	Alcoholics	1 death observed/0.4 expected			No information regarding alcohol consumption, relative risk or CI was reported

Table 2.90 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Adami *et al*. (1992a), Uppsala, Sweden	9353 patients (8340 men; mean age at entry, 49.8 years; at diagnosis, 68.1 years; 1013 women; mean age at entry, 49.4 years; at diagnosis, 60.0 years) with a hospital discharge diagnosis of alcoholism in 1965–83	Follow-up through to 1984 (average follow-up, 7.7 years; maximum, 19 years)	Thyroid	No data on individual alcohol or tobacco use	Men: 3 Women: 0	**SIR** *Men* 1.7 (0.3–4.9) *Women* 0.0 (0.0–8.0)	Sex	

Table 2.90 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment factors	Comments
General population								
Iribarren *et al*. (2001), California, USA, Kaiser-Permanente Medical Care Program Cohort	94 549 men and women, aged 10–89 years, subscribers to the Kaiser Permanente Medical Care Program, northern California, who underwent regular health check-ups in 1964–73; follow-up based on the Cancer Incidence File (San Francisco Bay Area) through to 1997; median follow-up, 19.9 years	Self-administered questionnaire	Thyroid	*Alcohol consumption (drinks/day)* 0 1–2 3–5 ≥6		 0.9 (0.6–1.3) 1.0 1.0 (0.5–1.8) 1.0 (0.3–3.0)	Age, sex, race, education, goitre, treatment to neck with X-rays, family history	Alcohol intake of 1–2 drinks/ day = referent category; 73 cases of thyroid cancer in men and 123 cases in women; relative risk by gender not given

Table 2.90 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Navarro Silvera *et al*. (2005), Canada, Canadian National Breast Screening Study Cohort	49 613 women, aged 40–59 years, from the general Canadian population, recruited into the cohort between 1980 and 1985; average follow-up, 15.9 years	Self-administered questionnaire	Thyroid	*Alcohol intake (g/day)* None Any 1–3 3–10 ≥10	103 total	*Hazard ratio* 1.0 1.2 (0.7–1.8) 1.2 (0.7–2.0) 0.7 (0.4–1.2) 0.8 (0.5–1.4) *p*-trend=0.56	Age, education, pack–years of smoking, body mass index	No association for papillary or follicular subtype

CI, confidence interval; ICD, International Classification of Diseases

Table 2.91 Case–control studies of alcoholic beverage consumption and thyroid cancer

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Ron *et al.* (1987), Connecticut, USA, 1978–80	159 identified via Connecticut Tumor Registry; 100% histologically confirmed; response rate, 80%	285 population (random-digit dialling, Medicare records); 2:1 frequency-matched by sex, age; response rate, 65%	Interviewer-administered questionnaire	*Alcohol use* Non-user Any beer Any wine Any hard liquor	 87 37 56 59	 1.0 0.7 (0.4–1.3) 0.8 (0.5–1.3) 0.9 (0.6–1.5)	Age, sex, prior radiotherapy to the head and neck, thyroid nodules, goitre	Non-user: consumer of <1 drink per week
Kolonel *et al.* (1990), Hawaii, USA, 1980–97	191 (140 women, 51 men), identified through Hawaii Tumor registry, aged ≥18 years; 100% histologically confirmed; response rate, 79%	441 from Health Surveillance of the Department of Health; matched by age, sex; response rate, 74%	Self-administered questionnaire plus diet history	**Regular alcohol use** *Men* Never Ever *Women* Never Ever	 	 1.0 0.6 (0.3–1.4) 1.0 1.0 (0.6–1.6)	Age, ethnicity	Number of cases not reported

Table 2.91 (continued)

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Galanti *et al*. (1997), Norway/ Sweden, 1993–94	*Norway*: 87 identified through Norwegian Cancer Register, born in Norway and living in the Tromsø Health Care Region, aged 18–75 years; response rate, 75% *Sweden*: 165 identified through registry, aged 18–75 years; response rate, 86%	*Norway*: 192 from population register; matched by age, sex; response rate, 56% *Sweden*: 248 from population register; matched by age, sex, county of residence; response rate, 69%.	Self-administered questionnaire	**No. of drinks/month** *Wine (1.5 dL)* <1 1–3 >3 *Light beer (2–5 dL)* <1 1–4 >4 *Strong beer (2–5 dL)* <1 >1 *Mild liquor (0.4 dL)* <1 >1 *Hard liquor (0.4 dL)* <1 >1 *Ethanol (g/day)* <1 1–3.95 >3.95	 107 54 52 113 61 49 181 35 184 34 147 71 89 80 67	**Odds ratio** (univariate analysis) 1.0 1.1 (0.7–1.7) 0.7 (0.4–1.1) 1.0 1.0 (0.7–1.6) 0.8 (0.5–1.2) 1.0 0.9 (0.5–1.6) 1.0 0.8 (0.5–1.2) 1.0 0.8 (0.5–1.1) 1.0 0.8 (0.6–1.2) 0.7 (0.5–1.1)		Not adjusted; results not changed after adjustment for smoking status, education

Table 2.91 (continued)

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Chatenoud *et al*. (1999), Italy, 1983–93	428, aged <75 years; 100% histologically confirmed; refusal rate for interview, <3%	3526 hospital patients (non-malignant); excluded alcohol and tobacco- or dietary-related diseases	Interviewer-administered questionnaire	*Alcohol intake 2 years before* Lowest Highest		**Odds ratio** 1.0 1.7 (1.3–2.3)	Age, sex	The main focus of this study was on refined-cereal intake and risk for cancer; the quantity of alcohol consumed was not specified.

Table 2.91 (continued)

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Rossing *et al*. (2000), Washington State, USA, 1988–94	410 papillary tumours identified via the Washington State Cancer Surveillance System, aged 18–64 years; response rate, 84%	574 population (random-digit dialling); matched by age, county of residence; response rate, 74%	Interviewer-administered questionnaire	***Alcohol intake***		**Odds ratio**	Age	* Never drank ≥12 alcoholic drinks within 1 year; cases and controls were only women
				Never*	126	1.0		
				>10 years ago	28	1.0 (0.5–1.7)		
				6–10 years ago	23	0.8 (0.5–1.5)		
				≤5 years ago	33	1.0 (0.6–1.8)		
				Current drinkers	200	0.7 (0.5–0.9)		
				Amount (drinks/week)				
				Current drinkers				
				Never*	128	1.0		
				≤1	59	0.7 (0.4–1.0)		
				2–3	55	0.6 (0.4–0.9)		
				4–7	44	0.6 (0.4–0.9)		
				>7	42	0.9 (0.5–1.4)		
				Former drinkers				
				Never*	128	1.0		
				≤1	42	1.2 (0.7–1.9)		
				2–3	16	0.9 (0.5–1.9)		
				4–7	6	0.3 (0.1–0.8)		
				>7	18	1.2 (0.6–2.4)		
Pooled analyses								
Franceschi *et al*. (1991), 4 hospital-based case–control studies	385, aged <75 years; 100% histologically confirmed; response rate, ~97%	798 hospital patients (non-malignant)	Interviewer-administered questionnaire	*Alcohol intake*		**Odds ratio**	Age, sex, education, study centre	CI not reported
				Low	103	1.0		
				Intermediate	122	1.1		
				High	160	1.3		
						χ^2 (trend), 2.72		

Table 2.91 (continued)

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of cases	Relative risk (95% CI)	Adjustment factors	Comments
Mack *et al*. (2003), 10 case–control studies	370 men, 1296 women; six studies provided information on wine and beer combined	702 men, 2106 women	Pooled analysis	*Weekly drinks of wine and beer* None ≤2 >2–7 7–14 >14	 787 263 321 146 149	*Men* 1.0 0.8 (0.6–1.0) 0.8 (0.7–1.0) 1.0 (0.8–1.3) 0.9 (0.7–1.1) *p* for trend 0.12	Stratification on study, age, sex, ethnicity, current smoking	No difference in cancer risk between men and women

CI, confidence interval

Table 2.92 Cohort studies of alcoholic beverage consumption and melanoma

Reference, location, name of study	Cohort description	Exposure assesment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Sigvardsson *et al*. (1996), Sweden, Swedish Cancer Registry Study	15 508 alcoholic women individually matched for region and age with one non–alcoholic women; incidence data from the Swedish Cancer Registry	Alcoholic women from the records of the Temperance boards in Sweden	Reference Alcoholic women	28 14	1.0 0.5 (0.3–1.0)		[May be confounded by differences in smoking, dietary habits and/or other factors.]

Table 2.92 (continued)

Reference, location, name of study	Cohort description	Exposure assesment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Freedman *et al.* (2003), USA, 1926–98 Radiologic Technologists Study	68 588 white cancer-free radiological technologists (54 045 women, 14 543 men); follow-up, 698 028 person–years; cases identified through SEER	Baseline questionnaire 1983–89 on height, weight, smoking, alcohol use, female hormonal factors, work history, other factors; participation rate, 86%; Second questionnaire 1994–98 updated information on risk factors, skin pigmentation, hair and eye colour, family medical history; participation rate, 83%	**Alcohol (drinks/ week)**			Gender, years smoked, skin pigmentation, hair colour, personal history of non-melanoma skin cancer, decade of starting work as a technologist, education, proxy measures for residential childhood and adult exposure to sunlight	
			Women	159			
			Never	23	1.0		
			Ever	136	1.2 (0.8–1.9)		
			<1–6	114	1.2 (0.7–1.9)		
			7–14	19	1.7 (0.9–3.1)		
			>14	3	2.1 (0.6–7.0)		
					p for trend 0.05		
			Men	48			
			Never	8	1.0		
			Ever	40	1.5 (0.7–3.3)		
			<1–6	32	1.5 (0.7–3.4)		
			7–14	4	0.9 (0.2–3.0)		
			>14	4	2.4 (0.7–8.2)		
					p for trend 0.61		
			All	207			
			Never	31	1.0		
			Ever	176	1.3 (0.9–1.9)		
			<1–6	146	1.2 (0.8–1.8)		
			7–14	23	1.4 (0.8–2.5)		
			>14	7	2.1 (0.9–4.8)		
					p for trend 0.08		

CI, confidence interval, SEER, Surveillance, Epidemiology and End Result

Table 2.93 Case–control studies of alcoholic beverage consumption and melanoma

Reference, ocation, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Number of exposed cases	Odds ratio (95% CI)	Adjustment factors
Østerlind *et al*. (1988), East Denmark	474 incident, identified in the Danish Cancer Registry, aged 20–79 years; response rate, 92%	926 selected from National Population Register; response rate, 82%	Face-to-face structured questionnaire at home	*Alcoholic beverage* Beer Wine Fortified wine Distilled liquor *Alcohol (kg/year)* 0–1.1 1.2–3.3 3.4–8.4 ≥8.5		 0.7 (0.5–1.1) 0.7 (0.5–1.1) 0.8 (0.5–1.2) 0.7 (0.5–1.1) 1.0 0.8 (0.6–1.1) 0.8 (0.5–1.1) 0.6 (0.4–0.9)	Sunbathing, socioeconomic status
Stryker *et al*. (1990), Massachussets, USA, 1982–85	196 Caucasians; biopsy-confirmed cases older than 18 years; response rate, 92%	232 Caucasians; response rate, 92%	Face-to-face food-frequency questionnaire	**Alcoholic bev.** *Beer* None <10 g/day ≥10 g/day *Red wine* None <10 g/day ≥10 g/day *White wine* None <10 g/day ≥10 g/day		 1.0 1.1 1.6 *p* trend=0.2 1.0 0.9 1.1 *p* trend=0.9 1.0 0.9 0.8 *p* trend=0.9	Age, sex, hair colour, ability to tan

Table 2.93 (continued)

Reference, ocation, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Number of exposed cases	Odds ratio (95% CI)	Adjustment factors
Stryker *et al.* (1990) (contd)				*Liquor*			
				None		1.0	
				<10 g/day		1.3	
				≥10 g/day		1.2	
						p trend=0.7	
				All types			
				None		1.0	
				<10 g/day		1.2	
				≥10 g/day		1.8 (1.0–3.3)	
						p trend=0.03	
Bain *et al.* (1993), Brisbane, Queensland, Australia, 1983–85	41 women, aged <80 years; histologically confirmed; [response rate, 63%]	297, aged <80 years; response rate not given	Mailed food-frequency questionnaire plus home interview	*Alcohol drinking (g/day)*			Age, hair colour, number of painful sunburns, total energy intake, number of years of schooling
				None		1.0	
				0.1–9.9		0.78 (0.32–1.94)	
				10.0–19.9		1.40 (0.46–4.30)	
				≥20.0		2.50 (0.87–7.40)	
Kirkpatrick *et al.* (1994), Washington State, USA, 1984–87	256 white, aged 25–65 years, identified from SEER cancer registry; response rate, 80%	234 identified by random-digit dialling to approximate age, sex, county of cases; response rate, 73%	Mailed food-frequency questionnaire plus telephone interview	*Drinks/month*			
				≤1	103	1.0	Age, sex, education
				2–10	69	1.55	
				>10	62	1.18 (0.52–2.62)	Age, sex, education, total energy intake
				≤1	103	1.0	
				2–10	69	1.31	
				>10	62	1.16 (0.53–2.59)	

Table 2.93 (continued)

Reference, ocation, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Number of exposed cases	Odds ratio (95% CI)	Adjustment factors
Westerdahl *et al*. (1996), southern Sweden, 1988–90	400 men and women, aged 15–75 years, from Regional Tumour Registry; histopathological diagnosis; response rate, 88.1%	640 population-based, selected by random sampling, matched 2:1 by sex, age, parish; response rate, 70.1%	Mailed comprehensive questionnaire	Any versus none		1.0 (0.7–1.4)	History of sunburn, hair colour, number of raised naevi
				Distilled alcohol >1/month		1.4 (1.0–1.9)	
				Total alcohol intake (g/day)			
				0	84	1.0	
				1–9	160	0.8 (0.6–1.1)	
				10–19	37	0.9 (0.5–1.5)	
				≥20	25	0.9 (0.5–1.8)	
						p trend>0.05	
Millen *et al*. (2004), Philadelphia, California, USA, 1991–92	497 newly diagnosed invasive cutaneous melanoma in two clinics, aged 20–79 years; 100% histologically confirmed; response rate, 84%	561 hospital-based; dermatological or psychiatric problems for clinic visit excluded; response rate, 66%	Food-frequency questionnaire	*Alcohol (times/week)*			Education, skin response after repeated sun exposure, age, sex, study site, presence of dysplastic nevi
				0	154	1.0	
				0.7	77	1.04 (0.69–1.57)	
				1.4–7.0	160	1.55 (1.09–2.20)	
				7.7–59	106	1.53 (1.03–2.29)	
				p for trend		0.04	

Table 2.93 (continued)

Reference, ocation, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Number of exposed cases	Odds ratio (95% CI)	Adjustment factors
Naldi *et al*. (2004), 27 centres in Italy, 1992–94	542 (226 men, 316 women), aged 15–87 years; 100% histologically confirmed; participation rate 99%	538 hospital-based (230 men, 308 women), aged 15–92 years; participation rate, 99%	Structured questionnaire, standardized examination	*Alcohol (drinks/week)*			Age, sex, education, body mass index, history of sunburns, propensity to sunburn, number of naevi, number of freckles, skin, hair and eye colour, tobacco smoking
				Never	131	1.0	
				<1	89	0.81 (0.53–1.22)	
				1–13	132	0.91 (0.62–1.33)	
				14–27	132	1.26 (0.83–1.91)	
				≥28	58	0.83 (0.49–1.40)	

Table 2.93 (continued)

Reference, ocation, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Number of exposed cases	Odds ratio (95% CI)	Adjustment factors
Vinceti *et al.* (2005), Modena, Italy, 3 years	59 (28 men, 31 women newly diagnosed cutaneous melanomas attending the Dermatologic Clinic of Modena University Hospital (only centre for diagnosis, therapy and follow-up); 100% histologically confirmed; participation rate, 72%	59 randomly selected residents of Modena; matched on sex, age	Self-administered questionnaire on diet and lifestyle habits	*Alcohol (g)* <1.6 ≥1.6–23.3 >23.3		 1.0 1.86 (0.64–5.42) 0.97 (0.17–5.50)	Dietary factors, energy intake

Table 2.93 (continued)

Reference, ocation, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Number of exposed cases	Odds ratio (95% CI)	Adjustment factors
Le Marchand *et al*. (2006), Hawaii, USA, 1986–92	278 prevalent and incident (167 men, 111 women) invasive or in situ identified through Hawaii Tumor Registry with four grandparents of pure Caucasian origin; aged 18–79 years 100% histopathologically confirmed; participation rate, 67.5%	278 Caucasians randomly selected from local residential; registries matched to each case on sex, age; participation rate, 60.6%	Standardized interview by trained interviewers, including demographics, sun exposure, vacations, lifetime smoking, alcohol use, quantitative food-frequency questionnaire, skin colour, naevi, hair colour	**Alcohol drinking status** *Men* Never Former Current *Women* Never Former Current **Lifetime ethanol intake (kg)** *Men* ≤45 >45–265 >265 *Women* ≥0 1–48.6 >48.6	 22 35 110 35 30 46 47 52 68 35 36 40	 1.0 1.6 (0.8–3.4) 1.9 (1.0–3.4) 1.0 1.3 (0.6–2.6) 1.5 (0.7–2.9) 1.0 1.2 (0.6–2.2) 2.3 (1.2–4.4) 1.0 1.1 (0.5–2.4) 1.7 (0.7–3.8)	Height, education, hair and eye colour, number of blistering sunburns at ages 10–17 years, ability to tan, family history

CI, confidence interval; SEER, Surveillance, Epidemiology and End Result

Table 2.94 Cohort studies of alcoholic beverage consumption and other female cancers

Reference, location, name of study	Cohort description	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Sigvardsson *et al.* (1996), Sweden, Temperance Boards Study	Nested case–control study; 15 508 alcoholic women born in 1870–1961 obtained from Temperance Boards; controls matched for region and day of birth; case ascertainment, Swedish Cancer Registry	Vulva, vagina and other female genital (ICD-7 176)	Alcohol abusers	16	4.0 (1.3–12)	Age, region	Estimate not adjusted for smoking
Weiderpass *et al.* (2001b), Sweden, National Board of Health and Welfare/Study of Alcoholic Women	36 856 women registered and hospitalized with alcoholism between 1965 and 1994; data from Inpatients Register; linkages to nationwide Registers of Causes of Death and Emigration and national Register of Cancer; mean age, 42.7 years; average follow-up time, 9.4 years				**SIR**		Using expected rates specifically for squamous-cell carcinoma of the vulva, the overall SIR was 1.1 (0.5–2.2)
		Vulva (ICD-7 176.0)	Total	8	1.0 (0.4–2.0)		
			Age at cancer diagnosis				
			<50 years	0	–		
			≥50 years	8	1.2 (0.5–2.4)		
		Vagina (ICD-7 176.1)	Total	10	4.6 (2.2–8.5)		
			Age at cancer diagnosis				
			<50 years	1	2.5 (0.1–14.1)		
			≥50 years	9	5.1 (2.3–9.7)		

CI, confidence interval; ICD, International Classification of Diseases; SIR, standardized incidence ratio

risk for vaginal cancer but not for vulvar cancer (Weiderpass *et al*., 2001b). The other study presented high relative risk estimates for both vulvar and vaginal cancers combined. The cohort studies could not adjust risk estimates for factors that may have confounded the association between alcoholic beverage and vulvar and vaginal cancers, such as HPV infections, number of sexual partners and tobacco smoking. It is possible that women who abuse alcohol have other behavioural patterns that may affect risks for vulvar and vaginal cancer.

(b) Case–control studies (Table 2.95)

Three case–control studies investigated the association between alcoholic beverage consumption and risk for vulvar cancer in Italy (Parazzini *et al*., 1995b) and in the USA (Mabuchi *et al*., 1985b; Sturgeon *et al*., 1991). Two of these were hospital-based (Mabuchi *et al*., 1985b; Parazzini *et al*., 1995b) and one was population-based (Sturgeon *et al*., 1991).

Confounding factors were considered in two studies (Sturgeon *et al*., 1991; Parazzini *et al*., 1995b), but only one provided risk estimates adjusted for smoking and sexual behaviour (Sturgeon *et al*., 1991), which are potential confounders.

The three case–control studies reported no association between alcoholic beverage consumption and risk for vulva cancer.

(c) Evidence of a dose–response

One case–control study (Parazzini *et al*., 1995b) and the cross-sectional study (Williams & Horm, 1977) presented information on dose–response for alcoholic beverage consumption and vulvar cancer. Neither study found evidence of a dose–response.

(d) Types of alcoholic beverage

Three studies (Williams & Horm, 1977; Mabuchi *et al*., 1985b; Sturgeon *et al*., 1991) investigated differences in risk according to the type of beverage and found no evidence of an effect.

Table 2.95 Case–control studies of alcoholic beverage consumption and other female cancers

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Williams & Horm (1977), The Third National Cancer Survey (cross-sectional study), USA, 1967–71	3856 cancer patients (all sites); age range not given; response rate, 57%	Randomly selected patients with cancers thought to be unrelated to tobacco and alcohol use	Personal interview	Vulva	Wine ≤51* >51 Beer ≤51 >51 Hard liquor ≤51 >51 Total alcohol ≤51 >51	 0.63 – 1.61 0.84 1.67 0.43 1.20 0.39	Age, race, smoking	None of the values were significantly increased (p>0.05) *less/more than one drink per week during a year

Table 2.95 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Mabuchi *et al.* (1985b), New York, Michigan, Florida, Minnesota, USA, 1972–75	149 patients with vulvar carcinoma from 155 hospitals; patient identification abstracted from hospital records; 100% histologically confirmed; participation rate, 79.7%	149 patients, admitted to the hospital for circulatory, digestive, nervous system, musculoskeletal, respiratory, genitourinary, endocrine, orthopaedic diseases, accidents and others; free of any cancer; matched to cases on hospital, sex, race, age (in 3-year range), marital status	Interview by blinded interviewers, mostly at hospital	Vulva	No association between alcohol consumption or specific alcoholic beverages and risk for vulvar cancer			

Table 2.95 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Sturgeon *et al*. (1991), Chicago and Upstate New York, USA, 1985–87	201 incident cancer obtained from 34 hospitals in Chicago and Upstate New York, aged 53.9 years; 100% pathologically confirmed; participation rate, 61%	342 randomly selected using digit dialling techniques for controls <65 years and Health Care Financing Administration for women ≥65 years; mean age, 52.6 years; matched to cases by age in 5-year groups, race, residence; participation rate, 51%	Structured interview and food-frequency questionnaire at home	Vulva	No association between overall ethanol consumption and vulvar cancer; specific types of alcoholic beverage showed no appreciably increased risk with increasing intake.		Age, sexual behaviour, cigarette smoking	

Table 2.95 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Parazzini *et al.* (1995b), Milan, Italy, 1987–93	125 admitted to general and teaching hospitals in the greater Milan area, aged 30–80 years; invasive vulvar cancer histologically confirmed	541 patients randomly selected, admitted to the same hospitals for acute conditions, not hormonal, gynaecological or neoplastic, aged 27–79 years; matched by age, interview year	Standard questionnaire; interview during hospital stay	Vulva	***Alcohol drinking*** Never Occasional Regular	 1.0 0.7 (0.4–1.2) 1.1 (0.7–1.7) χ^2 trend=0.17 p=0.68	Age, education, body mass index	Limited statistical power due to small study sample size; possible information bias

CI, confidence interval; ICD, International Classification of Diseases

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3. Studies of Cancer in Experimental Animals

3.1 Ethanol and alcoholic beverages

Previous studies

Ethanol was evaluated by an IARC Working Group in 1988 (IARC, 1988). At the time, some early studies were available in which ethanol was administered to mice (Krebs, 1928: Ketcham *et al.*, 1963, Horie *et al.*, 1965) and hamsters (Elzay, 1966; Henefer, 1966; Elzay, 1969; Freedman & Shklar, 1978) by use of various protocols, but these studies were found to be inadequate for evaluation.

The 1988 Working Group evaluated studies published between 1965 and 1987, most of which were criticized for various reasons, including small numbers of experimental animals, absence of histopathological examination, absence of an untreated control group, limited dose of ethanol administered, short duration of the study and unpaired feeding regimen. Thus, the conclusion was that ethanol *per se* could not be considered to be carcinogenic in animal experiments.

Studies on the administration of ethanol and the development of cancer in experimental animals that have been published since that time are reviewed below.

3.1.1 *Oral administration*

(a) Mouse

As part of a study to investigate the effects of ethanol on the carcinogenicity of NDMA, three groups of 50 male strain A (A/JNCr) mice (a strain that is prone to develop spontaneous lung tumours), 4 weeks of age, received 10% ethanol in the drinking-water. One group received ethanol from week 1 to week 16, the second group received ethanol from week 4 to week 16 and the third group received ethanol from week 5 to week 16. [Ethanol intake calculated from the average water consumption was between 0.4 and 0.48 g per day per animal.] The lung-tumour incidence was between

12 and 14%, which was not significantly different from that in two control groups that did not receive ethanol. The spontaneous lung-tumour occurrence was 10% (Anderson, 1988).

As part of a study to investigate the effect of ethanol on the carcinogenicity of ethyl carbamate, 15 female strain A/Ph mice, 6.5 weeks of age, received 5, 10 or 20% ethanol in the drinking-water for 12 weeks; 15 animals that did not receive ethanol served as controls. Body weight (bw) was reduced with 20% ethanol. The percentages of mice with lung tumours were 67, 47 and 67%, respectively, compared with 40% in the control group, a difference that was not statistically significant. The tumour multiplicity also did not differ (Kristiansen *et al.*, 1990). [The Working Group noted the small number of animals, and that ethanol blood concentrations and intake data were not specified.]

As part of another study to investigate the effect of ethanol on the carcinogenesis of ethyl carbamate, 25 female NMRI mice, 10 weeks of age, were treated daily for 3 days with 10% ethanol by gavage (0.3 mL/25 g bw) and then with 20% ethanol for a total of 8 weeks. Eight weeks after the last dose, the animals were killed; 9–24% of mice in the ethanol-treated group developed lung adenomas compared with 17–21% in the control group, a difference that was not significant (Altmann *et al.*, 1991). [The Working Group noted the short duration of exposure to ethanol.]

Groups of 30 male and 30 female inbred Swiss mice, 8 weeks of age, received either 10% Indian country liquor or 1% ethanol in the drinking-water or pure water only from the age of 2 months until 18 months. The experiment was terminated at 26 months of age. The total tumour incidence in untreated male and female mice was 3% (1/29; one lung and forestomach) and 4% (1/27; one forestomach), respectively, compared with 5% (1/22; one lung) and 11% (2/19; two forestomach), respectively, in animals that received 1% ethanol in the drinking-water. Indian country liquor at 10% induced a tumour incidence of 28% (7/25; one liver, one lung, four forestomach, one lung and forestomach) [$P = 0.0186$] in male mice and 7% (2/29; one kidney and one forestomach) in female mice (Zariwala *et al.*, 1991). [The Working Group noted that Indian country liquor may contain a wide variety of congeners that may be responsible for the results obtained. No significantly different effect was observed between controls and animals treated with 1% ethanol. One per cent ethanol is a rather low dose and may not be sufficient to induce tumours. The Working Group also noted that very few animals survived to the end of the study.]

Groups of 30 male BALB/c mice, 8 weeks of age, received 10% Indian country liquor or 1% ethanol in the drinking-water or pure water from the age of 2 months until 18 months. The experiment was terminated when the mice were 26 months of age. Untreated controls had a 4% tumour incidence (1/24; one forestomach); 10% liquor and 1% ethanol resulted in a tumour incidence of 22% (5/23; three lung, two forestomach) and 0% (0/28), respectively (Zariwala *et al.*, 1991). [The Working Group noted that Indian country liquor may contain a wide variety of congeners that may be responsible for the results obtained. No difference in effect was observed between untreated

controls and animals that received 1% ethanol in the drinking-water. One per cent ethanol in the drinking-water is a rather low dose and may not be sufficient to induce tumours. The Working Group noted also that very few animals survived to the end of the study.]

To investigate the effect of ethanol on the carcinogenesis of *N*-nitrosodimethylamine (NDMA), a group of 25 male A/JNCr mice, 4–6 weeks of age, received a 10% solution of ethanol in the drinking-water for 4 weeks and was then kept for another 12 weeks. [Intake of ethanol could be calculated from the amount of water consumed and was approximately 0.34 g per mouse per day.] The experiment was terminated at 16 weeks. In the ethanol-treated group, 16% (4/25) developed lung tumours compared with 8% (2/25) in the control group, a difference that was not statistically significant. In another experiment, 48 animals received 10% ethanol in the drinking-water for 69 ± 6 weeks and another 48 animals served as a control group for 70 ± 5 weeks without ethanol. The lung tumour rate was 69% in the ethanol-treated group and 83% in the control group (difference not significant). In a third experiment, groups of 30 animals each received 0 (controls), 5, 10 or 20% ethanol in the drinking-water for 16 weeks. The experiment was terminated at 16 weeks. The numbers of animals with lung tumours were 3.3, 20, 23.3 and 13.3%, respectively. These values were not statistically different (Anderson *et al.*, 1992). [The Working Group noted that no blood ethanol measurements were taken.]

Two groups of 15 female C3H/Ou mice, 6 weeks of age, received 12% ethanol in the drinking-water or water alone for 65 weeks. In the ethanol-treated group, development of mammary tumours was delayed ($P = 0.03$). The median incidence was reached 17 weeks later than in the controls. Ethanol consumption was approximately 15 g/kg bw per day. Ethanol-treated animals gained less weight and consumed fewer calories (controls consumed 13% more calories) and drank 40% less fluid (Hackney *et al.*, 1992). [The Working Group noted that the number of animals was small, that variables such as calories and drinking-water were not controlled for and that no ethanol blood concentrations were given.]

Ten female C3H/Ou mice, 6 weeks of age, received 4 g/kg bw ethanol per day by gavage five times per week for 65 weeks, while 16 animals received a control gavage with Sustacal. The animals received the same calories per day in an isocaloric pair-feeding model provided by semipurified solid diets. Diet restriction was necessary for controls but water was given *ad libitum*. Both groups developed similar numbers of mammary tumours at a similar rate. The highest ethanol blood level achieved was 0.25% (250 mg/100 mL) (Hackney *et al.*, 1992). [The Working Group noted the small number of animals, the adequate design with pair feeding and the adequate blood ethanol concentrations.]

Two groups of 20 and 14 female C3H/Ou mice, 6 weeks of age, received Lieber-DeCarli diets with 29% ethanol as total calories (20 g/kg per day) and control diet for 65 weeks, respectively. No difference in weight gain and no difference in mammary tumour development were observed (Hackney *et al.*, 1992). [The Working Group noted the small number of animals and the adequate design with pair feeding.]

As part of a study to investigate the effect of ethanol on the carcinogenesis of *N*-nitrosomethylbenzylamine (NMB_zA), groups of 13 and 12 female C57BL/6 mice, 4–6 weeks of age, received ethanol [purity not specified] as 30% of total calories (Lieber-DeCarli diets) for 22 weeks or control diet, respectively. The experiment was terminated at 22 weeks. No difference in tumour incidence was observed between the ethanol-treated and control groups (one tumour in each group) (Eskelson *et al.*, 1993). [The Working Group noted the small number of animals. One control mouse developed an oesophageal tumour without carcinogen treatment, which is difficult to explain.]

As part of a study that investigated the effect of ethanol on the carcinogenicity of nitrosamines, 25 male strain A/JNCr mice, 4 weeks of age, received 10% ethanol in the drinking-water for 4 weeks. The experiment was terminated 32 weeks later. The incidence of lung tumours in the ethanol-treated group was 60% [15/25], which was slightly, but not significantly, greater than that in the untreated control group (38% [9/24]). In a second experiment, 49 female Swiss NIH:Cr(S) mice, 4 weeks of age, received 15% ethanol for 12 weeks [presumably in the drinking-water] and were killed when ill or at 18 months of age; 48 animals served as a saline control group. No difference in body weight or survival was observed. No significant difference in tumour yield was reported. In the ethanol-treated group, besides lung tumours, five lymphomas, one thymic tumour, four uterine tumours and two sarcomas were also reported. In the control group, six lymphomas, one thymic tumour, one uterine tumour and one sarcoma were noted (Anderson *et al.*, 1993). [The Working Group noted that blood ethanol concentrations were not determined.]

A group of 20 female ICR mice, 40 days of age, was administered 10% ethanol (v/v) [purity not specified] in the drinking-water for 2 months and then 15% ethanol (v/v) in the drinking-water for 23 months. An additional group of 20 females was given tap-water as their drinking fluid. The experiment was terminated after 25 months. Mammary tumours were assessed macroscopically and microscopically. Body weights did not differ between the two groups. Mice that received drinking-water that contained ethanol consumed 4.7 ± 0.60 mL/day (13.2 ± 2.66 g/kg bw ethanol per day), which did not differ from that consumed by control mice (5.3 ± 0.64 mL/day). Beginning 8 months after treatment, mammary gland tumours (papillary or medullary adenocarcinoma) were detected in 45% (9/20) mice given ethanol in the drinking-water compared with 0/20 control mice [$P = 0.0012$; two-tailed Fisher's exact test] (Watabiki *et al.*, 2000).

As part of a study that investigated the effect of ethanol on the carcinogenicity of ethyl carbamate, three groups of 48 male and 48 female $B6C3F_1$ mice, 28 days of age, received either 0, 2.5 or 5.0% ethanol orally in the drinking-water for 104 weeks. No impurities except water were detected. The average daily consumption of ethanol was 100 and 180 mg in male mice that received 2.5 and 5% ethanol, respectively. The comparable values for females were 80 and 155 mg. [This is equivalent to approximately 2.2 and 4.2 g/kg bw per day for both sexes.] No serum ethanol concentrations could be measured with the doses of ethanol administered (< 8 mg/100 mL). Increasing ethanol

content in the drinking-water had no effect on cell-cycle distribution in the liver or on cell proliferation in the lungs. Increasing ethanol content in the drinking-water increased cytochrome P-450 2E1 (CYP2E1) in the livers of female but not of male animals. Ethanol had no effect on body weight. Male mice showed a dose-related increase in survival as a function of increasing ethanol concentrations ($P = 0.053$), while female mice did not. Complete histopathology was performed. In female mice, ethanol had no effect on tumour incidence. In male mice, a dose-related trend ($P < 0.05$; Poly-3 test) was found for the incidence of hepatocellular adenoma (control, 15% (7/46); 2.5% ethanol, 25% (12/47); 5% ethanol, 39% (19/48) and for that of hepatocellular adenoma or carcinoma (control, 26% (12/46); 2.5%, 34% (16/47); 5%, 52% (25/48)). The increase in the incidence of hepatocellular adenoma was significant in the 0.5% ethanol-treated group (National Toxicology Program, 2004; Beland *et al.*, 2005). [The Working Group noted that the ethanol serum concentrations were too low to measure and that the lack of induction of hepatic CYP2E1 in the liver of male animals could be due to low ethanol levels. Despite the low amount of ethanol given, it is remarkable that the incidence of hepatocellular tumours was increased in male animals. The Working Group also noted that the maximum tolerated dose may have not been used in this study.]

(b) Rat

As part of a study to investigate the effect of ethanol on the carcinogenicity of synthetic estrogens and progestins, one group of female and one group of male Wistar JCL rats, 4 weeks of age, received 10% ethanol in the drinking-water on 5 days a week *ad libitum*. On the remaining 2 days of each week, the animals received pure water. In addition, 0.5 mL olive oil per day was given through a stomach tube. The treatment lasted 12 months and rats were killed at 2, 4, 6, 8 (five females and four males for each time point) and 12 months (10 females and eight males). Control rats that did not receive ethanol were also available (five female and four males for each time point). No hepatocellular carcinoma or hyperplastic nodules were found in any of the animals during the experimental period (Yamagiwa *et al.*, 1994). [The Working Group noted the small number of animals, the non-pair-feeding regime and the lack of measurements of ethanol blood levels.]

Eight groups of 50 male and 50 female Sprague Dawley rats, 6–7 weeks of age, received a semi-synthetic liquid diet either with low (1%) or high (3%) ethanol content or low glucose or high glucose content (20.2 or 62.0 g/L of diet glucose to serve as equicaloric controls). Males were given 70 mL/day and females were given 60 mL/day [which corresponded to an alcohol (and glucose) intake of 0.56 g/day (11.1 g glucose/day) and 1.68 g/day (14 g glucose/day) in males and 0.48 g/day (9.5 g glucose/day) and 1.44 g/day (12 g glucose/day) in females]. Liquid diet was given to the animals until death, but no glucose or ethanol was added after 104 weeks. Animals were killed when moribund or when the study was terminated, after 120 weeks. Treatment with 3% ethanol led to lower body weight in males after 13 weeks and in females after 69

weeks. Statistical analysis of survival showed that females treated with 3% ethanol survived longer than the controls ($P = 0.002$). Those treated with 1% ethanol also had a longer survival, which was not statistically significant. No statistical difference in organ weights was noted. For males, no effect of ethanol was observed on the occurrence of overall neoplasms (benign or malignant). In females, there was a statistically significant decrease in the incidence of all tumours among ethanol-exposed animals ($P < 0.01$). Pituitary tumours [not specified] were more common among high-dose ethanol-treated females (80%) than among high-dose glucose-treated animals (58%) ($P < 0.05$). Among low-dose ethanol-treated females, there was a statistically significant increase in the incidence of benign tumours in all organs as well as in mammary gland fibroma, fibroadenoma or adenoma [no incidence provided] (Holmberg & Ekström, 1995). [The Working Group noted that the ethanol intake was low relative to the high rate of ethanol metabolism in these rats and the low dose used, and that ethanol blood concentrations were not measured.]

As part of a study to investigate the influence of various chemicals on the carcinogenesis of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG), 16 male Fischer 344 rats, 5 weeks of age, received 10% ethanol in the drinking-water for 51 weeks starting at 7 weeks of age; 15 untreated male Fischer 344 rats served as a control. No forestomach tumours or glandular stomach neoplasms were observed in any of the groups (Wada *et al.*, 1998). [The Working Group noted the poor reporting of the study, the small number of animals, that the rats were not pair fed and the absence of ethanol blood measurements.]

Groups of 110 male and 110 female Sprague-Dawley rats and their offspring (30 males and 39 females) received 10% ethanol (purity > 99.8%) or no ethanol (49 male and 55 female offspring) in the drinking-water *ad libitum* starting at 39 weeks of age (breeders), 7 days before mating or from embryo life (offspring) until spontaneous death (last death at 179 weeks for offspring). Control animals received tapwater. The intake of fluid was lower in the treated compared with the control group, but no difference in body weight was noted. No significant differences in survival occurred with the exception of lower survival of female offspring treated with ethanol from 104 to 152 weeks. Full necropsies and histopathology were performed. An increase in the incidence of total malignant tumours was noted in female breeders (72% (79/110) versus 43% (48/110); $P < 0.0001$) and male offspring (76% (23/30) versus 47% (23/49); $P < 0.02$). This was due to an increase in the incidence of head and neck carcinoma (oral cavity, lips, tongue) in male breeders (13% (15/110) versus 2.7% (3/110); [$P = 0.0054$] 33% (10/30) versus 4% (2/49); [$P = 0.0014$]) and female offspring (41% (16/39) versus 5% (3/55); [$P = 0.0001$]) and that of carcinoma of the forestomach in male (7% (8/110) versus 0/110; [$P = 0.0012$]) and female (2.7% (3/110) versus 0/110 [not significant]) breeders. Increases in the incidence of interstitial-cell adenomas of the testis (21% (23/110) versus 8% (9/110); [$P = 0.013$]) and osteosarcoma of the head and other sites were also observed in male breeders (11% (12/110) versus 0.9% (1/110); [$P = 0.0042$]) (Soffritti *et al.*, 2002a). [The Working Group noted that this was not a

pair-feeding experiment, that the number of animals per litter was not reported, that ethanol intake may have been low and that no ethanol blood concentrations were measured. However, even under these experimental conditions, administration of ethanol caused an increase in tumour development, which is important to note. The Working Group also noted that some statements reporting increased incidences were not supported by statistical analyses performed by the Working Group.]

(c) Hamster

A total of 90 male and 90 female Syrian golden hamsters, 8 weeks of age, were divided into six groups and received 10% Indian country liquor or 1% ethanol in the drinking-water or pure drinking-water from the age of 2 months until 18 months. No tumours were observed after treatment with liquor in either sex. A 3% (1/29) incidence of forestomach papillomas was seen in untreated control male hamsters (Zariwala *et al.*, 1991).

3.1.2 *Dermal application*

Mouse

As part of a study on modifying effects, 24 female C3H/HeNCr(MTV-) mice, 9–10 weeks of age, were treated locally with a 25% ethanol solution on the dorsal skin, ear and tail three times a week for 30 weeks. None of the animals developed skin tumours (melanoma, squamous-cell carcinoma or fibrosarcoma) (Strickland *et al.*, 2000). [The Working Group noted the small number of animals and the absence of untreated controls.]

3.1.3 *Transplacental and neonatal administration*

(a) Mouse

A group of 27 female Swiss mice, 8 weeks of age, received 10% Indian country liquor in the drinking-water from day 12 of gestation until weaning of the progeny (total, 38 days). Weaned offspring were kept under observation until death with no further treatment. No significant changes in tumour incidence [tumour type not specified] were observed in either sex of offspring of mothers treated with liquor (3% (2/62) of males, 4% (2/53) of females) compared with untreated controls (6% (2/34) of males, 2% (1/45) of females). Breeders treated with liquor had 1/18 (5%) lung adenoma compared with none in controls (Zariwala *et al.*, 1991). [The Working Group found that the data reported were insufficient to evaluate.]

(b) Hamster

A group of four female Syrian hamsters received 10% ethanol in the drinking-water on days 5–16 of pregnancy. A control group received water only. No difference

in tumour incidence in the offspring was observed between the ethanol-treated and control groups (Schüller *et al.*, 1993).

3.1.4 *Genetically modified animals*

Mouse

Twenty-four male C57/B6 APC MIN mice, 7–8 weeks of age, received alternately 15 and 20% ethanol [purity not specified] in the drinking-water every other day for 10 weeks. The experiment was terminated after 10 weeks and histopathology was performed. Ethanol supplementation resulted in a 35% increase in intestinal tumour multiplicity (26.8 ± 8.9 versus 36.9 ± 10.1; $P < 0.05$). The increase in tumour incidence was most pronounced (67%) [multiplicity not given] in the distal small bowel ($P < 0.05$) (Roy *et al.*, 2002). [The Working Group noted that the effect of ethanol was investigated in a genetically susceptible mouse model of intestinal cancer.]

3.2 Modifying effects of ethanol on the activity of known carcinogens

Previous studies

More than 30 studies were included in this section of the previous Monograph (IARC, 1988). Long-term experiments were performed in mice, rats and hamsters, with different known carcinogens, mostly *N*-nitrosamines (see Table 3.1 for details and reference).

In experiments in which various carcinogens were administered orally with ethanol as a vehicle, ethanol enhanced the incidence of tumours of the nasal cavity induced in mice by NDMA and that of oesophageal/forestomach tumours and lung tumours induced in mice by *N*-nitrosodiethylamine (NDEA) or *N*-nitrosodi-*n*-propylamine.

In further studies, various carcinogens were administered by different routes simultaneously with ethanol in water as the drinking fluid or in liquid diets. Ethanol enhanced the incidence of benign tumours of the nasal cavity induced in rats by *N'*-nitrosonornicotine (NNN) given in a liquid diet and the incidence of nasal cavity and tracheal tumours and of neoplastic nodules of the liver induced in hamsters by *N*-nitrosopyrrolidine (NPYR) given by intraperitoneal injection. Administration of ethanol in the drinking-water enhanced the incidence of hepatocellular carcinomas and liver angiosarcomas induced in rats by inhalation of vinyl chloride.

In several other experiments, ethanol had no modifying effect on the overall incidence of tumours in mice, rats or hamsters given *N*-nitrosomethylbenzylamine (NMB_zA), *N*-nitrosobis(2-oxopropyl)amine, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG), 7,12-dimethylbenz[*a*]anthracene (DMBA) or 1,2-dimethylhydrazine (DMH) by various routes of administration.

An increase in tumour morbidity (mostly in target organs characteristic of the carcinogens used) was observed in all experiments in which ethanol was used as a vehicle

Table 3.1 Modifying effects of ethanol on the activity of various carcinogens in experimental animals (studies published before 1987 in their order of citation in IARC Monograph Volume 44, 1988)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Mice, C57BL	Groups of 29–37 males and females; 8 weeks	NDMA 0.03 mg × 2/week ig; total dose, 3 mg	40%; 0.2 mL as vehicle; total dose 20 mL	NDMA in water	50 weeks	72 weeks	Increase; olfactory tumours infiltrating brain in 12/36 (33%) males, 12/30 (40%) females; 0 in controls	Griciute *et al*. (1981)
Mice, hybrid CBA × C57BL/6	50 or 100 females/ group; weighing 10–12 g	NDMA 10 mg/L as drinking fluid	6000 mg/L as drinking fluid with NDMA	NDMA in drinking-water	9 months	9 months	No effect	Litvinov *et al*. (1986a)
Rats, Sprague-Dawley	17 females/ group; weighing 130 g	NDMA 1.5 mg ip, 5 days/week × 4 weeks; total dose, 30 mg	In liquid diet (36% of total calories) 3 weeks before carcinogen; no ethanol 1 week during and 1 week after carcinogen; 5-week cycles repeated 4 times	NDMA in isocaloric liquid diet	20 weeks	For life	No effect	Teschke *et al*. (1983)

Table 3.1 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Mice, hybrid CBA × C57BL/6	100 females/ group; weighing 10–12 g	NDEA 10 mg/L as drinking-water	6000 mg/L as drinking-water simultaneously with NDEA	NDEA in drinking-water	12 months	12 months	Increase in pulmonary tumours, mainly adenomas; 49/86 (57%) ethanol-treated, 22/79 (27.8%) controls	Litvinov *et al*. (1986b)
Mice, C57BL	32 or 38 females/ group; 8 weeks	NDPA 0.03 mg ig, 2 × week; total dose, 3 mg	40% (w/v) 0.2 mL; total dose, 20 mL (6.4 g 100% ethanol) as vehicle	NDPA in water	50 weeks	72 weeks	Increase in spinocellular carcinoma, oesophagus/ forestomach carcinoma; 36/70 (51%) ethanol-treated, 7/70 (10%) controls; $p<0.00005$	Griciute *et al*. (1982)
Rats, albino (similar to BDII)	28 or 20 animals/ group, sex distribution unspecified; 10–12 weeks	NDEA 3 mg/kg bw in drinking-water daily; total dose, 700 ± 71 mg/kg bw; 730 ± 67 mg/kg bw in brandy-treated group	40 mL commercial brandy (38% alcohol) as drinking fluid simultaneously; total dose, 8100 mL/kg bw	NDEA in drinking-water	For life	For life	Reduction in hepatocellular carcinoma; 16/20 (80%) brandy-treated, 28/28 (100%) controls [no weight gain and high mortality in brandy-treated group]	Schmähl *et al*. (1965)

Table 3.1 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Sprague-Dawley	13–27 males and females/ group; 3 months	NDEA 2.5 or 10 mg/kg bw daily ig; total dose, 607 or 1867 mg/kg bw; 529 or 1806 mg/kg bw in ethanol-treated group	0.5 mL 30% (w/v) as vehicle; total dose 106 or 90 mL/kg bw	NDEA in water	For life	For life	Increase in benign and malignant oesophago-forestomach tumours	Gibel (1967)
Rats, Sprague-Dawley	90 males/ group; 14 weeks	NDEA 0.1 mg/ kg bw day in drinking-water; 5 days/week	5 mL 25% in water as drinking fluid; 5 days/week	NDEA in water	For life	For life	Decrease in oesophago-forestomach and liver tumours	Habs & Schmähl (1981)
Rats, Sprague-Dawley	72 females; weighing 100 g	NDEA 100 mg/ kg bw ip 1 day prior to the start of ethanol and 2 months later; 1 group choline-supplemented, another choline-deficient diet	32–25% w/v as drinking fluid	NDEA without ethanol (2 groups); choline-deficient diet only (neither NDEA nor ethanol; 1 group)	10 months	10 months	No effect; several lung and kidney tumours in rats fed choline-deficient diet only	Porta *et al.* (1985)

Table 3.1 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Wistar	Males [number not indicated]; weighing 120 g	NDEA 30 mg/kg bw ip × 1	5% in water as drinking fluid 1 week after carcinogen	NDEA in tap-water	18 months	18 months	Carcinoma formation with a high incidence of clear-cell foci or basophilic foci and hyperplastic nodules	Driver & McLean (1986)
Wistar rats	10 or 5 males/group; weighing 180–200 g	NDEA 10 mg/kg bw; 24 h after partial hepatectomy	20% ethanol + 10% sucrose as drinking fluid; 110 mL/kg bw (15.4 g/kg bw daily) 8 weeks after	NDEA in tap-water	40 weeks	40 weeks	Increase in hepatocellular nodules in ethanol-treated group $p<0.05$	Takada *et al*. (1986)

Table 3.1 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Mice, C57BL	38 males and 32 females/ group; 8 weeks	NDEA 0.03 mg ig, 2 ×/week; total dose, 3 mg	40% 0.2 mL ethanol:water solution; total dose, 20 mL (6.4 g 100% ethanol) as vehicle	NDEA in tap-water	50 weeks	78 weeks	Increase in spinocellular oesophageal/ forestomach cancer in ethanol-treated group: 13/38 (34%) males, 19/31 (61%) females versus 4/38 (10%) male, 3/32 (9%) female controls; decrease in lymphomas in ethanol-treated group: 21/69 (30%) versus 45/70 (64%) controls	Griciute *et al*. (1984)

Table 3.1 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Mice, C57BL	70 animals/ group; [age and weight unspecified]	Mixture of 0.01 mg NDMA, 0.01 mg NDEA, 0.01 mg NDPA; ig 2 ×/week; total doses: NDMA, 1.0 mg; NDEA, 1.0 mg; NDPA, 1.0 mg	40% as vehicle	NDMA in water	50 weeks	79 weeks	Increase in forestomach/ oesophageal carcinoma: 35/70 (50%) versus 8/70 (11%) controls; pulmonary adenoma, 55/70 (78%) versus 34/70 (48%) controls; olfactory tumours: 2/70 (3%) versus 0/70 controls	Griciute *et al*. (1987)
Rats, Sprague-Dawley	40 males/ group, weanling	NMB_zA 2 mg/ kg bw ig 2 × week, 4 weeks; zinc-deficient diet	4% in deionized water as drinking fluid, 4 weeks before carcinogen	NMB_zA in deionized water without ethanol	29 weeks	29 weeks	No effect	Gabrial *et al*. (1982)

Table 3.1 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Sprague-Dawley	48 animals/ group; 13 weeks	NMPhA 2.0 or 10.0 mg/kg bw sc weekly for 39 or 24 weeks; or 0.3 or 1.5 [presumably mg/kg bw] in drinking-water for 29 or 22 weeks	25% (about 30 mL/kg bw) in water 5 ×/week	NMPhA without ethanol in drinking-water or sc	22–39 weeks	For life	No effect	Schmähl (1976)
Rats, Fischer 344	28 males/ group; weighing 160 g	NPIP 0.06% in basal diet; 8 weeks	10% in drinking-water for 12 weeks; 1 mL 50% into pharynx 2 ×/week for 8 weeks with or without 10% in drinking-water for 12 weeks	NPIP without ethanol	20 weeks	20 weeks	No effect	Konishi *et al*. (1986)

Table 3.1 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Sprague-Dawley	20 animals/group [sex distribution unspecified]; 3 months	DNPIP 5 mg/kg bw ig/day; total dose, 2605 mg; 2250 mg in ethanol-treated group	0.5 mL 30% (v/v) as vehicle ig for life	DNPIP	For life	For life	No differences in number of tumours; appearance of the first tumour at day 450 in ethanol-treated groups and day 521 in control group	Gibel (1967)
Rats, Fischer 344	26–30 males/group; 9 weeks	NNN at 13 weeks of age; groups 1, 2: 10 mg/kg bw sc; 3 alternate days/week (56–66 injections); total dose, 177 mg/rat; groups 3, 4: 17.5 mg/L NNN in liquid diet for 27 weeks; total dose, 177 mg/rat	Groups 2 and 4 6.6% w/v (35% of calories) in liquid diet simultaneously	Control liquid diet (groups 1 and 3)	22–27 weeks	To 98 weeks of age	Groups 1 and 2, no effect; groups 3–6 increase in nasal cavity tumours ($p<0.05$)	Castonguay *et al*. (1984)

Table 3.1 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, BD	50 animals/ group; young adult	NNN 0.3, 1.0 or 3.0 mg/rat ig 2 ×/week; total dose, 46.8, 156 or 468.0 mg/rat	40% aqueous solution as vehicle	NNN in water	78 weeks	Until 120 weeks of age	Morbidity from olfactory tumours slightly elevated in ethanol-treated groups; time of appearance of the first tumour shorter in all ethanol-treated groups	Griciute *et al*. (1986)
Hamsters, Syrian golden	21 males/ group; 9 weeks	NNN at 13 weeks of age; 0.5 mL ip of 2.37 or 4.74 mg/animal 3 ×/week, 25 weeks; total dose, 177 or 354 mg	6% w/v; 35% caloric intake in liquid diet before and during administration of NNN	NNN and liquid diet without ethanol	29 weeks	4 weeks and 18 months	No effect	McCoy *et al*. (1981)
Hamsters, Syrian golden	21 males/ group; 9 weeks	NPYR at 13 weeks; 0.5 mL ip of 1.33 or 2.67 mg/animal 3 ×/week, 25 weeks; total dose, 100 or 200 mg	6% w/v; 35% in isocaloric diet before and during administration of NPYR	NPYR in liquid diet without ethanol	29 weeks	4 weeks and 18 months	Higher morbidity from nasal cavity and tracheal tumours; $p<0.05$	McCoy *et al*. (1981)

Table 3.1 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Hamsters, Syrian golden	27 males/ group; 9 weeks	NPYR 1.33 mg/ animal ip 3 ×/week, 25 weeks; total dose, 100 mg/ animal	7.4% or 18.5% in water as drinking fluid for 4 weeks before and during NPYR administration	NPYR and tap-water without ethanol	29 weeks	4 weeks and 17 months	Increase in hepatic neoplastic nodules; $p<0.01$	McCoy *et al*. (1981)
Hamsters, Syrian	15 males/ group; 6 weeks; weighing 80–100 g	NDOPA 20 mg/ kg bw sc × 1, 2 weeks after the start of ethanol treatment	25% in water w/v as drinking fluid	Water	24 weeks	24 weeks	Reduction in pancreatic tumours: 0/13 ethanol-treated, 11/14 (78%) non-ethanol-treated	Tweedie *et al*. (1981)
Hamsters, Syrian golden	20 or 40 animals/ group; 8 weeks	NDOPA 20 mg/ kg bw sc before or 4 weeks after beginning of ethanol treatment	5% (w/v) in water as drinking fluid	NDOPA single injection, no ethanol	46 weeks	46 weeks	No significant difference in pancreatic tumours	Pour *et al*. (1983)
Rats, Wistar	21 or 30 males/group; 7 weeks	MNNG 100 mg/L in drinking-water simultaneously with a 10% saline-supple-mented diet for 8 weeks	10% in drinking-water after MNNG administration	MNNG for 8 weeks in drinking-water	40 weeks	40 weeks	No increase in adenocarcinomas in glandular stomach	Takahashi *et al*. (1986)

Table 3.1 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, inbred Fischer	4–12 animals/ group; 4–6 weeks	OH-AAF 160 mg/kg in semisynthetic diet	10 or 20% by vol. in drinking-water simultaneously with or after treatment with OH-AAF	Drinking-water, without ethanol	12–20 weeks	40 weeks	No effect	Yamamoto *et al*. (1967)
Rats, NIH random-bred black	20 animals/ group; weanling	OH-AAF 80 mg/kg in the diet	10% in drinking-water	Water alone	64 weeks	64 weeks	No significant increase in hepatomas	Yamamoto *et al*. (1967)
Rats, Fischer 344	26 males/ group; 10 weeks; weighing 170–210 g	Azoxymethane 7 mg/kg bw sc in sterile water 1 ×/week, 10 weeks, 3 weeks after start of experiment	Isocaloric liquid diet containing 12 or 23% of calories as beer, 9 or 18% as ethanol (before and during carcinogen administration)	Liquid diet without ethanol	26 weeks	26 weeks	Decrease in colon cancers in high-dose group (18 versus 45 controls); no effect with low dose (37 versus 45 controls)	Hamilton *et al*. (1987a)

Table 3.1 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Fischer 344	35 males/ group; 10 weeks; weighing 210–260 g	Azoxymethane 7 mg/kg bw sc 1 ×/week, 10 weeks	11, 22, 33% of calories from ethanol in liquid diets either 3 weeks before and during or for 16 weeks after carcinogen treatment	Liquid diet without ethanol	29 weeks	29 weeks	No effect when liquid ethanol diet given after carcinogen; decrease in colon cancer when higher doses given before and during carcinogen treatment	Hamilton *et al*. (1987b)
Mice, NMRI	30 or 20 females/ group [age unspecified]	DMBA 0.02 mL of a 1% solution v/v skin applications 3 ×/week	Vehicle (purity 99.5%)	Acetone as solvent	20 weeks	Unknown	Increase in skin tumours: 11/20 (55%) ethanol-treated, latency 6 weeks; 4/30 (13%) acetone-treated, latency 9 weeks; p=0.002	Stenbäck (1969)
Mice, CF1	72 and 70 males; 2 months	DMBA 0.02 mL in 1.5% acetone skin application × 1	50% aqueous solution; 0.04 mL applications in same region 1 month after DMBA; 2 ×/ week, 40 weeks	No further treatment after DMBA	Ethanol: 1 month and 40 weeks	20 weeks	No effect	Kuratsune *et al*. (1971)

Table 3.1 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Mice, CF1	46–55 males/ group; 1 month	DMBA 0.025 mL in 1.5% acetone skin application × 1	0, 12, 43% applications in same region 1 month after DMBA; 2 ×/ week, 40 weeks	No applications of ethanol	Ethanol: 1 month and 40 weeks	20 weeks	No effect at the end of treatment period	Kuratsune *et al*. (1971)
Rats, Sprague-Dawley	16 males/ group; 60 days	DMH 30 mg/ kg bw sc 1 ×/ week, 4 weeks, 4 weeks after beginning ethanol	36% of total calories (6.6 v/v) in liquid diet for 4 weeks; 3 weeks standard diet during DMH; ethanol again for 4 weeks; 4 cycles	Isocaloric diet without ethanol	28 weeks	32 weeks	Number of rectal tumours significantly higher in group given ethanol (17 versus 6)	Seitz *et al*. (1984)
Rats, D/A	20 or 40 males/group; 4–6 weeks; weighing 150–250 g	DMH 20 mg/kg bw sc 1 ×/week, 20 weeks; high- or low-fat diet	Beer or 4.8% ethanol as drinking fluid	No applications of beer or ethanol	28 weeks	28 weeks	No effect	Howarth & Pihl (1984)

Table 3.1 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Sprague-Dawley	22 males/ group; 5 weeks	DMH 15 mg/kg bw sc 1 ×/week, 16 weeks	5% (95% laboratory grade) v/v as drinking fluid from 3 weeks before carcinogen	Water as drinking fluid	19 weeks	25 weeks	No difference in number of colonic cancers	Nelson & Samelson (1985)
Rats, Sprague-Dawley	12 males/ group; 5 weeks	DMH 20 mg/kg bw sc 1 ×/week, 10 weeks	Beer as drinking fluid from 3 weeks before carcinogen	Water as drinking fluid	13 weeks	27 weeks	Decrease in gastrointestinal tumours in beer-treated (8/12 (66%) versus 12/12 (100%) DMH alone)	Nelson & Samelson (1985)
Rats, Sprague-Dawley	80 males/ group [age unspecified]	VC 600 ppm (1560 mg/m^3) inhalation 4 h/ day, 5 days/ week	5% in water as drinking fluid for life from 4 weeks before carcinogen	Water without ethanol as drinking fluid	1 year	10 months	Increases in hepatocellular carcinomas (35/80 (43%) VC, 48/80 (60%) VC + ethanol) and liver angiosarcomas (18/80 (22%) VC, 40/80 (50%) VC + ethanol); p=0.002	Radike *et al*. (1981)

Table 3.1 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Mice, C3H	30 males/ group; 8 weeks	Ethyl carbamate 2 mg/animal ig 2 ×/week; total dose, 10 mg	40% 0.2 mL as vehicle simultaneously or 24 h after ethyl carbamate	Ethyl carbamate in water	5 weeks	6 months	Increase in pulmonary adenomas with ethanol as vehicle; no effect with ethanol given 24 h after ethyl carbamate	Barauskaite (1985)
Mice, white outbred [strain unspecified]	12 males and 14 females/ group; 8 weeks	Ethyl carbamate 10 mg in 0.2 mL saline ip 2 ×/ week; total dose, 100 mg	40% 0.2 mL as vehicle	Ethyl carbamate in saline	5 weeks	12 weeks	Increase in average no. of lung adenomas per animal: 30 ethanol-treated, 13 saline-treated; p=0.002	Griciute (1981)

From IARC (1988) DMBA, 7,12-dimethylbenz[*a*]anthracene; DMH, 1,2-dimethylhydrazine; DNPIP, *N*,*N*′-dinitrosopiperazine; ig, intragastric intubation; ip, intraperitoneal injection; NDEA, *N*-nitrosodiethylamine; NDMA, *N*-nitrosodimethylamine; NDOPA, *N*-nitrosobis(2-oxopropyl)amine; NDPA, *N*-nitrosodi-*n*-propylamine; NMBzA, *N*-nitrosomethylbenzylamine; NMPhA, *N*-nitrosomethylphenylamine; MNNG, *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine; NNN, *N*′-nitrosonornicotine; NPIP, *N*-nitrosopiperidine; NPYR, *N*-nitrosopyrrolidine; OH-AAF, *N*-hydroxy-2-acetylaminofluorene; sc, subcutaneous injection; VC, vinyl chloride

for *N*-nitrosamines and other carcinogens (DMBA). Similar results were obtained in some but not all experiments when the animals received ethanol just before the administration of the carcinogen or separately but at the same time as the carcinogen. There was no effect on carcinogenesis in most experiments when ethanol was given separately and after administration of the carcinogen, or when the concentration of ethanol in the fluid used was low (5%). This suggests that ethanol may influence the initiation of carcinogenesis in some manner, but it is also possible that the process is enhanced due to some mechanistic events: the facilitation of entry into the target cell by ethanol, a change in intracellular metabolism or suppression of DNA repair. The hypothesis of competitive inhibition of hepatic metabolism of the carcinogen, which allows it to reach the target organs, has also been proposed. A change in the target organ specificity of NDMA by ethanol was observed: when NDMA was given in combination with ethanol, rats and mice developed tumours in the nasal cavity, which is not a target site for this nitrosamine.

Studies published after 1987 are reviewed below and summarized in Table 3.2.

3.2.1 *Aflatoxin B1*

Rat

A group of 29 male inbred ACI/N rats [age unspecified] received twice-weekly intraperitoneal injections of 1.5 mg/kg bw aflatoxin B_1 [purity not specified] in 200 µL dimethyl sulfoxide (DMSO) for 10 weeks (total dose, 30 mg/kg bw). One week after the last injection, 15 of the aflatoxin B_1-injected rats were given drinking-water that contained 10% ethanol [purity not specified] for 56 weeks, while the remaining 14 rats continued to receive control drinking-water. Additional rats received injections of DMSO without aflatoxin B_1 and received drinking-water that contained ethanol (15 rats) or control drinking-water (10 rats) for 56 weeks. The experiment was terminated after a total of 67 weeks, at which time the extent of liver neoplasia was assessed macroscopically and microscopically. The body weights in all groups were similar. The tumour incidence in rats treated with aflatoxin B_1 and ethanol was 13% (2/15) neoplastic nodules and 7% (1/15) hepatocellular carcinoma. Neither neoplastic nodules nor hepatocellular carcinoma were detected in any of the other groups (Tanaka *et al.*, 1989).

3.2.2 *Acetoxymethylnitrosamine*

Rat

Two groups of 20 male Sprague-Dawley rats [age unspecified], weighing 215–220 g, were fed liquid diets that contained 36% of total calories as ethanol or for which 36% was isocalorically replaced by carbohydrates for 2 weeks, after which time 2 mg/kg bw acetoxymethylnitrosamine were applied locally to the rectal mucosa once every 2 weeks. At weeks 15 and 18, the animals underwent colonoscopy and were then killed

Table 3.2 Modifying effects of ethanol on the activity of various carcinogens in experimental animals (studies published after 1987)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, inbred ACI/N	10–15 males/ group [age unspecified]	AFB_1 1.5 mg/ kg bw in 200 µL DMSO ip; 2 ×/week; total dose, 3 mg/ kg bw	10% in drinking-water, 1 week after last injection	DMSO without AFB_1 + ethanol or + drinking-water	10 weeks	67 weeks	AFB_1 + ethanol: 2/15 (13%) neoplastic nodules; 1/15 (6%) hepatocellular carcinoma; none in other groups	Tanaka *et al*. (1989)
Rats, Sprague-Dawley	20 males/ group; weighing 215–220 g	AMMN 2 mg/kg bw on rectal mucosa 1 ×/2 weeks; colonoscopy	36% of total calories 2 weeks before and during AMMN	Isocaloric diet	21 weeks	21 weeks	Incidence of tumours significantly increased in ethanol-treated at week 15 (p<0.05) but not at weeks 18 or 21	Seitz *et al*. (1990)
Rats, Sprague-Dawley	20 males/ group; weighing 215–220 g	AMMN 2mg/ kg bw on rectal mucosa 1 ×/2 weeks	2.5 mL (4.8 g/kg bw) by gavage 2 ×/day, 10 weeks before AMMN	Saline by gavage before AMMN	21 weeks	21 weeks	No effect on incidence; time to tumour occurrence significantly decreased (p=0.0295)	Seitz *et al*. (1990)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Fischer 344/ DuCrj	5–40 males/ group; 21 days	MeIQx 200 ppm in diet	0.1, 0.3, 1, 3. 10 or 20% (purity, 99.%) in drinking-water 8 weeks after start of MeQIx	Drinking-water only	24 weeks	24 weeks	Dose-dependent increase in incidence (p<0.001) and multiplicity (p<0.01) of liver tumours with 10 and 20%, and 20% ethanol, respectively	Kushida *et al*. (2005)
Rats, SPF albino Wistar	20 males/ group [age unspecified]	Azaserine 30 mg/kg bw ip × 1 at 19 days of age; high-fat diet	5% for first 2 weeks increased to 10% by 6 weeks in high-fat diet	No ethanol	447–448 days	447–448 days	No effect on pancreatic tumours	Woutersen *et al*. (1989)
Rats, Fischer 344	20 and 23 males/group; 10 weeks; weighing 210–260 g	Azoxymethane 14 mg/kg bw sc 1 ×/week, 10 weeks	33% of total calories in diet 3 weeks before and during azoxymethane	Isocaloric diet	13 weeks	29 weeks	Decrease in incidence and multiplicity of all tumours and colonic and small intestine tumours	Hamilton *et al*. (1988)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Sprague-Dawley	11–18 males/group; [age unspecified] weighing 340 g	Azoxymethane 15 mg/kg bw ig 1 ×/week, 2 weeks	8 g/kg bw/day ig in diet increased to 13 g/kg bw/day at day 10; 35 days later, reduced to no ethanol on day 39, at 9 h before and during azoxymethane; resumed 6 h later; 1-week cycle repeated once then stopped	Diet with no ethanol ig or water ig and standard diet	49 days + 2 weeks	49 days + 30 weeks	Azoxymethane and ethanol: 2/18 (11%) mucinous duodenal adenocarcinomas and 1/18 (5%) duodenal focal adenomatous changes; none in other groups	Hakkak *et al.* (1996)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Fischer 344	53 or 40 males/group; 4.5 weeks	Azoxymethane 15 mg/kg bw in saline sc 1 ×/ week, 2 weeks	Beer as drinking-water 1 week before azoxymethane	No beer and no beer and saline sc only drinking-water	42 weeks	42 weeks	Azoxymethane and beer: decreased incidence and multiplicity of colonic adenomas (46% versus 82% [p<0.01] and 0.55±0.67/rat versus 1.41±1.10/ rat [p<0.005]) and adenocarcinomas (5% versus 64% [p<0.01] and 0.09±0.43/rat versus 1.00±0.98 [p<0.05]) compared with azoxymethane and control drinking-water	Nozawa *et al*. (2004)
Mice, BALB/c	111 animals [sex unspecified]; 8 weeks	Benzo[*a*]pyrene 2 mg in 200 µL olive oil sc 1 ×	10% in drinking-water after benzo[*a*] pyrene	No ethanol	58 weeks	58 weeks	Ethanol reduced incidence of subcutaneous fibrosarcomas from 84.0% to 65.4%	Uleckiene & Domkiene (2003)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Sprague-Dawley	50 females/ group; 21 days; weighing 40–55 g	DMBA 20 mg/ kg bw in 0.1–0.2 mL sesame oil by gavage at 55 days of age	20% of calories × 3 days; 10% of calories × 4 days then 20% of calories in liquid diet	Pair fed no ethanol	34 days + 20–25 weeks	25–30 weeks	No statistically significant effect	Rogers & Conner (1990)
Rats, Sprague-Dawley	32 or 20 females/ group; 21 days; weighing 40–55 g	DMBA 30 mg/ kg bw in 0.1–0.2 mL sesame oil by gavage at 55 days of age	10% of calories × 4 weeks; 3.5 g/kg bw ethanol by gavage; control diet 1 day before and 1 day after DMBA; 10% of calories × 1 week then 25% of calories	10% fat × 1 week; no ethanol	34 days + 12–13 weeks	17–18 weeks	No effect on mammary tumorigenesis	Rogers & Conner (1990)
Rats, Sprague-Dawley	15 or 17 females; 30 days; weighing 72.6±1.0 (SE) g	DMBA 5 mg/ rat in 0.5 mL corn oil ig at 58 days of age	20% of calories in diet 4 weeks before and 1 week after DMBA	No ethanol	5 weeks	25 weeks	Incidence of mammary tumours: 82% versus 47–48% in controls ($p<0.05$)	Singletary *et al*. (1991)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Sprague-Dawley	24–33 females/ group; 25 days; weighing 49.0 ± 0.5 (SE) g	DMBA 5 mg/ rat in 0.5 mL corn oil ig at 53 days of age	10 or 20% of calories in diet 4 weeks before and 1 week after DMBA	No ethanol	5 weeks	31 weeks	Incidence of mammary tumours (mainly adenocarcinoma): 74% in 20% ethanol-treated (p<0.05) versus 47–48% in controls; no increase with 10% ethanol	Singletary *et al*. (1991)
Rats, Sprague-Dawley	92 females; 42 days; weighing 177.4±2.3 (SE) g	DMBA 5 mg/ rat in 0.5 mL corn oil ig at 56 days of age	15 or 30% of calories from 63 days of age	No ethanol	21 weeks	21 weeks	T_{50}: 150, 84 and 105 days for 0%, 15% and 30% ethanol; 0% versus 15% (p<0.05)	Singletary *et al*. (1991)
Rats, Sprague-Dawley	20 females/ group; 40 days	DMBA 15 mg in 1 mL sesame oil ig at 50 days of age	5% v/v in drinking-water	No ethanol	130 days	130 days	Tumour incidence: 100% in controls versus 40% in ethanol-treated (p<0.001)	McDermott *et al*. (1992)
Rats, Sprague-Dawley	15 pregnant females/ group; [age not specified]; 23–25 female offspring/ group	DMBA 10 mg in 1 mL peanut oil on postnatal day 47	16 or 25 g/kg diet (7 and 15% of total energy) on days 7–18 of gestation	No ethanol		17 weeks	Total number of palpable tumours/ rat significantly increased with 16 g/kg diet ethanol (p<0.006)	Hilakivi-Clarke *et al*., 2004)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Hamster, Syrian golden	36 males; 4–6 weeks	DMBA 1% solution in heavy mineral oil on right buccal pouch × 3	5% ethanol (v/v) in liquid diet 1 week after DMBA	No ethanol (pair-fed isocaloric diet)	33 weeks	35 weeks	Tumour multiplicity significantly greater with ethanol (3.29±1.02 versus 1±0.0 in controls)	Nachiappan *et al*. (1993)
Rats, Sprague-Dawley	16 males/ group; weighing 250–300 g	DMH 30 mg/ kg bw sc × 1/ week, 4 weeks; 4 cycles	36% of total calories, 4 weeks; control diet 4 weeks during DMH	No ethanol; isocaloric carbohydrates	32 weeks	32 weeks	No change in number, size or distribution of largee bowel tumours	McGarrity *et al*. (1988)
Rats, Sprague-Dawley	20–30 males and females/ group; 10 weeks	DMH 21 mg/ kg bw in water + EDTA sc 1 ×/ week	1.23 g/kg bw ethanol in drinking-water	No ethanol	18 weeks	25–27 weeks	No significant difference in tumour incidence or multiplicity	Pérez-Holanda *et al*. (2005)
Mice, A/ Ph	15 females/ group; 6.5 weeks	Ethyl carbamate 200, 500 or 1000 ppm in drinking-water	5, 10 or 20% as drinking fluid	No ethanol; no ethyl carbamate	12 weeks	12 weeks	Ethanol decreased ethyl carbamate-induced tumour multiplicity (p<0.001 with 10% and 20% ethanol)	Kristiansen *et al*. (1990)
Mice, Han/ NMRI	25 females/ group; approximately 10 weeks	0.3 mL/25 g bw of 1.5, 3.0, 7.5 or 15 g/L ethyl carbamate in tap-water by gavage daily	10% for first 3 days then 20% by gavage daily	No ethanol	8 weeks	16 weeks	No effect on ethyl carbamate-induced lung adenomas	Altmann *et al*. (1991)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Mice, C3H/HeJ	18–21 males/ group; weanling	Ethyl carbamate 10 or 20 mg/kg bw per day	12% as drinking-water or Concord red, Concord white or Johannesburg Riesling as drinking-water	No ethanol; no ethyl carbamate only water	41 weeks	41 weeks	Ethanol and wine decreased frequency of ethyl carbamate-induced tumours	Stoewsand *et al*. (1991)
Mice, BALB/c	20 males and 20 females/ group; 8 weeks	Ethyl carbamate 10 mg ip; 2 ×/ week; total dose, 100 mg	10% in drinking-water [duration not specified]	No ethanol	5 weeks	4 months	No significant differences in tumour mulciplicity	Uleckiene & Domkiene (2003)
Mice, $B6C3F_1$	48 males and 48 females/ group; 28 days	Ethyl carbamate 10, 30 or 90 ppm in drinking-water	2.5 or 5% ethanol in the drinking-water	No ethanol; no ethyl carbamate	104 weeks	104 weeks	Ethanol increased tumour incidence in females and decreased tumour incidence in males	National Toxicology Program (2004); Beland *et al*. (2005)
Rat, Wistar JCL	Females [initial number unspecified]; 4 weeks	Ethinylestradiol (0.075 mg) and norethindrone acetate (6.0 mg) in 0.5 mL olive oil ig daily	10% w/v in the drinking-water, 2–5 days/week	No ethanol; no hormones	12 montths	12 months	Ethanol increased incidence of hepatocellular carcinomas from 1/12 (8%) to 8/21(38%) ($p<0.05$)	Yamagiwa *et al*. (1991)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, ACI/N	20 or 19 males/group; 6 weeks	MAMA 25 mg/kg bw in saline ip 1 ×/week, 2 weeks	10% in drinking-water	No ethanol	414 days	414 days	Ethanol increased incidence of large intestinal adenocarcinomas (15/17 (94%) versus 9/16 (56%) controls; p=0.040) and rectal neoplasms (10/17 (59%) versus 3/16 (19%); p=0.019)	Niwa *et al.* (1991)
Rats, ACI/N	15 females/group; 6 weeks	MAMA 25 mg/kg bw in saline ip 1 ×/week, 2 weeks	Saké (ethanol content, 15–16%), 50% saké (ethanol content, 7.5%), 15% ethanol, 7.5% ethanol	No ethanol; no MAMA	280 days	294 days	Ethanol increased non-significantly incidences of rectosigmoidal colonic neoplasms	Niwa *et al.* (1991)
Rats, Wistar	80 males/group; 55 weeks	MeDAB 0.06% in diet, 4 weeks	5, 10 or 15% in drinking-water 2 weeks after MeDAB	No ethanol; no MeDAB	47 weeks	53 weeks	No significant effect	Yanagi *et al.* (1989)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Fischer 344	Males [initial number unspecified]; 4–6 weeks	NNK 20 mmol/kg gavage 3 ×/week, 4 weeks	36% of total calories in liquid diet	No ethanol	55 weeks	55 weeks	Ethanol increased incidences of tumours of oesophagus, oral cavity, lungs and liver (p<0.05); increase in mean frequency and size of tumours (p<0.001)	Nachiappan *et al*. (1994)
Hamster, Syrian	4 pregnant females/group; [age unspecified]	NNK 50 mg/kg bw on day 15	10% in drinking-water on gestation days 5–16	No ethanol	2 weeks	45 weeks	Ethanol increased incidence of tumours in male and female offspring (p<0.01)	Schüller *et al*. (1993)
House musk shrews, Jic:SUN	4, 25 or 30 females/group; 5 weeks	MNNG 50 ppm in tap-water	2, 5 or 10% in drinking-water	Tap-water	30 weeks	45 weeks	No significant effect	Shikata *et al*. (1996)
Rats, Wistar	15 males/group; 6 weeks	MNNG 50 µg/mL in drinking-water, 20 weeks	2.5 mL/kg 20% in saline ip, every other day from week 21 to week 52	No ethanol	52 weeks	52 weeks	Ethanol increased tumour incidence (p<0.02) and multiplicity (p<0.01)	Iishi *et al*. (1989)
Rats, ACI	30 and 25 males; 4 weeks; weighing 58 g	MNNG 0.25 mL/10 g bw of 5 g/L solution ig × 1	10% in drinking-water	No ethanol	1 year	1 year	No effect	Watanabe *et al*. (1992)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Wistar	20 males/ group; weighing 150–200 g	MNNG 100 µg/mL in drinking-water	MNNG in 11% ethanol or wine	No ethanol	6 months	13 months	Ethanol significantly reduced the development of gastroduodenal tumours	Cerar & Pokorn (1996)
Rats, Fischer	15 males/ group; 6 weeks	MNNG 150 mg/kg bw ig × 1	10% in drinking-water 1 week after MNNG, 51 weeks	No ethanol	51 weeks	52 weeks	Ethanol significantly reduced incidence of stomach and oesophageal papillomas and carcinomas	Wada *et al*. (1998)
Mice, Swiss (NIH: Cr(S))	Females [initial number unspecified]; 4 weeks	MNA 60 or 180 mg/kg bw ig 3 ×/week, 12 weeks	15% in drinking-water	No ethanol	12 months	18 months	Ethanol significantly increased incidence of thymic lymphomas (from 21/49 (43%) to 32/50 (64%); $p<0.05$)	Anderson *et al*. (1993)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Sprague-Dawley	32 females/ group; 23 days	30 mg/kg bw MNU ip × 1 at 50 days of age	15, 20 and 30% of calories in diet 22 days before MNU and 26 days after	No ethanol	4 weeks	8 weeks	15% ethanol significantly increased incidence of mammary adenocarcinomas/ rat (2.2±0.3 versus 1.4±0.2); no effect with other doses. No significant difference was observed for 20% and 30% ethanol-treated groups.	Singletary *et al*. (1995)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Sprague-Dawley	30–32 females/ group; 38 days	30 mg/kg bw MNU ip × 1 at 51 days of age	15, 20 and 30% of calories in diet 1 week after MNU	No ethanol	4 weeks	7 weeks	15% ethanol significantly increased incidence of palpable mammary tumours/rat (3.2±0.4 versus 2.0±0.3) and mammary adenocarcinomas/ rat (4.4±0.5 versus 2.3±0.4); adenocarcinomas also increased with 20% ethanol compared with calorically restricted controls (3.0±0.5 versus 1.8±0.3)	Singletary *et al*. (1995)
Hamsters, Syrian golden	40 males; weanling [age unspecified]	BOP 20 mg/ kg bw sc × 1 at 6 weeks of age and × 1 at 7 weeks of age	5–10% in high-fat diet	No ethanol	372–373 days after BOP	372–373 days after BOP	No effect	Woutersen *et al*. (1989)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Mice, A/JNCr	Males [initial number unspecified]; 4 weeks	NDEA 6.8 ppm in drinking-water	10% in drinking-water	No ethanol	4 weeks	36 weeks	Ethanol increased incidence (from 42/50 (84%) to 50/50 (100%)) and multiplicity (from 1.5±1.2 to 5.8±2.2; $p<0.01$) of lung tumours and forestomach tumours (from 1/50 (2%) to 16/50 (32%))	Anderson *et al*. (1993)
Rats, Fischer 344	30 or 28 males/group; 6 weeks	NDEA 50 ppm in drinking-water	10% in drinking-water	No ethanol	8 weeks	104 weeks	Ethanol increased incidence of oesophageal papillomas and carcinomas (from 2/28 (7%) and 1/28 (3%) to 10/26 (38%) and 8/26 (30%), respectively; $p<0.01$)	Aze *et al*. (1993)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Mice, A/JNCr	50 males/group; 4 weeks	NDMA 0.5, 1 or 5 ppm in drinking-water	10 or 20% in drinking-water	No ethanol	16 weeks	16 weeks	10% ethanol increased incidence of lung tumours; 20% ethanol increased average number of lung tumours with high-dose but not low-dose NDMA	Anderson (1988)
Mice, A/JNCr	25–50 males/group; 4–6 weeks	NDMA 5 ppm in drinking-water, 4 weeks; 1 ppm in drinking-water, 16, 32, 48 or 72 weeks; 1 or 5 mg/kg bw ig × 1; 1 mg/kg bw ig, ip, sc or iv 5 ×/week, 4 weeks	5, 10 or 20% in drinking-water	No ethanol	4 weeks; 16, 32, 48 or 72 weeks; 16 weeks; 36 weeks	16 weeks; 16, 32, 48 or 72 weeks; 16 weeks; 36 weeks	Ethanol at all doses increased the incidence and multiplicity of tumours in mice treated with NDMA in drinking-water or 5 mg/kg bw ig; no effect with other routes of administration	Anderson *et al*. (1992)
Rats, MRC Wistar	25 or 40 males/group; 6 weeks	NMAA 25 mg/kg bw in 5 mL water ip × 1/week, 3 weeks, at 7, 8 and 9 weeks of age	20% (21% of 95%) in water, 2 weeks; then 10%	No ethanol	For life	For life	No significant difference in tumour incidence	Mirvish *et al*. (1994)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Mice, C57BL/6	15 or 17 females/ group; 4–6 weeks of age	NMB_zA 0.2 mg/kg bw orally in corn oil; 3 ×/week, 3 weeks (total dose, 1.8 mg/ kg bw)	30% total calories, 3 weeks	No ethanol	25 weeks	25 weeks	Ethanol increased incidence of oesophageal tumours (from 6/15 (40%) to 10/17 (59%)) and multiplicity (from 8.2±2.5 to 14.3±2.8; $p<0.001$)	Eskelson *et al*. (1993)
Rats, Sprague-Dawley	Males [initial number unspecified]; weanling; weighing 70–120 g	NMB_zA 2.5 mg/kg bw ip 3 ×/week, 3 weeks	7% in diet 1 week after NMB_zA or 9 weeks before and during NMB_zA	No ethanol	17 months or 13 weeks	20 months of age	Ethanol after NMB_zA decreased frequency and size but increased incidence of oseophageal tumours; ethanol before NMB_zA significantly decreased incidence of oesophageal tumours (from 10/26 (38%) to 3/13 (23%) ; $p<0.01$)	Mufti *et al.* (1989)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Rats, Sprague-Dawley	39 or 35 males; [age unspecified]	NMB_zA 2.5 mg/kg bw in diet × 2/week, 3 weeks	10% in drinking-water 2 weeks before NMB_zA	No ethanol	5 weeks	~20 weeks	No difference in tumour incidence	Newberne *et al*. (1997)
Rats, Fischer 344/DuCrj	15 males/group; 6 weeks	NMB_zA 500 µg/kg bw in DMSO sc 3 ×/week, 5 weeks	3.3 and 10% in drinking-water after end of NMB_zA, 15 weeks	No ethanol; no NMB_zA	20 weeks	20 weeks	No difference in incidence or multiplicity of oesophageal tumours	Morimura *et al*. (2001)
Rats, Fischer 344/DuCrj	15 males/group; 6 weeks	NMB_zA 100 or 500 µg/kg bw in DMSO sc 3 ×/week, 5 weeks	10% in drinking-water, 5 or 24 weeks	No ethanol	24 weeks	29 weeks	No difference in incidence or multiplicity of oesophageal tumours	Kaneko *et al*. (2002)
Rats, albino Wistar	10 males/group; weighing 156±15 g	NMB_zA 100 µg/kg bw ip 2 ×/week, 10 weeks	5% (36% of total calories) in liquid diet 8 weeks before and after NMB-zA	No ethanol	30 weeks	30 weeks	Ethanol increased the incidence, mean size and mean number per rat of oesophageal tumours	Tsutsumi *et al*. (2006)
Rats, Fischer 344	Males [initial number unspecified]; 4–6 weeks	NNN 40 mmol/kg by gavage 3 ×/week, 4 weeks	7% (36% of total calories) in diet 1 week after end of NNN	No ethanol	60 weeks	60 weeks	Ethanol increased incidence ($p<0.05$), mean frequency and size ($p<0.001$) of tumours of oesophagus, oral cavity and lung	Nachiappan *et al*. (1994)

Table 3.2 (continued)

Species, strain	No., sex, age or weight	Carcinogen: doses, route of administration	Ethanol: doses, route of administration	Control	Duration of experiment	Length of observation	Results	Reference
Mice, *Mus musculus*	16–48 females/ group; 3 months	NDEA/NNN: 0.04 mL/L NDEA on days 4–7; 30 mg/L NNN on days 1–3 then NDEA on days 4–7 in drinking-water	6% in drinking-water	No ethanol	28 weeks	28 weeks	No difference in incidence of invasive oesophageal carcinoma	Gurski *et al*. (1999)
Mice, A/ JNCr	Males [initial number unspecified]; 4 weeks	NPYR 6.8 or 40 ppm in drinking-water, 4 weeks	10% in drinking-water	No ethanol	4 weeks	36 weeks	Ethanol increased incidence and multiplicity of lung tumours	Anderson *et al*. (1993)
Rats, white [not further specified]	140 males; [age unspecified]	NSEE 50 mg/ kg bw io 5 ×/ week, 4 months	0.5 mL 40% io 3 ×/week, 8 months	No ethanol	8 months	8 months	No effect on incidence or multiplicity of tumours	Alexandrov *et al*. (1989)

AFB_1, aflatoxin B_1; AMMN, acetoxymethylnitrosamine; BOP, *N*-nitrosobis(2-oxopropyl)amine; DMBA, 7,12-dimethylbenz[*a*]anthracene; DMH, dimethylhydrazine; DMSO, dimethylsulfoxide; EDTA, ethylene diamine tetraacetic acid; ig, intragastric administration; io, intraoesophageal administration; ip, intraperitoneal injection; iv, intravenous injection; MAMA, methylazoxymethanol acetate; MeDAB, 3′-methyl-4-dimethylaminobenzene; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline; MNA, N^6-(methylnitroso)adenosine; MNNG, *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine; MNU, *N*-methyl-*N*-nitrosourea; NDEA, *N*-nitrosodiethylamine; NDMA, *N*-nitrosodimethylamine; NMAA, *N*-nitrosomethylamylamine; NMB_zA, *N*-nitrosomethylbenzylamine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)butanone; NNN, *N*′-nitrosonornicotine; NPYR, *N*-nitrosopyrrolidine; NSEE, *N*-nitrososarcosin ethyl ester; sc, subcutaneous injection; SE, standard error; T_{50}, number of days required for 50% of rats to develop palpable tumours

after 21 weeks. The tumour incidence was significantly increased in ethanol-treated rats compared with controls at week 15 ($P < 0.05$), but not at weeks 18 or 21. The time-to-tumour occurrence was significantly decreased in ethanol-treated rats compared with controls ($P = 0.0245$, two-sided). In a second experiment, 40 male Sprague-Dawley rats [age unspecified], weighing 280–290 g, received either 2.5 mL ethanol (4.8 g/kg bw) or saline by gavage twice daily for 10 weeks, followed by local application of 2 mg/kg bw acetoxymethylnitrosamine to the rectal mucosa once every 2 weeks. No significant difference in tumour incidence was seen between ethanol-treated and control rats at weeks 15, 18 or 21; the time-to-tumour occurrence was significantly decreased in ethanol-treated rats compared with controls ($P = 0.0295$, two-sided) (Seitz *et al.*, 1990).

3.2.3 *2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx)*

Rat

A total of 210 male Fischer 344/DuCrj rats, 21 days of age, were fed 200 ppm 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) [purity not specified]. Water was provided *ad libitum* for the first 8 weeks. After 8 weeks and during 16 weeks, the rats continued to receive MeIQx in the diet but were subdivided such that 40 rats received control drinking-water, 30 rats each received 0.1%, 0.3%, 1%, 3% or 10% ethanol (purity, 99.5%) in the drinking-water and 20 rats received 20% ethanol in the drinking-water. An additional 10 rats were fed control diet for the first 8 weeks. Five of these rats were then given 20% ethanol in the drinking-water, while the other five continued to receive control drinking-water. The experiment was terminated after 24 weeks and livers were examined histologically. Rats administered 20% ethanol had significantly decreased body weights. Liver neoplasms were present only in groups administered MeIQx. [The Working Group noted the small number of rats that were not exposed to MeIQx.] In rats that were given MeIQx in the diet, the incidence of hepatocellular adenoma, hepatocellular carcinoma and hepatocellular adenoma plus hepatocellular carcinoma was increased by consumption of ethanol in a dose-dependent manner ($P < 0.001$). The incidence of hepatocellular adenoma and hepatocellular adenoma plus hepatocellular carcinoma was significantly and dose-dependently increased in groups administered MeIQx and 10% or 20% ethanol compared with the group that received MeIQx alone ($P < 0.01$); the incidence of hepatocellular carcinoma was increased significantly in rats that received MeIQx and 20% ethanol ($P < 0.01$). The multiplicity of hepatocellular adenoma and hepatocellular adenoma plus hepatocellular carcinoma was significantly and dose-dependently increased in the groups administered MeIQx and 20% ethanol compared with the group that received MeIQx alone ($P < 0.01$) (Kushida *et al.*, 2005).

3.2.4 *Azaserine*

Rat

A group of 40 male weanling SPF albino Wistar rats [age not specified] received either a high-fat diet (25% corn oil) or a high-fat diet plus ethanol. Ethanol was dissolved in tap-water and the concentration was gradually increased starting at day 25 from 5% during the first 2 weeks to a final concentration of 10% which was reached within 6 weeks. The animals received a single intraperitoneal injection of 30 mg/kg bw azaserine at 19 days of age and were killed on days 447 and 448 thereafter. No effect of ethanol on pancreatic adenomas or carcinomas was noted (Woutersen *et al*., 1989).

3.2.5 *Azoxymethane*

Rat

Groups of 20 and 23 male Fischer 344 rats, 10 weeks of age and weighing 210–260 g, were fed diets that contained 33% of total calories as ethanol or for which 33% was isocalorically replaced by carbohydrates for 3 weeks before and during subcutaneous administration of 14 mg/kg bw azoxymethane per week for 10 weeks. The ethanol-fed group was then given the ethanol-free diet until they were killed, 16 weeks after the last injection. The prevalence and multiplicity of all tumours observed as well as those of colonic and small intestinal tumours separately were found to be decreased by ethanol (Hamilton *et al*., 1988).

Male Sprague-Dawley rats [age not specified], weighing 340 g, were implanted with a single gastric cannula; 14 days later, rats were randomly assigned to three different groups. One group of 18 rats was infused with a liquid diet that contained ethanol, a second group of 11 rats was infused with the same diet without ethanol and a third group of 13 rats was infused with a volume of water equal to that of the liquid diet given to the other two groups. The liquid diets were infused at a rate of 160 kcal/kg$^{0.75}$/day over 23 hours. Ethanol was initially provided at a dose of 8 g/kg bw per day and this was gradually increased to 13 g/kg bw ethanol per day by day 10. All rats had ad-libitum access to drinking-water. Rats in the third group were given ad-libitum access to standard rat chow. Thirty-five days after the start of gastric infusion, the amount of ethanol was gradually decreased over a period of 4 days, for rats on the ethanol diet, at which time the dietary infusions were stopped. Nine hours later, 15 mg/kg bw azoxymethane [purity not specified] in sterile water were infused and dietary infusion was resumed 6 hours later. This sequence was repeated 1 week later. After the second azoxymethane infusion, all rats were maintained on standard rat chow until the end of the experiment at 30 weeks, at which time the extent of gastrointestinal neoplasia was determined histologically. Two of 18 rats that received azoxymethane and ethanol developed well-differentiated mucinous adenocarcinomas in the duodenum and another rat in the same group had focal adenomatous changes in the duodenum. No

neoplastic or preneoplastic changes were observed in the gastrointestinal tract in any of the other groups (Hakkak *et al.*, 1996).

A group of 93 male Fischer 344 rats, 4.5 weeks of age, were administered either control drinking-water (53 rats) or drinking-water consisting of beer (brewed from Munich malt, Pilsner malt and hops; 40 rats). One week later, 40 of the rats that received the control drinking-water and all of the rats that received beer were given two subcutaneous injections of 15 mg/kg bw azoxymethane [purity not stated] in saline [volume not stated] at 1-week intervals. The remaining 13 rats that received control drinking-water were given two subcutaneous injections of saline. The experiment lasted 42 weeks. Body weights of the rats injected with azoxymethane were significantly lower than those of rats injected with saline ($P < 0.05$). All of the saline-treated rats survived to the end of the experiment; 45% of the rats from each of the azoxymethane-treated groups died. Colonic tumours were assessed histologically: none were observed in rats treated with saline. In rats administered azoxymethane and control drinking-water, the incidence and multiplicity (± SD) of colonic adenomas were 46% and 0.55 ± 0.67 tumours/rat and those of colonic adenocarcinomas were 82% and 1.41 ± 1.10 tumours/rat, respectively. The incidence ($P < 0.01$) and multiplicity ($P < 0.005$) of adenomas was significantly decreased in rats that were injected with azoxymethane and received beer compared with rats that were injected with azoxymethane and received control drinking-water. In rats administered azoxymethane and beer, the incidence and multiplicity of adenomas were 5% and 0.09 ± 0.43 tumours/rat and those of adenocarcinomas were 64% and 1.00 ± 0.98 tumours/rat, respectively. The multiplicity ($P < 0.05$) of adenocarcinomas was significantly decreased in rats that were injected with azoxymethane and received beer compared with rats that were injected with azoxymethane and received control drinking-water (Nozawa *et al.*, 2004).

3.2.6 *Benzo[a]pyrene*

Mouse

Male and female BALB/c mice [number and sex distribution per group not specified], 8 weeks of age, were given a single subcutaneous injection of 2 mg benzo[*a*]pyrene in 200 µL olive oil and were then administered 0 or 10% ethanol in the drinking-water *ad libitum* [duration of ethanol administration not specified]. All mice survived until 58 weeks after the start of the experiment, at which point it was terminated. At 10 weeks, 20% of the mice in the benzo[*a*]pyrene-treated group and 3.8% of the mice in the benzo[*a*]pyrene plus ethanol-treated group had developed tumours. At 18 weeks, the tumour incidence was 60 and 46.1% in the benzo[*a*]pyrene- and benzo[*a*]pyrene plus ethanol-treated groups, respectively. At the end of the experiment, the tumour incidences were 84.0 and 65.4%, respectively. All tumours were subcutaneous fibrosarcomas (Uleckiene & Domkiene, 2003).

3.2.7 *7,12-Dimethylbenz[a]anthracene (DMBA)*

(a) Rat

Two experiments were performed to investigate the effect of ethanol on DMBA-induced mammary gland carcinogenesis. Three groups of 50 female Sprague-Dawley rats, 21 days of age and weighing 40–55 g, were fed a liquid diet that supplied 20% of calories as fat for 3 days. One group was then continued on the same diet (*ad libitum*), one group was fed 10% of calories as ethanol for 4 days and then 20% of calories as ethanol for the remainder of the experiment (*ad libitum*) and the third group was fed control diet pair-fed by calories (20% of calories as fat) each day to an individually matched ethanol-treated rat (experiment 1). Rats had free access to distilled water at all times. At 55 days of age, the animals were given a single dose of 20 mg/kg bw DMBA in 0.1–0.2 mL sesame oil by gastric gavage. All animals were necropsied 20–25 weeks after exposure to DMBA. No statistically significant effect of ethanol ingestion on mammary gland tumorigenesis was observed between the ethanol-treated and pair-fed control groups or between the control group and either of the other groups (64–70% mammary tumour incidence). [Blood ethanol concentrations were measured.] In the second experiment, female Sprague-Dawley rats, 21 days of age, were fed a liquid diet that provided 10% of calories as fat for 1 week and were then kept on the same diet (20 rats), or paired by weight into ethanol-treated (32 rats) and pair-fed control (32 rats) groups. Ethanol-treated rats were fed 10% of calories as ethanol for 4 weeks; at the beginning of the 4th week, all ethanol-treated rats were given a single dose of 50% ethanol (3.5 g/kg bw by gavage); their pair-fed partners were given the equivalent calories as sucrose. One week later, at 55 days of age, all rats were given 30 mg/kg bw DMBA in 0.1–0.2 mL sesame oil by gavage; ethanol-treated rats were fed control diet for 1 day before and 1 day after DMBA administration, returned to 10% of calories as ethanol for 1 week and then fed 25% of calories as ethanol for the remainder of the experiment. For one 24-hour period at 10, 13, 14, 15 and 18 weeks of age, dietary ethanol was raised to 35% of calories. The experiment was terminated and rats were necropsied 12–13 weeks after exposure to DMBA. Histological diagnoses were made of mammary tumours, liver and other organs when abnormal. No detectable effect of ethanol ingestion on mammary tumorigenesis (80–94% mammary tumour incidence) was observed (Rogers & Conner, 1990). [The Working Group noted the very high tumour response in all groups.]

The influence of chronic ethanol intake on the initiation and promotion stages of mammary tumour development was evaluated in three separate studies. Experiments 1 and 2 were designed to evaluate the influence of ethanol intake on the initiation stage of DMBA-induced mammary tumorigenesis. Female Sprague-Dawley rats, 21–22 days of age, were fed a liquid control diet. At 30 days of age, rats in experiment 1, weighing 72.6 ± 1.0 (SE) g, were fed diets that contained ethanol at 0 (15 rats) and 20% (17 rats) of calories. At 25 days of age, rats in experiment 2, weighing 49.0 ± 0.5 (SE) g, were fed ethanol at 0 (33 rats), 10 (24 rats) and 20% (31 rats) of calories. Rats were

pair-fed on a daily basis. Serum ethanol concentration was measured after 4 and 12 hours in subgroups of animals fed the diet that contained ethanol. Diets were removed 18–24 hours before intragastric administration of 5 mg/rat DMBA in 0.5 mL corn oil at 58 (experiment 1) or 53 (experiment 2) days of age. The rats were returned to the diets that contained ethanol until 1 week after DMBA treatment, after which time all rats were fed a powdered control diet. Experiments 1 and 2 were terminated at 20 and 26 weeks after administration of DMBA, respectively. Experiment 3 was designed to evaluate the effect of ethanol intake on the promotion or post-initiation stage: 92 female Sprague-Dawley rats, 42 days of age, were fed the powdered control diet for 2 weeks. At 56 days of age, all rats were administered 5 mg/rat DMBA in 0.5 mL corn oil intragastrically. At 63 days of age, the animals, weighing 177.4 ± 2.3 (SE) g, were separated into three treatment groups that were pair-fed diets that contained ethanol at 0 (31 rats), 15 (30 rats) or 30% (31 rats) of calories for the remainder of the study. The experiment was terminated 21 weeks after administration of DMBA. At necropsy, tumours were removed and examined histologically. For statistical analysis, the χ^2 test, median test and the Student's *t* test were applied. Rats that consumed ethanol at 20% of total calories before administration of DMBA had a mammary tumour incidence of 82 (experiment 1; $P < 0.05$) and 74% (mainly adenocarcinomas; experiment 2; $P < 0.05$) compared with an incidence of 47–48% in rats fed the control diet. No increased tumour incidence was found in rats fed the 10% ethanol diet in experiment 2. Classification of tumours from experiment 1 was not performed. No differences in multiplicity or latency of tumours were observed in experiments 1 and 2. In experiment 3, the final tumour incidence in rats that consumed ethanol at 15% of calories was significantly increased compared with rats fed the control diet. In rats fed ethanol at 30% of calories, the tumour incidence did not differ from that of rats fed the control diet. The number of days required for 50% of rats to develop palpable tumours (T_{50}) was 150, 84 and 105 for rats fed the diets containing ethanol at 0, 15 and 30% of calories, respectively (0% versus 15%, $P < 0.05$). The tumours were mainly adenocarcinomas (Singletary *et al.*, 1991).

Two groups of 20 female Sprague-Dawley rats, 40 days of age, were given 95% laboratory-grade ethanol diluted in tap-water to 5% by volume as their sole water source or tap-water alone. At 50 days of age, under general anaesthesia, all animals were given 15 mg DMBA in 1 mL sesame oil by intragastric instillation. The animals were killed at 120 days after administration of DMBA or when a tumour bulk was apparent. Tumours were counted and measured by calipers. Two animals in the control group died within 24 hours after administration of DMBA and were excluded from further analysis. No animal in the ethanol-treated group died before the end of the study. All 18 surviving animals in the control group had developed tumours by 116 days after administration of DMBA in contrast with a tumour incidence of 40% ($P < 0.001$) in the 20 ethanol-treated rats. The mean time to first tumour appearance following administration of DMBA was 67.3 ± 19 days for the control group and 63 ± 16.3 days for the ethanol-treated group. The mean number of tumours per tumour-bearing animal in

control and ethanol-treated groups was 2.9 ± 2.7 and 3.2 ± 2.2, respectively. The mean tumour growth rate was 25.5 ± 11.8 mm^3 per day in the control group versus 30.7 ± 17.7 mm^3 per day in the ethanol-treated group. The histology of the tumours was similar in both groups (McDermott *et al.*, 1992). [The Working Group noted that the intake of ethanol was rather low considering the high rate of metabolism of these animals. Blood levels of ethanol were not measured.]

Groups of 15 pregnant Sprague-Dawley rats [age not specified] were pair-fed isocaloric liquid diets that contained either 0, 16 (7% ethanol of total energy) or 25 g/kg diet (15% ethanol of total energy) ethanol [purity not stated] on days 7–18 of gestation. Blood levels of ethanol were not measured but, based upon previous experiments, were estimated to be 61.3 ± 5.0 mg/dL and 95.8 ± 6.1 mg/dL for the 16-g and 25-g groups, respectively. On postnatal day 47, 23–25 female offspring per group were administered 10 mg (~50 mg/kg bw) DMBA [purity not stated] in 1 mL peanut oil, after which mammary gland tumour development was monitored for 17 weeks. The total number of palpable tumours per rat was significantly higher ($P < 0.006$) in rats exposed *in utero* to diets that contained ethanol than in those exposed to the control diet. Post-hoc analysis indicated that the increase in the incidence of mammary gland tumours was significant in rats exposed *in utero* to 16 g/kg diet ethanol compared with those not exposed to ethanol in the diet. The mean tumour latency did not differ among the groups (Hilakivi-Clarke *et al.*, 2004).

(b) Hamster

The right buccal pouch of 36 male Syrian golden hamsters, 4–6 weeks of age, was painted three times on alternate days for 1 week with a 1% solution of DMBA [purity not specified] in heavy mineral oil. The left buccal pouch remained unpainted to serve as a control. One week later, 16 of the hamsters were placed on a liquid diet that contained 5% ethanol (v/v) and the remaining 20 hamsters were pair-fed an isocaloric control diet. Periodic sampling indicated blood–ethanol levels at a concentration range of 80–180 mg/dL (mean, 95 mg/dL) in ethanol-fed hamsters. At 22 weeks after the start of the experiment, seven control and six ethanol-treated hamsters were killed; the remaining seven controls and 10 ethanol-treated hamsters were killed at 35 weeks. At the end of the experiment, the ethanol-treated hamsters weighed significantly less than the pair-fed controls ($P < 0.005$). Buccal pouch tumours were assessed macroscopically and representative tumours were examined histologically. The incidence and multiplicity of tumours (epidermoid carcinomas) in the right buccal pouch of hamsters treated with DMBA and the control diet was 38% (5/13) and 1 ± 0.0 tumours/tumour-bearing hamster. The incidence and multiplicity of tumours in the right buccal pouch of hamsters treated with DMBA and fed the ethanol diet was 70% (7/10) and 3.29 ± 1.02 tumours/tumour-bearing hamster. Tumour multiplicity in the ethanol-treated hamsters was significant greater than that in pair-fed controls. No tumours were observed in the left buccal pouches of any of the hamsters, which served as an internal control (Nachiappan *et al.*, 1993).

3.2.8 *Dimethylhydrazine (DMH)*

Rat

The effect of chronic administration of ethanol on DMH-induced colorectal carcinogenesis was evaluated in two groups of 16 adult male Sprague-Dawley rats [age unspecified], initially weighing 250–300 g, that were pair-fed nutritionally complete liquid diets that contained 36% of total calories as ethanol or isocaloric carbohydrates, respectively, for 4 weeks. Thereafter, the animals were given the first of four weekly subcutaneous injections of 30 mg/kg bw DMH, during which time standard laboratory chow replaced the liquid diet to avoid competitive inhibition of pro-carcinogen activation by ethanol. This 8-week cycle was completed four times during a total of 32 weeks. At the end of each 8-week cycle, two to five rats from each group were killed. All surviving rats were killed at the end of 32 weeks. The incidence, size and distribution of colon tumours was recorded. Sample specimens of normally appearing proximal and distal colon and rectum and gross tumours were studied microscopically. At the end of the first 4 weeks of ethanol consumption, blood ethanol levels were measured in five randomly chosen rats. Chronic ethanol consumption did not alter the number, size or distribution of large-bowel tumours in DMH-treated animals (McGarrity *et al*., 1988).

Groups of 20–30 male and 20–30 female Sprague-Dawley rats, 10 weeks of age, were given 18 weekly subcutaneous injections of 21 mg/kg bw DMH [purity not specified] in distilled water [concentration not specified] (pH 6.5) that contained ethylene diamine tetraacetic acid (EDTA) as a stabilizing agent (37 mg EDTA:400 mg DMH) and 0 or 1.23 g/kg bw ethanol [purity not specified] daily in the drinking-water for the duration of the study. Daily food consumption and ethanol intake were controlled throughout the experiment. All surviving animals were killed between weeks 25 and 27. At the end of the study, 28% (2/14) male and 78% (11/14) female rats in the DMH-treated group were tumour-free compared with 14% (1/7) and 55% (5/9), respectively, in the group that received DMH and ethanol. The mean numbers of tumours (adenocarcinomas and mucinous carcinomas) per rat (± SD) in the DMH-treated group were 1.83 ± 1.34 and 1.00 ± 0.00 for male and female rats, respectively. The corresponding numbers in the DMH/ethanol-treated group were 2.00 ± 0.89 and 1.00 ± 0.00, respectively. No significant differences in tumour incidence or multiplicity were found between the two groups (Pérez-Holanda *et al*., 2005).

3.2.9 *Ethyl carbamate (urethane)*

Mouse

Groups of 15 female specific pathogen-free strain A/Ph mice, 6.5 weeks of age, were administered 0, 200, 500 or 1000 ppm ethyl carbamate (purity, < 99%) dissolved in tap-water and 0, 5, 10 or 20% ethanol solutions as drinking fluid for 12 weeks, after which time the mice were killed. Survival was > 90%. Lung tumours were counted.

Table 3.3 Pulmonary tumours in female strain A/Ph mice treated for 12 weeks with combinations of ethanol and ethyl carbamate in the drinking-water

Concentration of ethyl carbamate (ppm)	Concentration of ethanol (%)	No. of tumours/mouse (mean±SD)
0	0	0.4±0.7
0	5	1.1±1.5
0	10	1.0±1.7
0	20	1.0±1.0
200	0	11.8±3.8
200	5	9.9±4.7
200	10	4.7±2.7*
200	20	3.8±3.2*
500	0	45.4±12.0
500	5	46.0±9.4
500	10	22.1±6.5*
500	20	9.6±4.9*
1000	0	70.9±15.5
1000	5	61.3±12.4
1000	10	39.3±9.9*
1000	20	21.6±6.9*

From Kristiansen *et al.* (1990) SD, standard deviation * $p<0.001$ in comparison with the respective control group representing 0% ethanol and equivalent concentration of ethyl carbamate (Wilcoxon rank test)

Random samples of nodules were taken from the lungs for histopathological evaluation and confirmation of adenoma. The numbers of nodules were analysed by the Spearman rank correlation and Wilcoxon rank test (see Table 3.3). Ethyl carbamate induced lung tumour multiplicity in a dose-dependent manner both alone and in combination with all three concentrations of ethanol. Ethanol inhibited ethyl carbamate-induced lung tumour multiplicity in a dose-dependent manner. The inhibition was not statistically significant with 5% ethanol but was highly significant with 10 and 20% ethanol (Kristiansen *et al.*, 1990).

In two series of experiments, 12 groups of 25 female Han/NMRI mice, approximately 10 weeks of age, received 0.3 mL/25 g bw of one of the following solutions: 1.5, 3.0, 7.5 or 15 g/L ethyl carbamate [purity unspecified] in tap-water or in 20% ethanol [during the first 3 days of the experiment, 10% ethanol rather than 20% ethanol was administered] by gavage daily during the first 8 weeks of the study. After a further 8 weeks without treatment, the animals were weighed and killed. The fixed lungs were inspected for the presence of lung adenomas using a binocular magnifying glass, then confirmed histologically. The rank sum test was used for statistical significance. Simultaneous application of 20% ethanol [approximately 2.3 g/kg bw per day] had no effect on the number of ethyl carbamate-induced lung adenomas (Altmann *et al.*, 1991).

Groups of 18–21 male weanling C3H/HeJ mice [age unspecified] were given control drinking-water, 12% ethanol [purity not stated] as the drinking-fluid or Concord white, Concord red or Johannesburg Riesling wine as the drinking-fluid simultaneously with 0, 10 or 20 mg/kg bw ethyl carbamate [purity not specified] per day. The ethanol content of the wines had been adjusted to 12%. The experiment lasted 41 weeks. Survival was > 80%, except for the group given 20 mg/kg bw ethyl carbamate and control drinking-water in which survival was 57%. Livers and lungs were examined histologically. Hepatocellular adenoma was detected in all treatment groups (5.6–57.1% incidence) except in those treated with Concord red wine in the absence of ethyl carbamate. Compared with the respective control groups that received only 0, 10 or 20 mg/kg bw ethyl carbamate, the frequency of hepatocellular adenoma/tumour-bearing mouse was decreased significantly in all groups except in mice administered 20 mg/kg bw ethyl carbamate plus 12% ethanol or Concord red wine, respectively. Liver haemangiosarcomas were detected in mice given 10 mg/kg bw ethyl carbamate without ethanol or wine (4.8% incidence) and in all groups given 20 mg/kg bw ethyl carbamate (4.8–23.8% incidence) except for those that also received 12% ethanol. Compared with the control group that was given only 20 mg/kg bw ethyl carbamate, the frequency of haemangiosarcoma/tumour-bearing mouse was decreased significantly in all groups given 20 mg/kg bw ethyl carbamate plus 12% ethanol or wine. Lung Clara-cell adenomas were detected in all treatment groups given 10 or 20 mg/kg bw ethyl carbamate (4.8–57.1% incidence). Compared with the control group that was given only 10 mg/kg bw ethyl carbamate, the frequency of Clara-cell adenoma/tumour-bearing mouse was decreased significantly in all groups given 20 mg/kg bw ethyl carbamate plus wine. Lung alveolar adenomas were detected in all treatment groups given 10 or 20 mg/kg bw ethyl carbamate (4.8–47.6% incidence), except for mice given 10 mg/kg bw ethyl carbamate plus 12% ethanol. Compared with the control group that was given only 20 mg/kg bw ethyl carbamate, the frequency of alveolar adenoma/tumour-bearing mouse was decreased significantly in all groups administered 20 mg/kg bw ethyl carbamate plus ethanol or wine (Stoewsand *et al.*, 1991).

Groups of 20 male and 20 female BALB/c mice, 8 weeks of age, received twice-weekly intraperitoneal injections of 10 mg ethyl carbamate ('pure'; total dose, 100 mg). Two groups also received 10% ethanol [purity not specified] in the drinking-water *ad libitum* [duration of ethanol administration not specified]. All surviving mice were killed after 4 months. The lungs were examined macroscopically and microscopically. The tumour incidence (lung adenomas) was 100% in all groups. Seventeen males and 20 females in the ethyl carbamate-treated group and 20 males and 19 females in the ethyl carbamate plus ethanol-treated group survived until the end of the experiment. Tumour multiplicities (± SD; males and females combined) were 9.9 ± 3.2/mouse in the ethyl carbamate-treated group and 8.1 ± 2.5/mouse in the ethyl carbamate plus ethanol-treated group. No significant differences between sexes or between dose groups were observed (Uleckiene & Domkiene, 2003).

Groups of 48 male and 48 female B6C3F$_1$ mice, 28 days of age, were exposed to 0, 10, 30 or 90 ppm ethyl carbamate in the presence of 0, 2.5 or 5% ethanol in the drinking-water *ad libitum* for 104 weeks. Complete histopathology was performed. Serum levels of ethyl carbamate and ethanol were assessed. The results are summarized in Table 3.4. In female mice administered 10 and 90 ppm ethyl carbamate, ethanol caused dose-related increases in the incidence of alveolar/bronchiolar adenoma or carcinoma and haemangiosarcoma of the heart, respectively. In male mice, a different relationship was observed: ethanol caused a dose-related decrease in the incidence of alveolar/bronchiolar adenoma or carcinoma and of Harderian gland adenoma or carcinoma after exposure to 30 ppm ethyl carbamate. The decrease in the incidence of alveolar/bronchiolar adenoma or carcinoma was significant at 5% ethanol (National Toxicology Program, 2004; Beland *et al.*, 2005).

3.2.10 *Hormones*

Rat

Four groups of female Wistar JCL rats, 4 weeks of age, received 0.075 mg ethinylestradiol and 6.0 mg norethindrone acetate in 0.5 mL olive oil by stomach tube daily for 12 months; the same doses administered by the same method and 10% ethanol w/v in the drinking-water on 2–5 consecutive days a week and pure water for the 2 remaining days each week; 0.5 mL olive oil alone and 10% ethanol and water as in the previous group; or 0.5 mL olive oil only daily throughout the experiment, which lasted 12 months. Daily ethanol intake in the group administered ethinylestradiol and norethindrone acetate was 9.6 ± 2.6 g/kg bw at the beginning of experiment and 11.3 ± 3.7 g/kg bw at 12 months. In the ethanol-treated group, the corresponding intakes were 9.9 ± 2.5 g/kg bw at the beginning and 11.7 ± 4.1 g/kg bw at 12 months. Animals were killed at 2, 4, 6, 8 and 12 months. Histological analysis of liver tissue was performed. Statistical analysis was carried out using the paired Student's *t* and χ^2 tests. Liver tumours observed were well differentiated hepatocellular carcinoma. There was an increased incidence of hepatocellular carcinoma in the group treated with ethinylestradiol and norethindrone acetate plus ethanol (38%; 8/21) compared with the group treated with ethinylestradiol and norethindrone acetate alone (8% (1/12); $P < 0.05$) (Yamagiwa *et al.*, 1991).

3.2.11 *Methylazoxymethanol acetate*

Rat

Two experiments were performed to evaluate the effect of ethanol or saké on methylazoxymethanol acetate-induced large bowel cancer. In the first experiment, 39 male ACI/N rats, 6 weeks of age, were divided into two groups. All animals were given two weekly intraperitoneal injections of 25 mg/kg bw methylazoxymethanol acetate

Table 3.4 Incidence of neoplasms in B6C3F$_1$ mice administered 0, 10, 30 or 90 ppm ethyl carbamate with 0, 2.5 or 5% ethanol in the drinking-water for two years[a]

Neoplasm	Ethanol (%)	Ethyl carbamate (ppm)		
		10	30	90
Females				
Alveolar/bronchiolar adenoma or carcinoma	0	8/48 (16.7%)[&]	28/48 (58.3%)[*]	39/47 (83.0%)[*]
	2.5	11/47 (23.4%)	21/48 (43.8%)[*]	38/48 (79.2%)[*]
	5	17/48 (35.4%)[*,‡]	24/48 (50.0%)[*]	37/48 (77.1%)[*]
Heart haemangiosarcoma	0	0/48 (0.0%)	1/48 (2.1%)	0/48 (0.0%)[&]
	2.5	0/47 (0.0%)	0/48 (0.0%)	3/48 (6.3%)
	5	0/48 (0.0%)	0/48 (0.0%)	6/47 (12.8%)[*,‡]
Males				
Alveolar/bronchiolar adenoma or carcinoma	0	18/48 (37.5%)[*]	29/47 (61.7%)[*,&]	37/48 (77.1%)[*]
	2.5	19/48 (39.6%)	24/47 (51.1%)[*]	43/48 (89.6%)[*]
	5	11/48 (22.9%)	14/48 (29.2%)[‡]	40/48 (83.3%)[*]
Harderian gland adenoma or carcinoma	0	12/47 (25.5%)[*]	30/47 (63.8%)[*,&]	38/47 (80.9%)[*]
	2.5	14/48 (29.2%)[*]	21/47 (44.7%)[*]	38/48 (79.2%)[*]
	5	14/48 (29.2%)[*]	17/48 (35.4%)[*,‡]	35/45 (77.8%)[*]

From National Toxicology Program (2004); Beland *et al*. (2005) [a] The data are reported as the number of animals with a neoplasm per number of animals examined microscopically and (in parentheses) the percentage incidence. An ampersand (&) associated with a 0% ethanol incidence indicates a significant ($p<0.05$) dose-related trend with respect to ethanol. An asterisk (*) associated with a specific treatment indicates a significant ($p<0.05$) difference compared with the 0 ppm urethane incidence. (A double dagger (‡) associated with a specific treatment indicates a significant ($p<0.05$) difference compared with the 0% ethanol incidence. *p* Values for the effects of ethanol are two-sided.

[purity unspecified] dissolved in normal saline. One week after the termination of the injections, one group of 20 rats was given 10% ethanol as drinking-water and a second group of 19 rats received distilled water alone. The experiment was terminated 414 days after the study began. Most tumours in the large intestine were macroscopically sessile or pedunculated polyps and, histologically, were diagnosed as adenomas or adenocarcinomas. In ethanol-treated rats, 16/17 effective animals developed large bowel neoplasms (94%); among these, adenomas were seen in seven rats (41%) and adenocarcinomas in 15 animals (88%). In control rats, 11/16 effective animals had large bowel neoplasms (69%); four animals developed adenomas (25%) and nine had adenocarcinomas (56%). The incidence of large intestinal adenocarcinomas in the ethanol-treated group (88%, 15/17) was significantly higher than that in controls (56% (9/16); $P = 0.040$). No significant differences were noted for the incidence of adenomas between the two groups. The incidence of rectal neoplasms in ethanol-treated rats (59%, 10/17) was significantly higher than that in controls (19% (3/16); $P = 0.019$). In

the second experiment, six groups of 15 female ACI/N rats, 6 weeks of age, were given two weekly intraperitoneal injections of 25 mg/kg bw methylazoxymethanol acetate. A group of seven rats received two injections of saline alone. After a 1-week interval, rats in all treated groups were given isocaloric drinks (105–110 cal/100 mL) as follows: one group was given commercially available saké (approximately 110 cal/100 mL; ethanol content, 15–16%); one group was given 50% saké (approximately 110 cal/100 mL; ethanol content, 7.5%); two groups were given 15% ethanol (approximately 105 cal/100 mL); one group was given 7.5% ethanol (approximately 105 cal/100 mL); and one group was given water without ethanol supplement (approximately 105 cal/100 mL). Glucose (4 cal/g) was added to the 50% saké, 7.5% ethanol and water to make isocaloric drinks. The volume of all drinks was adjusted to 15 mL/rat/12 hour, because the mean fluid intake was found to differ among the groups in a preliminary experiment. The experiment was terminated 280 days after the first administration of methylazoxymethanol acetate. All surviving animals were killed and autopsied. All major organs, especially the intestines, were carefully inspected grossly, and suspected lesions were taken for histological examination. To determine tumour distribution, the large bowel was divided into three parts, and the distal 5 cm from the anus was treated as the rectosigmoidal colon. The first intestinal tumour was observed in an animal that died on the 189th day. [The group was not indicated.] No significant differences among the groups were noted. The incidence of rectosigmoidal colonic neoplasms in the groups given saké (53%, 8/15 effective animals), 50% saké (46%, 6/13) and 15% ethanol (50%, 5/10) was non-significantly higher than that in the group given water (38%, 5/13). The numbers of rectosigmoidal colonic neoplasms per total large intestinal neoplasms in the groups given saké (68%, 11/16) and 50% saké (67%, 8/12) were also non-significantly higher those than in the group given water (45%, 5/11). The incidence of colonic tumours in the second experiment was lower than that in the first, which may have been due to the shorter duration of the former (Niwa *et al.*, 1991).

3.2.12 *3′-Methyl-4-dimethylaminobenzene (MeDAB)*

Rat

Groups of 80 male Wistar rats, 5 weeks of age, were fed powdered diets containing 0 or 0.06% 3′-methyl-4-dimethylaminoazobenzene (MeDAB) [purity not specified] for an initiation period of 4 weeks. Another group of 80 rats was fed the same diets without carcinogen. After a 2-week recovery period on a pelleted diet, each of the two groups was divided in four identical subgroups that were given distilled drinking-water that contained 0, 5, 10 or 15% ethanol (‘of the highest grade’). The rats were fed a pelleted diet and the drinking solutions *ad libitum*. Rats not treated with MeDAB were killed 45 weeks after the start of ethanol administration at week 51. The rats fed MeDAB were killed at the end of week 53 after initiation. In the groups that were not initiated with MeDAB, no macroscopic tumours were observed in the liver or other organs. In contrast, macroscopical liver changes, including variable tumour size and irregularity

of the surface, were observed in rats initiated with MeDAB. The incidence of hepatocellular carcinomas in the initiated groups was 37% (7/19), 37% (7/19), 16% (3/19) and 42% (8/19) in the rats administered 0, 5, 10 and 15% ethanol, respectively (Yanagi *et al.*, 1989).

3.2.13 *4-(Methylnitrosamino)-1-(3-pyridyl)butanone (NNK)*

(a) Rat

Male Fischer 344 rats [initial number unspecified], 4–6 weeks of age, were treated by gavage with a total dose of 20 mmol/kg 4-(methylnitrosamino)-1-(3-pyridyl) butanone (NNK) three times a week for 4 weeks. One week after initiation, the animals received liquid diets that contained 36% of total calories as ethanol or an isocaloric equivalent of carbohydrates for 55 weeks. Ethanol increased the incidence of tumours of the oesophagus, oral cavity, lungs and liver initiated by NNK ($P < 0.05$) and caused an increase in the mean frequency and size of the tumours ($P < 0.001$) (Nachiappan *et al.*, 1994).

(b) Hamster

Two groups of four pregnant female Syrian hamsters [age not specified] received 10% ethanol in the drinking-water on days 5–16 of pregnancy and two groups of four hamsters served as untreated controls. On day 15, 50 mg/kg bw NNK were intratracheally instilled into animals that did or did not receive the ethanol. The control group received identical intratracheal instillation with distilled water only. The offspring were weaned at 4 weeks of age and were observed until weight loss or symptoms occurred and were then killed. Treatment with ethanol and NNK resulted in a significant increase in the incidence of tumours in male and female offspring compared with those treated with NNK alone ($P < 0.01$). This was also found for tumours of the nasal cavity in females, of the pancreas in males and females and of pheochromocytoma in both sexes (Schüller *et al.*, 1993).

3.2.14 N-*Methyl*-N′-*nitro*-N-*nitrosoguanidine (MNNG)*

(a) Shrew

Groups of female Jic:SUN house musk shrews, 5 weeks of age, were administered tap-water (four animals), 2% ethanol (purity, > 99.5%) in tap-water (four animals), 50 ppm MNNG [purity not specified] in tap-water (25 animals), or 50 ppm MNNG in tap-water that contained 2% (25 animals), 5% (30 animals) or 10% (25 animals) ethanol. The treatment lasted for 30 weeks, after which the animals were returned to tap-water. Average water consumption (approximately 10 mL/day) was not affected by the presence of MNNG and/or ethanol. All animals were autopsied. No significant differences in body weight or organ weights were observed among groups. All MNNG-treated

animals that survived to 20 weeks of age were included in the analysis. Randomly selected animals were killed sequentially at 20, 30, 35, 40 and 45 weeks of age. The animals in the 2% ethanol-treated control group were killed at 35 weeks of age. Organs and tissues were examined grossly and microscopically after routine histological procedures and haematoxylin/eosin staining. At the highest doses (5 and 10%), co-administration of ethanol with 50 ppm MNNG produced an acute toxic response: 20% (6/30) of the animals in the 5% ethanol-treated group died within 7 days and 40% (10/25) of the animals in the 10% ethanol-treated group died within 4 days after the start of the treatment. Acute toxicity was not observed in any of the other groups. Thus, the MNNG- and MNNG plus 2% ethanol-treated groups were selected for the long-term (30-week) study. Five animals were selected from each of these two groups for analysis at 20, 30, 35, 40 and 45 weeks of age. Oesophageal papillomas or squamous-cell carcinomas were not observed in either of the two groups at 20 weeks of age. At 30 weeks of age, two papillomas in the MNNG-treated group and one papilloma in the MNNG plus ethanol-treated group were observed. At later time-points, the incidence of papillomas and squamous-cell carcinomas, respectively, was: five and four in the MNNG-treated group compared with three and three in the MNNG plus ethanol-treated group at 35 weeks of age; five and five in the MNNG-treated group compared with five and five in the MNNG plus ethanol-treated group at 40 weeks of age; and five and five in the MNNG-treated group compared with five and five the MNNG plus ethanol-treated group at 45 weeks of age. Oesophageal tumours were not found in the water-treated or ethanol-treated control groups (Shikata *et al*., 1996).

(b) Rat

Two group of 15 male Wistar rats, 6 weeks of age, received 50 μg/mL MNNG in the drinking-water for 20 weeks. The average dose of MNNG consumed by each rat was 120 mg. From week 21, the rats received tap-water *ad libitum*. The rats also received intraperitoneal injections of either 2.5 mL/kg 0.9% saline solution or 2.5 mL/kg 20% ethanol in 0.9% saline solution per day every other day until week 52, at which time the animals were killed. Animals that survived 50 weeks were included. Ethanol treatment increased tumour incidence ($P < 0.02$) and multiplicity ($P < 0.01$) (Iishi *et al*., 1989).

Groups of 30 and 25 male ACI rats, 4 weeks of age and weighing 58 g, received 0.25 mL/10 g bw of a stock solution of 5 g/L MNNG by gastric intubation. Thereafter, the animals received either tap-water or 10% ethanol in the drinking-water for 1 year. Additional groups of rats that received water or ethanol only served as controls. Ethanol had no effect on the incidence of squamous-cell carcinoma of the forestomach or adenocarcinoma of the glandular stomach induced by MNNG. Ethanol alone had no effect on tumour yield compared with rats that received water (Watanabe *et al*., 1992).

Three groups of 20 male Wistar rats [age unspecified], weighing 150–200 g, were given 100 μg/mL MNNG in tap-water (control group), 100 μg/mL MNNG in 11% ethanol or 100 μg/mL MNNG in wine for 6 months, and the experiment was terminated

at 13 months. In the glandular stomach, six carcinomas, one carcinoma and one carcinoma plus one sarcoma were observed in the control, ethanol- and wine-treated groups, respectively. In the forestomach, one carcinoma, two carcinomas plus one papilloma and one carcinoma were found in the same groups, respectively. In the duodenum, four carcinomas were found in the control group (Cerar & Pokorn, 1996). [The Working Group noted that the application of MNNG solutions in the experimental groups was prolonged for 10 days to equalize the MNNG consumption per group, which confounds the interpretation of the study.]

Two groups of 15 male Fischer 344 rats, 6 weeks of age, received a single intragastric administration of 150 mg/kg bw MNNG [solvent not specified.]. One week later, one group was administered 10% ethanol in the drinking-water for 51 weeks. Animals were killed at 52 weeks and histopathological examination of the stomach and oesophagus was performed. In the MNNG plus ethanol-treated group, the incidence of papilloma and carcinoma was 2/15 (18%) (significantly reduced; $P < 0.01$) and 6% (1/15) versus 66% (10/15) and 6% (1/15), respectively, in the MNNG-treated group (Wada *et al.*, 1998).

3.2.15 N^6-*(Methylnitroso)adenosine*

Mouse

Groups of female Swiss (NIH:Cr(S)) mice [initial number unspecified], 4 weeks of age, received three intragastric doses of 60 or 180 mg/kg bw N^6-(methylnitroso) adenosine per week with or without 15% ethanol for 12 weeks. Thereafter, the mice were killed when ill or at 18 months of age. A complete necropsy was performed and tumours were examined histologically. Ethanol statistically significantly increased the incidence of thymic lymphomas induced by N^6-(methylnitroso)adenosine (at the 180-mg/kg bw dose): the incidence increased from 43% (21/49) in the N^6-(methylnitroso) adenosine-treated group to 64% (32/50) in the N^6-(methylnitroso)adenosine plus 15% ethanol-treated group ($P < 0.05$) (Anderson *et al.*, 1993).

3.2.16 N-*Methyl*-N-*nitrosourea (MNU)*

Rat

A study was conducted to evaluate the influence of low and high ethanol intake (15, 20 or 30% of calories) as part of a liquid diet on both the initiation and promotion stages of *N*-methyl-*N*-nitrosourea (MNU)-induced rat mammary tumorigenesis. In the first experiment (an initiation study), groups of 32 female Sprague-Dawley rats, 23 days of age, were fed a powdered control diet until 28 days of age, after which time the animals were randomly assigned to groups and fed *ad libitum* diets that contained ethanol at 0, 15, 20 and 30% of calories. At 50 days of age, 30 mg/kg bw MNU were administered intraperitoneally; all animals received the control diet between 18

and 24 hours before treatment. Four hours following the injections, the animals were returned to the previous control diets or diets that contained ethanol until 57 days of age. At this time, all animals were fed the powdered control diet for the remainder of the study. Two additional control groups were added in case the diet intake for rats fed the 20% and 30% ethanol diets decreased significantly compared with controls fed *ad libitum*. Beginning 4 weeks after treatment with MNU, animals were palpated weekly for the appearance of mammary tumours. Analysis of the incidence of cumulative, palpable mammary tumours indicated a significant difference in trends between the 15% ethanol-treated and control groups. A significant 64% increase in the number of adenocarcinomas per rat was observed for animals in the 15% ethanol-treated group (2.2 ± 0.3) compared with the control group (1.4 ± 0.2). No significant differences in the numbers of tumours were observed for the 20 and 30% ethanol-treated groups compared with their respective controls. In the second experiment (influence of ethanol intake on promotion), female Sprague-Dawley rats were fed a powdered control diet from 38 to 51 days of age, at which time MNU was administered intraperitoneally at a dose of 30 mg/kg bw. At 58 days of age, the animals were randomized into four groups to be fed *ad libitum* diets that contained ethanol at 0% (32 rats), 15% (30 rats), 20% (30 rats) or 30% (30 rats) of calories. A fifth group of 32 rats was pair-fed the 0% ethanol diet according to the average daily intakes of the rats fed the diet that contained 30% ethanol. At necropsy, tumours were removed and examined histopathologically. No significant difference in trends was observed for the incidence of cumulative, palpable mammary tumours between the 0 and 15% ethanol-treated groups nor between the group that underwent caloric restriction and the 20 or 30% ethanol-treated groups. The average number of palpable tumours and adenocarcinomas per rat increased significantly in animals in the 15% ethanol-treated group compared with those in the 0% ethanol-treated group (3.2 ± 0.4 versus 2.0 ± 0.3 palpable tumours/rat; 4.4 ± 0.5 versus 2.3 ± 0.4 adenocarcinomas/rat). The number of adenocarcinomas per rat was also significantly increased in animals fed the 20% ethanol diet compared with the calorie-restricted controls (3.0 ± 0.5 versus 1.8 ± 0.3). No significant difference between the calorie-restricted and 30% ethanol-treated groups was observed with regard to palpable tumours and adenocarcinomas (Singletary *et al.*, 1995).

3.2.17 N'-*Nitrosobis(2-oxopropyl)amine*

A group of 40 male weanling Syrian golden hamsters [age not specified] received either a high-fat diet (25% corn oil) or a high-fat diet plus ethanol, the concentration of which was gradually increased starting at day 25 from 5% during the first 2 weeks to a final concentration of 10% within 6 weeks. The hamsters received two subcutaneous injections of 20 mg/kg bw *N*-nitrosobis(2-oxopropyl)amine at 6 and 7 weeks of age and were killed 372 and 373 days after the second injection. Ethanol had no effect on the incidence of pancreatic adenomas or carcinomas (Woutersen *et al.*, 1989)

3.2.18 N-*Nitrosodiethylamine (NDEA)*

(a) Mouse

Groups of male strain A/JNCr mice [initial number unspecified], 4 weeks of age, were administered 6.8 ppm NDEA in sterilized distilled drinking-water with or without 10% ethanol for 4 weeks and were held without further treatment for 32 weeks. Complete necropsy was performed and tumours were examined histologically. Treatment with 6.8 ppm NDEA resulted in an 84% (42/50) incidence of lung tumours. When 10% ethanol was included with the NDEA, 100% (50/50) of the mice developed tumours and the multiplicity of lung tumours was increased (5.8 ± 2.2 versus 1.5 ± 1.2; $P < 0.01$). Ethanol also strongly potentiated the tumorigenic effect of NDEA in the forestomach from 2% (1/50) in NDEA-treated animals (one carcinoma) to 32% (16/50) in NDEA plus ethanol-treated animals (16 forestomach tumours including 14 carcinomas) (Anderson *et al.*, 1993).

(b) Rat

The enhancing effect of ethanol on oesophageal tumour development in rats following initiation with NDEA was evaluated. Groups of 30 and 28 male Fischer 344 rats, 6 weeks of age, were administered 50 ppm NDEA (purity, > 99%) dissolved in 10% ethanol (purity, > 99%) solution and 50 ppm NDEA solution in distilled water, respectively, for 8 weeks and were maintained thereafter on tap-water and basal diet for 96 weeks, at which time all rats were killed. The total intake of NDEA in the group given NDEA plus water was 134% that of the group given NDEA dissolved in water that contained ethanol. The numbers of nodules and masses in the oesophagus were counted, and all gross lesions were examined histopathologically. The effective numbers of rats were 26 and 28, respectively, and the number of survivors after 104 weeks was four and 10, respectively. The first animal with an oesophageal tumour died in the group administered 50 ppm NDEA in water that contained ethanol at week 43. The incidence of papillomas and carcinomas in the group given NDEA in water that contained ethanol were 38% (10/26) and 30% (8/26), respectively, compared with 7% (2/28) and 3% (1/28), respectively, in the group that received NDEA alone ($P < 0.01$) (Aze *et al.*, 1993).

3.2.19 N-*Nitrosodimethylamine (NDMA)*

Mouse

Groups of 50 male A/JNCr mice, 4 weeks of age, received 0.5, 1 or 5 ppm NDMA in sterile distilled drinking-water with or without 10 or 20% ethanol for 16 weeks. When the animals were killed, the lungs were removed and examined for primary lung tumours. Questionable lesions were subjected to histopathology (see Table 3.5). Mice treated with 0.5, 1 or 5 ppm NDMA and 10% ethanol had an increased incidence

of lung tumours and/or average number of lung tumours per mouse compared with those that received only 0.5, 1 or 5 ppm NDMA. Mice treated with 5 ppm NDMA and 20% ethanol had an increased average number of lung tumours per mouse compared with those that received 5 ppm NDMA only; this increase was not observed in mice treated with 0.5 ppm NDMA and 20% ethanol compared with mice that received only 0.5 ppm NDMA. In an additional experiment, mice were treated with 5 ppm NDMA with or without 10% ethanol for 4 weeks and then kept for an additional 12 weeks. Another group received 5 ppm NDMA for 4 weeks and then 10% ethanol for 12 weeks. Mice treated simultaneously with 5 ppm NDMA and 10% ethanol for 4 weeks had an increased incidence of lung tumours and average number of lung tumours per mouse compared with mice that received 5 ppm NDMA only. Treatment with 10% ethanol after administration of the 5 ppm NDMA did not affect the tumour incidence or multiplicity (Anderson, 1988).

Groups of 25 and 50 male Strain A/JNCr mice, 4–6 weeks of age, received 0 and 5 ppm NDMA [purity unspecified] in sterilized distilled drinking-water, respectively, with or without 10% reagent-grade ethanol for 4 weeks and were then held for an additional 12 weeks before being killed (experiment 1). Further groups of 50 males received 0 or 1 ppm NDMA with or without 10% ethanol in the drinking-water for 16, 32, 48 or 72 weeks after which time they were killed (experiment 2). Groups of 30 males received a single intragastric dose of 1 or 5 mg/kg bw NDMA and 0, 5, 10 or 20% ethanol in the drinking-water and were killed after 16 weeks (experiment 3); and groups of 25 males received doses of 1 mg/kg bw NDMA five times a week for 4 weeks by intragastric, intraperitoneal, subcutaneous or intravenous administration, with or without 0 or 10% ethanol in the drinking-water, and were killed 32 weeks after the last treatment (experiment 4). Complete necropsies were performed on all animals. In experiment 1, in mice exposed to 5 ppm NDMA in the drinking-water, inclusion of 10% ethanol almost doubled the incidence of tumour-bearing mice and increased average multiplicity fourfold. A similar enhancement was obtained with 1 and 5% ethanol, with no significant difference in numbers of tumours among the NDMA–ethanol-treated groups (Table 3.6). In experiment 2, in mice exposed to 1 ppm NDMA for up to 72 weeks, the inclusion of 10% ethanol increased the incidence of lung tumours after 48 weeks of exposure and increased lung tumour multiplicity at 72 weeks of exposure (Table 3.7). The incidence of kidney tumours was increased after 72 weeks of exposure. In experiment 3, a single intragastric dose of 5 mg/kg NDMA co-administered with 5, 10 or 20% ethanol resulted in a significant increase in tumour incidence and multiplicity compared with administration of NDMA without ethanol. This was not observed with doses of 1 mg/kg NDMA (Table 3.8). In experiment 4, when 10% ethanol was included in the drinking-water, no effect on the incidence or multiplicity of lung tumours was observed, regardless of the route of administration (Anderson *et al.*, 1992).

Table 3.5 Lung tumour incidence in male A/JNCr mice treated with *N*-nitrosodimethylamine (NDMA) with or without ethanol

NDMA (ppm)	Ethanol (%)	Treatment period (weeks)	Lung tumour incidence	Tumours/mouse (SD)
0.5	0	1–16	3/50 (6%)	0.06 (0.24)
0.5	10	1–16	9/50 (18%)	0.22 (0.51)*
0.5	0	1–16	4/50 (8%)	0.08 (0.27)
0.5	20	1–16	8/50 (16%)	0.16 (0.37)
1	0	1–16	9/50 (18%)	0.18 (0.39)
1	10	1–16	14/50 (28%)	0.44 (0.90)*
5	0	1–16	32/39 (82%)	2.1 (1.0)
5	10	1–16	21/22 (95%)*	4.2 (2.9)*
5	0	1–16	31/48 (65%)	1.5 (1.7)
5	10	1–16	50/50 (100%)*	5.4 (3.4)*
5	20	1–16	43/45 (86%)	3.2 (3.6)*
5	0	1–4 (NDMA) 5–16 (nothing)	19/50 (38%)	0.6 (0.9)
5	10	1–4 (NDMA + ethanol) 5–16 (nothing)	47/50 (94%)*	3.6 (2.5)*
5	10	1–4 (NDMA) 5–16 (ethanol)	26/50 (52%)	0.8 (0.9)

From Anderson (1988) SD, standard deviation *Significantly different ($p<0.05$) from groups that did not receive ethanol.

3.2.20 N-*Nitrosomethylamylamine*

Rat

To evaluate the effect of ethanol on *N*-nitrosomethylamylamine-induced oesophageal carcinogenesis, groups of 25 and 40 male MRC Wistar rats were given intraperitoneal injections of 25 mg/kg bw *N*-nitrosomethylamylamine in 5 mL distilled water once a week at 7, 8 and 9 weeks of age and received either drinking-water (controls) or 20% ethanol (21% of 95% ethanol) in distilled water containing 2 g/L catechol from 6 weeks of age continuously for 2 weeks. The ethanol content was then reduced to 10% because liquid consumption had decreased by about 25%. All rats were maintained on these treatments until they died or appeared ill. Full necropsies were performed and all oesophagi (which were slit) and tissues with apparent tumours were sectioned and examined histologically. In the oesophagus, *N*-nitrosomethylamylamine alone induced

Table 3.6 Enhancement of lung tumorigenesis by 5 ppm *N*-nitrosodimethylamine (NDMA) at different concentrations of ethanol in the drinking-water

Ethanol concentration in water	No. with tumour/total (%)	Average no. of tumours per mouse at risk±SD
0	27/50 (54%)	1.0±1.4
1%	47/49 (96%)[a]	4.3[a]±3.2
5%	46/48 (96%)[a]	5.4[a]±4.0
10%	49/50 (98%)[a]	4.1[a]±2.8
No NDMA		
0	2/25 (8%)	0.1±0.3
10%	4/25 (16%)	0.2±0.4

From Anderson *et al*. (1992) SD, standard deviation Water consumption values are the average for the last week of the 4-week treatment period. [a] Difference statistically significant compared with controls, $p < 0.05$

papillomas in 69% (27/39) of the rats and squamous-cell carcinomas in 18% (7/39) of the rats. In rats administered ethanol, the incidence of oesophageal papilloma and carcinoma was 75% (18/24) and 29% (7/24), respectively. The tumour incidences were not significantly different (Mirvish *et al.*, 1994).

3.2.21 N-*Nitrosomethylbenzylamine (NMBzA)*

(a) Mouse

Groups of 15 or 17 female C57BL/6 mice, 4–6 weeks of age, were fed a control diet or a diet that contained ethanol and were administered 0.2 mg/kg bw NMB_zA orally in a corn oil vehicle three times a week for 3 weeks (total dose, 1.8 mg/kg bw). Following oesophageal tumour induction by NMB_zA, the ethanol-fed mice received a diet in which ethanol was isocalorically substituted for maltose dextrin to provide 30% of the total dietary calories. The experiment was terminated 22 weeks after the end of the NMB_zA treatment. The incidence of oesophageal tumours was 6/15 (40%) in the NMB_zA-treated group compared with 59% (10/17) in the NMB_zA plus ethanol-treated group. The mean multiplicity was 8.2 [± 2.5, estimated from a figure] compared with 14.3 [± 2.8, estimated from a figure]. [The Working Group found that this increase in multiplicity was statistically significant, Student's-*t*-test; $P < 0.001$] (Eskelson *et al.*, 1993).

(b) Rat

The effect of chronic dietary ethanol consumption on the initiation and promotion of chemically induced carcinogenesis was evaluated in male Sprague-Dawley weanling rats [initial number and age unspecified], weighing 70–120 g, that received thrice-weekly intraperitoneal injections of 2.5 mg/kg bw NMB_zA for 3 weeks. To study the effect of ethanol on tumour promotion, an ethanol (7% content) or carbohydrate control

Table 3.7 Tumorigenesis by 1 ppm *N*-nitrosodimethylamine (NDMA) in drinking-water with or without 10% ethanol at increasing time intervals

Exposure time and treatment	Lung tumour-bearing mice (no./total; average no.±SD)	Kidney tumours	Other tumours	Average terminal body weight (g±SD)
16 weeks				
NDMA	14/50 (28%); 0.3±0.6	0	0	35.9±4.6
NDMA + ethanol	22/50 (44%); 0.5±0.5	0	0	34.3±5.0
32 weeks				
NDMA	24/50 (48%); 0.7±0.9	0	0	37.8±6.9
NDMA + ethanol	30/50 (60%); 1.0±1.1	0	0	38.0±6.9
48 weeks				
NDMA	32/48 (67%)[a]; 1.6±1.7	0	0	35.2±6.6
NDMA + ethanol	45/49 (92%)[a]; 2.2±1.5	0	1 lymphocytic lymphoma	42.2±5.9
72 weeks				
NDMA (69±8 weeks)	42/48 (88%); 2.4[a]±1.9	1[b]	1 mammary CA, 1 FCC lymphoma	37.6±5.6
NDMA + ethanol (70±6 weeks)	48/49 (98%); 3.4[a]±1.8	7[b]	4 haemangiomas, 1 haemangiosarcoma (liver), 2 lymphomas (1 FCC, 1 myelogenous), 1 adrenal pheochromocytoma, 1 hepatocellular CA, 1 sarcoma (bladder)	35.3±8.3

From Anderson *et al*. (1992) CA, carcinoma; FCC, follicular centre cell; SD, standard deviation Average water consumption did not vary between groups or over time and averaged 4.1 (± 0.7) mL/mouse/day. [a] $p<0.05$ or better [b] $p=0.032$, one-tailed Fisher exact test

diet was administered 1 week following the NMB_zA treatment and continued until termination of the experiment at 20 months of age, by which time the animals had received ethanol for a total of 17 months. To study the effect of ethanol on initiation, the rats were given ethanol or control diet for 12 weeks, and the NMB_zA treatment was given during the last 3 weeks. The ethanol content of the diet was then gradually reduced over 1 week, and the animals were fed regular chow diet thereafter until termination of the experiment at 20 months of age. These rats had received ethanol before and during initiation; their oesophagi were excised and examined for the incidence of nodules. Lesions that exhibited a three-dimensional structure with a height of at least 1 mm were designated as tumours. When ethanol was administered after treatment with NMB_zA, the mean frequency and size of oesophageal tumours decreased; however, the

Table 3.8 Effects of co-administration of ethanol on lung tumorigenesis induced by a single intragastric dose of *N*-nitrosodimethylamine (NDMA)

Treatment	No. of mice with tumour/ total	Average no. of tumours per mouse at risk±SD
NDMA, 1 mg/kg		
No ethanol	7/30 (23.3%)	0.30±0.59
+ 5% ethanol	6/30 (20%)	0.20±0.40
+ 10% ethanol	6/30 (20%)	0.30±0.69
+ 20% ethanol	9/29 (31%)	0.37±0.66
NDMA, 5 mg/kg		
No ethanol	15/30 (50%)[a]	0.93[a]±1.40
+ 5% ethanol	27/30 (90%)[a]	1.80[a]±1.40
+ 10% ethanol	30/30 (100%)[a]	4.27[a]±2.00
+ 20% ethanol	30/30 (100%)[a]	7.10[a]±4.10

From Anderson *et al*. (1992) SD, standard deviation [a] Values statistically different, $p<0.05$ or better

incidence increased. There was only one small tumour among 32 of the control animals; 18.7% (14/75) of animals that received ethanol had tumours ($P < 0.05$) and two of these animals had multiple (two and four) tumours. Treatment with ethanol before and during initiation significantly reduced the incidence of oesophageal tumours: 38% (10/26) of control rats but only 23% (3/13) of ethanol-treated rats had such tumours ($P < 0.01$; reduction). [The Working Group did not confirm the significance of this reduction.] The oesophageal tumours were predominantly papillomas (Mufti *et al*., 1989). [The Working Group noted that, in the experiment on initiation, ethanol was given for 12 weeks and, in the experiment on promotion, it was given for 17 months.]

As part of a study to investigate the effect of zinc deficiency on oesophageal carcinogenesis, groups of 39 and 35 male Sprague-Dawley rats [age not specified] were given control drinking-water and drinking-water that contained 10% ethanol [purity not specified], respectively, for 2 weeks and were then dosed with 2.5 mg/kg bw NMB_zA [purity not specified] twice a week for 3 weeks [vehicle and route of administration not specified]. After 14 weeks, the weight of rats given control-drinking-water was 378 ± 16 g compared with 268 ± 28 g for rats given the drinking-water that contained 10% ethanol. The animals were observed for 20 or more weeks [exact time not specified], at which time the extent of oesophageal tumorigenesis was assessed macroscopically and microscopically. The incidence oesophageal tumours was 37% (13/35) in rats administered control drinking-water compared with 33% (13/39) in rats given 10% ethanol in the drinking-water, a difference that was not statistically significant (Newberne *et al*., 1997).

Three groups of 15 male Fischer 344/DuCrj rats, 6 weeks of age, received thrice-weekly subcutaneous injections of 500 μg/kg bw NMB_zA (purity, > 99%) in 20% DMSO [volume not specified] for 5 weeks. Two additional groups of 10 rats each were

similarly injected with 20% DMSO. After receiving the last injection of NMB_zA, two of the groups were given 3.3 and 10% ethanol (purity, > 98%) in the drinking-water; the other group continued to receive control drinking-water. After the last injection of 20% DMSO, one of the groups was given 10% ethanol in the drinking-water, while the other group continued to receive control drinking-water. The experiment was terminated 15 weeks after the rats were placed on drinking-water solutions that contained ethanol. Oesophageal tumours were examined macroscopically and microscopically, and were only present in rats administered NMB_zA. In rats that received NMB_zA only, the incidence and multiplicity (± SD tumours/rat) of oesophageal tumours were 47% (7/15) and 0.8 ± 1.1. The corresponding values for rats that received NMB_zA and 3.3% ethanol were 33% (4/12) and 0.9 ± 1.6 and those for rats that received NMB_zA and 10% ethanol were 46% (6/13) and 0.8 ± 1.0. All of the tumours were characterized as squamous-cell papillomas, with the exception of a single squamous-cell carcinoma that was detected in the NMB_zA and 10% ethanol-treated group. Neither the incidence nor the multiplicity of oesophageal tumours differed among any of the groups that had been treated with NMB_zA (Morimura *et al.*, 2001).

Groups of 15 male Fischer 344/DuCrj rats, 6 weeks of age, received thrice-weekly subcutaneous injections of 100 or 500 μg/kg bw NMB_zA (purity, > 98%) [injection volume and solvent not specified] for 5 weeks and were also given control drinking-water for 24 weeks, 10% ethanol (purity, > 99%) in the drinking-water for 5 weeks and then control drinking-water for 19 weeks or 10% ethanol in the drinking-water for 24 weeks. The experiment was terminated 24 weeks after the first injection of NMB_zA, at which time the extent of papillary oesophageal tumorigenesis was assessed macroscopically and microscopically. Rats that received 10% ethanol in the drinking-water for 24 weeks weighed significantly less than those that received control drinking-water or 10% ethanol in the drinking-water for 5 weeks. No oesophageal tumours were observed in rats treated with 100 μg/kg bw NMB_zA and either control drinking-water or drinking-water that contained ethanol. In rats that received 500 μg/kg bw NMB_zA, the incidence and multiplicity (± SD tumours/rat) of oesophageal tumours, respectively, were 13% (2/15) and 0.1 ± 0.4 in those given control drinking-water, 33% (5/15) and 0.4 ± 0.6 in those given 10% ethanol in the drinking-water for 5 weeks and 46% (7/15) and 0.6 ± 0.6 in those given 10% ethanol in the drinking-water for 24 weeks. Neither the tumour incidence nor tumour multiplicity differed significantly among these groups (Kaneko *et al.*, 2002).

Two groups of 10 male albino Wistar rats [age not specified], weighing 156 ± 15 g, were either fed a liquid diet that contained ethanol (5% ethanol (v/v) high-grade absolute, 36% of total calories) or pair-fed a diet in which the ethanol was replaced isocalorically with glucose. Eight weeks after being placed on the diets, each of the rats received twice-weekly intraperitoneal injections of 100 μg/kg bw NMB_zA [purity not specified] for 10 consecutive weeks. The liquid diets were removed 1 h before the injections, and blood was collected for analysis of ethanol; none was detected [limit of detection not specified]. The liquid diets were replaced 5 hours after the injections. The experiment

was terminated after 30 weeks and oesophageal tumours were assessed macroscopically and microscopically. The average intake for both groups was 80 mL/day (4.0 mL ethanol/day for the ethanol group). Body weights did not differ significantly between the groups. In NMB_zA-treated rats administered the ethanol diet, the oesophageal tumour incidence was 100% (10/10), the mean size of oesophageal tumours was 7.3 ± 3.6 mm, the mean number of oesophageal tumours per rat was 6.1 ± 1.0 and the incidence of squamous-cell carcinoma of the oesophagus was 50% (5/10). In NMB_zA-treated rats administered the pair-fed control diet, the oesophageal tumour incidence was 5/10 (50%), the mean size of oesophageal tumours was 5.0 ± 0.7 mm, the mean number of oesophageal tumours per rat was 0.5 ± 0.5 and the incidence of squamous-cell carcinoma of the oesophagus was 0/10. Each of these parameters was significantly increased in the ethanol-fed group compared with the pair-fed control rats (Tsutsumi *et al.*, 2006).

3.2.22 N-*Nitrosonornicotine (NNN)*

Rat

Male Fischer 344 rats [initial number unspecified], 4–6 weeks of age, were treated by gavage with NNN at a total dose of 40 mmol/kg three times a week for 4 weeks. One week after initiation, the animals received liquid diets that contained 36% of total calories either as ethanol or isocalorically as carbohydrates for 55 weeks. Ethanol increased the incidence of tumours initiated by NNN in the oesophagus (79%, 40/52), oral cavity (29%, 15/52) and lungs (15%, 8/52) ($P < 0.05$) compared with the control-fed rats (35%, 14/40), (17%, 7/40), (5%, 2/40) respectively) and caused an increase in the mean frequency and size of the tumours ($P < 0.001$) (Nachiappan *et al.*, 1994).

3.2.23 *NNN in combination with* N-*nitrosodiethylamine (NDEA)*

Mouse

Four groups of 48 female mice (*Mus musculus*), 3 months of age, received either water on days 1–3 and then 0.04 ml/L NDEA in the drinking-water on days 4–7, 30 mg/L NNN on days 1–3 followed by NDEA on days 4–7, 6% ethanol followed by NDEA or 6% ethanol plus NNN followed by NDEA. A control group of 16 mice received water only for 7 days. The experiment was terminated after 180 days. The incidence of invasive carcinoma of the oesophagus was 0% (control), 64%, 58%, 69% and 65% in the different groups, respectively, which was not significant (Gurski *et al.*, 1999).

3.2.24 N-*Nitrosopyrrolidine (NPYR)*

Mouse

Groups of male strain A/JNCr mice [initial number unspecified], 4 weeks of age, were administered 6.8 or 40 ppm NPYR in sterilized distilled drinking-water with or without 10% ethanol for 4 weeks. The mice were held without further treatment for 32 weeks. Complete necropsy was performed and tumours were examined histologically. NPYR alone did not cause a significant number of tumours at either dose. The inclusion of 10% ethanol with the 6.8 ppm dose increased the incidence of lung tumours from 41 (20/49) to 67% (33/49) and average multiplicity from 0.5 ± 0.8 to 1.2 ± 1.2 tumours/mouse (the differences were statistically significant). With the 40-ppm NPYR dose, inclusion of ethanol resulted in 98% (47/48) of the mice with lung tumours and a 5.5-fold increase in multiplicity (3.3 ± 1.7) compared with NPYR alone (0.6 ± 0.8; $P < 0.01$) (Anderson *et al.*, 1993).

3.2.25 N-*Nitrososarcosin ethyl ester*

One hundred and forty male white rats [age unspecified], average weight of 100 g, were divided into eight groups. Rats received an intraoesophageal dose of 50 mg/kg bw *N*-nitrososarcosin ethyl ester five times a week for 4 months. Some groups received in addition 0.5 mL 40% ethanol intraoesophageally three times a week for 8 months. Ethanol was given 5–10 minute after the carcinogen. Ethanol had no effect on the incidence or multiplicity of tumours in the oesophagus or forestomach (Alexandrov *et al.*, 1989).

3.3 Acetaldehyde

Previous studies

Acetaldehyde was considered by two previous Working Groups in June 1984 (IARC, 1985) and February 1998 (IARC, 1999).

The 1984 Working Group evaluated bioassays in which rats and hamsters had been exposed to acetaldehyde by inhalation and intratracheal instillation. Rats exposed by inhalation showed an increased incidence of adenocarcinomas and squamous-cell carcinomas of the nasal mucosa. Hamsters exposed by inhalation had an increased incidence of laryngeal carcinomas; however, in another inhalation study in hamsters with a lower level of acetaldehyde, an increase in tumours was not observed. Exposure of hamsters to acetaldehyde by inhalation enhanced the incidence of respiratory tract tumours induced by intratracheal instillation of benzo[*a*]pyrene. Intratracheal instillation of acetaldehyde into hamsters did not result in an increased tumour incidence. A study that involved subcutaneous administration of acetaldehyde to rats was judged to be inadequate for evaluation. From these data, the Working Group concluded that

there was *sufficient evidence* for the carcinogenicity of acetaldehyde to experimental animals (see IARC 1985 for details and references).

The 1998 Working Group evaluated one bioassay in which rats were exposed to acetaldehyde by inhalation. A preliminary report of this bioassay had been considered by the 1984 Working Group. Exposure to acetaldehyde vapour increased the incidence of respiratory tract tumours, particularly nasal adenocarcinomas and squamous-cell carcinomas. From these data and those considered by the previous Working Group, the 1998 Working Group concluded that there was *sufficient evidence* for the carcinogenicity of acetaldehyde to experimental animals (see IARC 1999 for details and references).

3.3.1 *Oral administration*

Rat

Groups of 50 male and 50 female Sprague-Dawley rats, 6 weeks of age, were exposed to 0, 50, 250, 500, 1500 or 2500 mg/L acetaldehyde (purity, > 99.0%) in the drinking-water for 104 weeks. The experiment was terminated when the last animal died at 161 weeks of age. The administration of acetaldehyde in the drinking-water did not affect water or food consumption, body weight or survival. Complete histopathology was performed on all animals. The incidence of malignant mammary tumours (adenocarcinomas) was 6% (3/50), 18% (9/50), 6% (3/50), 20% (10/50) [$P = 0.0357$ compared with controls; one-tailed Fisher's exact test], 16% (8/50) and 12% (6/50) in female rats administered 0, 50, 250, 500, 1500 and 2500 mg/L acetaldehyde, respectively. Slight treatment-related increases were observed in the incidence of Zymbal gland carcinomas, ear duct carcinomas and oral cavity carcinomas in both sexes [not statistically significant]. Nasal cavity carcinomas (4%, 2/50) were only observed in male rats administered 2500 mg/L acetaldehyde. Sporadic incidences of lung adenomas and adenocarcinomas, forestomach acanthomas and squamous-cell carcinomas and intestinal fibromas and adenocarcinomas were observed in male and/or female rats administered acetaldehyde [no statistically significant difference]. Testicular interstitial-cell tumours were observed in all groups [not statistically significant]. The incidence of uterine adenocarcinomas was increased in rats administered 250 mg/L acetaldehyde (10% (5/50) versus 0/50 controls) [$P = 0.0281$; one-tailed Fisher's exact test]. The incidence of cranial osteosarcomas was increased in male rats administered 50 mg/L (10% (5/50) versus 0/50 controls) [$P = 0.0281$; one-tailed Fisher's exact test] and 2500 mg/L acetaldehyde (14% (7/50) versus 0/50 controls) [$P = 0.0062$; one-tailed Fisher's exact test]. Lymphomas and leukaemias combined were observed in all groups; compared with the controls (12% (6/50) males and 4% (2/50) females), the incidences were increased in male rats administered 50 mg/L (28%, 14/50) [$P = 0.0392$; one-tailed Fisher's exact test] and 1500 mg/L acetaldehyde (30%, 15/50) [$P = 0.0239$; one-tailed Fisher's exact test] and in female rats administered 500 mg/L acetaldehyde (8/50) [$P = 0.0458$; one-tailed Fisher's exact test] (Soffritti *et al.*, 2002b). [The Working Group noted that a variety of tumours were observed in male and female rats administered acetaldehyde in the

drinking-water. In some instances, the incidence in the treated groups was significantly greater than that in the respective control groups; nevertheless, these increases may be due to chance because no obvious dose–response relationship was observed in any of the tissues. The Working Group expressed concerns whether the doses were accurate due to the volatility of acetaldehyde.]

3.3.2 *Administration with a known carcinogen*

Rat

Groups of 18–20 male Fischer 344 rats, 6 weeks of age, were given a single intraperitoneal injection of 200 mg/kg bw NDEA [purity not specified] dissolved in 0.9% saline [volume not specified]. Two weeks later, the rats were administered 0, 2.5 or 5% acetaldehyde [purity not specified] in the drinking-water for 6 weeks. One week after being transferred to drinking-water that contained acetaldehyde, all rats were subjected to a two-thirds partial hepatectomy. One additional group was injected intraperitoneally with 0.9% saline instead of NDEA in 0.9% saline. Two weeks after the injection of saline, this group was placed on 5% acetaldehyde in the drinking-water; the group was also subjected to a partial hepatectomy. The experiment was terminated 8 weeks after the initial intraperitoneal injection and liver sections were prepared for immunohistochemical examination of glutathione *S*-transferase (GST) (placental type)-positive foci, a short-term marker for liver carcinogenesis. Rats injected with NDEA and exposed to 5% acetaldehyde consumed more drinking-water than those exposed to 2.5% acetaldehyde [$P < 0.001$; Student's *t*-test]. The administration of NDEA did not affect water consumption in rats given 5% acetaldehyde. Body weights, absolute liver weights and relative liver weights were significantly decreased ($P < 0.05$; Student's *t*-test) in rats given NDEA and 2.5 or 5% acetaldehyde compared with those given NDEA only; the effect was greater with 5% acetaldehyde. Body weights and absolute liver weights were significantly decreased [$P \leq 0.007$; Student's *t*-test] in rats given NDEA in 0.9% saline and 5% acetaldehyde compared with those given 0.9% saline and 5% acetaldehyde. GST (placental type)-positive foci were not detected in rats injected with 0.9% saline and given 5% acetaldehyde in the drinking-water but were observed in rats injected with NDEA; however, the number/cm^2, total area and mean diameter of the foci were not affected by the administration of either 2.5 or 5% acetaldehyde (Ikawa *et al.*, 1986) (Table 3.9).

A total of 250 Sprague-Dawley rats, 1 day of age, were given a single intraperitoneal injection of 15 mg/kg bw NDEA [purity not specified] in 100 µL normal saline. At 3 weeks of age, a subgroup of the rats (females only [number not specified]) was given 5% acetaldehyde [purity not specified] in the drinking-water for 9 weeks, an additional subgroup (females only [number not specified]) was given twice weekly injections of a 250-µL solution of 33% carbon tetrachloride [purity not specified] in mineral oil and 5% acetaldehyde in the drinking-water; and a further subgroup (females only [number not specified]) was given twice weekly injections of a 250-µL solution of 33% carbon

Table 3.9 Quantitative values of glutathione *S*-transferase (GST) (placental type)-positive foci in liver of male Fischer 344 rats treated with combinations of *N*-nitrosodiethylamine (NDEA) and acetaldehyde

NDEA (mg/kg bw)	Acetaldehyde (%)	GST-positive focal lesion		
		No./ cm^2	Total area (mm^2/ cm^2)	Mean diameter of focus (mm)
200	5	9.6±2.9	0.45±0.22	0.24±0.03
200	2.5	10.9±3.0	0.55±0.18	0.25±0.02
0	5	0	0	0

From Ikawa *et al*. (1986)

tetrachloride in mineral oil and control drinking-water. An additional group of 10 rats received a single intraperitoneal injection of 100 μL normal saline at 1 day of age. This group and a subgroup [number not specified] of the NDEA-treated animals were given control drinking-water only. The experiment was terminated when the rats were 12 weeks of age. Liver sections were prepared for examination by haematoxylin/eosin staining and by immunohistochemistry for the presence of GST (placental type)-positive foci. Of the rats administered carbon tetrachloride and acetaldehyde, 27% died during the experiment. Rats that received NDEA and acetaldehyde or NDEA, acetaldehyde and carbon tetrachloride weighed significantly less than those that received NDEA and carbon tetrachloride, NDEA alone or the normal saline ($P < 0.001$; Student's *t*-test). Liver foci or nodules were not present in normal saline-treated rats. Liver foci were present in rats treated with NDEA (100%, 10/10) or with NDEA and acetaldehyde (90%, 18/20); the incidence did not differ between these groups [two-tailed Fisher's exact test]. Liver nodules were present in rats treated with NDEA and carbon tetrachloride (65%, 13/20) or with NDEA, carbon tetrachloride, and acetaldehyde (100%, 10/10); the incidence was significantly greater in the group treated with NDEA, carbon tetrachloride and acetaldehyde ($P < 0.05$; χ^2 test). [The Working Group felt it was inappropriate to use a χ^2 test in this situation; a two-tailed Fisher's exact test indicated $P = 0.064$]. The extent of GST (placental type)-positive foci and/or nodules, as measured by number/cm^2 or area/cm^2, did not differ between rats treated with NDEA or with NDEA and acetaldehyde or between rats treated with NDEA and carbon tetrachloride or with NDEA, carbon tetrachloride and acetaldehyde. These data indicate that acetaldehyde does not potentiate the hepatocarcinogenic response induced by NDEA or by NDEA and carbon tetrachloride (Cho & Jang, 1993; Table 3.10).

Table 3.10 Glutathione *S*-transferase (GST) (placental type)-positive foci and/or nodules in liver of female Sprague-Dawley rats treated with combinations of *N*-nitrosodiethylamine (NDEA), acetaldehyde and carbon tetrachloride

Treatment group (no. of animals)	Foci (%)	Nodules (%)
Untreated (10)	0 (0)	0 (0)
NDEA (10)	10 (100)	0 (0)
NDEA/acetaldehyde (20)	18 (90)	0 (0)
NDEA/acetaldehyde/carbon tetrachloride (10)	3 (30)	10 (100)

From Cho & Jang (1993)

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4. Mechanistic and Other Relevant Data Relevant

4.1 Absorption, first-pass metabolism, distribution and excretion

4.1.1 *Humans*

(a) Ethanol

(i) *Absorption*

After oral ingestion, alcohol is slowly absorbed by the stomach, but is rapidly absorbed by simple diffusion once it passes into the small intestine. The oral pharmacokinetics of ethanol is subject to large interindividual variation in blood alcohol concentrations, even when the dose of ethanol is adjusted for gender and given to subjects who have fasted or have received a standardized meal before the dose (O'Connor *et al.*, 1998). Total volumes of body water and liver per unit of lean body mass should be taken into consideration as factors that influence the results of metabolic studies of ethanol. Since women have more fat and less body water per unit of lean body mass, they have higher blood alcohol concentrations than men after a dose of ethanol based on total body weight. Men and women have nearly identical peak blood alcohol concentrations after the same dose of alcohol per unit of total body water (Goist & Sutker, 1985). Some studies still found higher alcohol elimination rates in women, despite adjustment of the dose for total body water (Thomasson *et al.*, 1995). Women have a proportionately larger volume of liver per unit of lean body mass than men. When alcohol elimination rates were obtained by the intravenous steady-state infusion method, no gender difference was found in the rates per unit of liver volume (Kwo *et al.*, 1998).

The variation in blood alcohol concentrations after meals is even more complicated, because of the changes in first-pass metabolism with gender and age, and the ability of some common drugs (aspirin, cimetidine) to reduce first-pass metabolism (Roine *et al.*, 1990; Caballeria *et al.*, 1989a). This, plus the well known inaccuracy of self-reported alcoholic beverage consumption, complicates attempts to correlate different levels of reported alcoholic beverage drinking with the overall risk for cancer,

or with specific cancers (i.e. to generate estimated dose–response curves or predict safe levels of drinking).

(ii) *First-pass metabolism*

First-pass metabolism is represented by the difference between the quantity of a drug (ethanol) consumed orally and the amount that reaches the systemic circulation. Conceptually, first-pass metabolism is due to metabolism of ethanol in the gastrointestinal mucosa or liver during its passage through these tissues. It reduces the amount of ethanol that reaches target organs. The gut contains cytochrome P450s (CYPs) and alcohol dehydrogenases (ADHs). Ethanol is absorbed slowly from the stomach and is therefore subject to oxidation, while the ethanol that leaves the stomach is very rapidly absorbed from the upper small intestine, leaving little time for metabolism by that tissue. After absorption, ethanol travels to the liver, where a certain percentage is metabolized before passing into the *vena cava* (Julkunen *et al.*, 1985; Caballeria *et al.*, 1987). The relative proportion of first-pass metabolism is greatest with low doses of ethanol (0.3 g/kg bw, equivalent to approximately 20 g ethanol or two social drinks) when gastric emptying is slowed down (typically by the presence of food). Larger doses of ethanol or rapid gastric emptying reduce the difference between the areas under the curve (AUCs), which may then be too small to measure accurately. The phenomenon of first-pass metabolism is well established, but there remains debate about the relative contribution of the stomach and the liver (Lim *et al.*, 1993). The gastric mucosa expresses ADH isozymes (ADH1C, ADH5 and ADH7; see Section 4.2.1) that can oxidize ethanol. Gastric ADH activity was decreased in certain populations, e.g. in women (Frezza *et al.*, 1990; Seitz *et al.*, 1993), in individuals with atrophic gastritis and in alcoholics (DiPadova *et al.*, 1987; Pedrosa *et al.*, 1996) and in individuals who used medication (Caballeria *et al.*, 1989a; Roine *et al.*, 1990; Caballería, 1992); under these circumstances, the magnitude of first-pass metabolism was reduced. ADH7, a major gastric ADH isozyme, had low activity in endoscopic mucosal biopsies of the stomach in about 46% of Asians. Those who have lower ADH7 enzyme activity had lower rates of first-pass metabolism (Dohmen *et al.*, 1996), which suggests that ADH7 participates in the gastric oxidation of ethanol. In addition, higher rates of gastric emptying yielded higher peak blood alcohol concentrations and AUCs, and lower rates of first-pass metabolism (Holt, 1981). Combinations of type of alcoholic beverage, volume and concentration with the prandial state influence the rate of gastric emptying of alcohol and the resulting blood alcohol concentrations and AUCs (Roine *et al.*, 1991, 1993; Roine, 2000). The fact that first-pass metabolism is reduced when gastric emptying is rapid suggests that contact of alcohol with the stomach favours the absorption of alcohol across the mucosa, where it would be subject to oxidation. Oral intake of alcohol caused significantly higher blood alcohol concentrations and AUC in the fasted as compared with the fed state (DiPadova *et al.*, 1987). All of these reports are consistent with a role for the stomach mucosa in first-pass metabolism of ethanol.

Levitt and Levitt (2000) have pointed out that calculating first-pass metabolism from the AUCs is valid when the elimination of the drug under consideration is first-order, and that ethanol is cleared by zero-order kinetics for most of the elimination curve. They argued, with the use of a two-compartment model, that first-pass metabolism is only observed at very low doses of alcohol that does not cause inebriation (Levitt & Levitt, 1998). They also found that only a small fraction of ethanol absorbed from the stomach is metabolized in humans, and that most first-pass metabolism is hepatic (Levitt *et al.*, 1997a). The assertion that gastric ADH (Yin *et al.*, 1997) or first-pass metabolism (Ammon *et al.*, 1996) is reduced in women has been contested. Some investigators found no correlation between gastric ADH activity and first-pass metabolism (Brown *et al.*, 1995). Further, the total ADH activity in the stomach, calculated from the mass of the mucosa and its ADH activity, does not account for the differences between the AUCs of oral and intravenous intake of alcohol caused by the degree of ethanol metabolism (Yin *et al.*, 1997). Additionally, while humans and rats have similar first-pass metabolism ratios, their gastric ADHs have markedly different kinetic properties. The Michaelis constant (K_m) for ethanol of the human enzyme is 40 mM, while that of the rat enzyme is 5M (~125 times greater). These arguments suggest that first-pass metabolism of ethanol also occurs in the liver. Hepatic first-pass metabolism depends on the rate of ethanol absorption because portal alcohol concentration depends on the rate of absorption. Low rates of absorption and low portal venous ethanol concentrations would permit ethanol to be extensively oxidized by the low-K_m hepatic ADH isozymes. At higher rates of absorption and higher portal ethanol concentrations, these enzymes are saturated soon after drinking begins.

Ammon *et al.* (1996) compared the metabolic fates of ethanol given intravenously and deuterated ethanol given orally or into the duodenum. Since individuals served as their own controls, this reduced the intra-subject variability. First-pass metabolism accounted for about 8–9% of the oral dose, and the gastric contribution was estimated to be about 6% of the oral dose.

In summary, first-pass metabolism of orally ingested ethanol usually contributes a small fraction (up to 10% when a small dose of ethanol is consumed) of its total body elimination. When gastric emptying is rapid or the ethanol dose consumed is high, first-pass metabolism is quantitatively less important and, similarly, gender differences are probably not a major factor (Ammon *et al.*, 1996). The importance of demonstrating gastric first-pass metabolism, even though it may be small in magnitude, lies in the potential for local metabolism of ethanol in the digestive tract and in the likelihood that ADHs with a higher K_m are active at the high concentrations of ethanol achieved in the stomach (Caballeria *et al.*, 1989b; Roine 2000). An extensive discussion of the different metabolic pathways of ethanol is given in section 4.2.

(iii) *Distribution and excretion*

Ethanol is distributed throughout the total body water. After the distribution phase, the concentration of ethanol in the saliva (Gubała & Zuba, 2002) and in the colon is the same as that in the blood (Halsted *et al.*, 1973).

It has been estimated that over 90% of the elimination of ethanol occurs through oxidation in the liver. The remaining elimination is a combination extrahepatic oxidation and losses of small amounts of ethanol in the breath (0.7%), sweat (0.1%) and urine (0.3–4%) (Holford, 1987; Ammon *et al.*, 1996). The rate of removal of ethanol from the blood in the pseudo-linear segment of the elimination curve varies by two- to three-fold between individuals (Kopun & Propping, 1977; Martin *et al.*, 1985). This large interindividual variation was recently confirmed by use of the alcohol clamp technique (O'Connor *et al.*, 1998). The reasons for this variation are incompletely understood, but probably include variation in the size of the liver, in the activity of enzymes that catalyse alcohol oxidation or in the steady-state concentrations of substrates and products. Kwo *et al.* (1998) determined that the metabolic rate of ethanol correlated well with liver volume measured by quantitative tomography scanning, and that the higher rate of elimination of ethanol reported in women (when expressed on the basis of body weight) was accounted for by the fact that women have similarly sized livers to men, and thus a larger liver:body weight ratio.

Ramchandani *et al.* (2001) reported that elimination of ethanol (measured by means of alcohol clamping) could be accelerated by about 50% by ingestion of a meal, and that the composition of the meal was not important in this effect. [The Working Group noted the surprising result of this study, and considered that replication is needed.] This effect may be the result of changes in liver blood flow or possibly in the intrahepatic redox state. The polymorphic ADH enzymes (see below) have also been considered to contribute to this variability in the metabolic rates of alcohol.

(b) Acetaldehyde

Acetaldehyde is metabolized by aldehyde dehydrogenases (ALDHs), which are widely expressed in the mitochrondria and cytosol of most tissues (reviewed in Crabb, 1995), especially the mitochondrial form with a low K_m, so that almost all of the acetaldehyde produced by hepatic metabolism of ethanol is converted into acetate in the liver (reviewed in Gemma *et al.*, 2006). Chronic ethanol consumption is reported to reduce ALDH activity in the livers of alcoholics and to elevate blood acetaldehyde concentrations (reviewed in Nuutinen *et al.*, 1983, 1984); interpretation of the latter finding is complicated by the fact that red blood cells also present ALDH activity. A useful five-compartment physiologically-based pharmacokinetic model has recently been developed for quantitative analysis of acetaldehyde clearance (Umulis *et al.*, 2005).

4.1.2 *Experimental systems*

(a) Ethanol

Lim *et al.* (1993) examined the effect of infusion of ethanol into the pylorus-ligated stomach, duodenum or portal vein of rats and found that first-pass metabolism was only noted when ethanol was administered into the stomach. Experimentally, the systemic AUC of ethanol concentration is very sensitive to the rate of portal venous administration of ethanol (Smith *et al.*, 1992; Levitt *et al.*, 1994), which also accounts for the lack of first-pass metabolism with high doses of ethanol or rapid gastric emptying and therefore rapid delivery of ethanol to the liver. Only small differences in ethanol metabolites were found across the stomach in rats. Levitt *et al.* (1997b) found negligible oxidation of ethanol in the gastric mucosa as it was absorbed from the pylorus-ligated stomach in rats. This controversy was reviewed by Crabb (1997).

(b) Acetaldehyde

In rats, chronic treatment with 30% ethanol in the drinking-water or with an acute dose of 5 g/kg bw caused increases in specific activities of low-K_m and high-K_m ALDH in hepatic mitochondria (Aoki & Itoh, 1989). Feeding rats with a liquid diet containing alcohol resulted in a significant reduction in low K_m ALDH in the rectum but no change in the stomach, small intestine or colon; high-K_m ALDH was not altered in any tissue (Pronko *et al.*, 2002). Induced CYP2E1 may also act on acetaldehyde: liver microsomes from starved or acetone-treated rats exhibited an eightfold increase in acetaldehyde metabolism, with a K_m of 30 μM and a maximum velocity (V_{max}) of 6.1 nmol/mg/min, and this activity was inhibited by anti-CYP2E1 antibody (Terelius *et al.*, 1991). However, CYP2E1 activity towards acetaldehyde was much lower than that towards ethanol and was markedly inhibited by ethanol, which suggests that, under normal conditions, CYP2E1 probably does not play a major role in acetaldehyde metabolism (Wu *et al.*, 1998).

4.2 Metabolism

4.2.1 *Humans*

(a) Ethanol

In this section, tissue distribution of ADHs and other enzymes that oxidize ethanol and generate or oxidize acetaldehyde are reviewed, in order to assess which tissues are probably subject to the eventual carcinogenic effects of ethanol and acetaldehyde.

(i) *Alcohol dehydrogenase (ADH) pathway*

General description

The enzymes responsible for the major part of ethanol oxidation are the ADHs. All are dimeric enzymes with a subunit molecular weight of about 40 kDa; subunits

are identified by Greek letters. They are grouped into classes based upon enzymatic properties and the degree of sequence similarities. Enzyme subunits that belong to the same class can heterodimerize. Class I contains α, β and γ isozymes that are encoded by *ADH1A, ADH1B* and *ADH1C* genes. These enzymes have a low K_m for ethanol and are highly sensitive to inhibition by pyrazole derivatives. They are very abundant in the liver, and play a major role in the metabolism of alcohol. Class II ADH (π ADH, encoded by *ADH4*) is also abundant in the liver, has a higher K_m for ethanol and is less sensitive to inhibition by pyrazole than class I enzymes (Ehrig *et al.*, 1990). Class III ADH (χ ADH, encoded by *ADH5*) is present in nearly all tissues, is virtually inactive with ethanol but can metabolize longer-chain alcohols, α-hydroxy-fatty acids and formaldehyde (as a GSH-dependent formaldehyde dehydrogenase). A recent study suggested that class III ADH may be more active towards ethanol in a hydrophobic environment, and argued that liver cytosol may be such an environment (Haseba *et al.*, 2006). The class IV enzyme, σ-ADH, was purified from the stomach and oesophagus (Parés *et al.*, 1994). σ-ADH, the product of the *ADH7* gene, has the highest V_{max} of the known ADHs and is very active towards retinol, an activity that is shared by class I ADHs. This may be relevant to its expression in numerous epithelia that are dependent on retinol for their integrity. Class V ADH, encoded by the *ADH6* gene, is expressed in the liver and in the stomach, but the enzyme itself has not been purified (Yasunami *et al.*, 1991). The enzyme expressed *in vitro* has a high K_m for ethanol (about 30 mM) and moderate sensitivity to pyrazole inhibition (Chen & Yoshida, 1991).

Human ADHs

Variation in the *ADH* genes is unique to humans. The isozymes in class I are polymorphic; two alleles exist for *ADH1C* and three for *ADH1B* (Burnell & Bosron, 1989). The kinetic properties and geographical distribution of these allelic enzymes are shown in Table 4.1. The isozymes encoded by the three *ADH1B* alleles, each differing from the others at a single amino acid residue, vary markedly in K_m for ethanol and in V_{max}. Subunit β1 is most common in Caucasians and has a relatively low V_{max} and a very low K_m for ethanol. Subunit β2 is found commonly in Asians and was originally designated 'atypical' ADH. This gene is common among Ashkenazi Jews in Israel and the USA (Neumark *et al.*, 1998; Shea *et al.*, 2001; Hasin *et al.*, 2002). It has a substantially higher V_{max} and somewhat higher K_m than β1. The β3 isozyme was first detected in liver extracts from African-Americans on the basis of its lower pH optimum than that of the other ADH isozymes. It has also been found in Southwest American Indians and in groups of African origin in the Caribbean. It has a high K_m for ethanol and high V_{max}. Smaller differences in enzymatic properties are observed between the products of the *ADH1C* alleles. The V_{max} of the γ1 isozyme is about twice as high as that of the γ2 isozyme, while the K_ms (K_m at half saturation) for ethanol are similar. The γ1 ADH isozyme is found at high frequency in Asians and African-Americans; Caucasians have about an equal frequency of γ1 and γ2 *ADH* alleles (Burnell & Bosron, 1989; Bosron & Li, 1986). A variant of *ADH1C* (with a threonine at position 351) was detected in Native American populations, but not in Europeans or Africans; the kinetic effect

of this variant is unknown (Osier *et al*., 2002). Variants of ADH4 (corresponding to ADH2 in the new nomenclature; see Duester *et al*., 1999) were recently described in a Swedish population (Strömberg *et al*., 2002). A substitution of valine for isoleucine at position 308 was detected; the valine variant was less thermostable *in vitro*, but its kinetic properties were similar.

The widely varying V_{max} and K_m of the ADH1B and ADH1C isozymes suggest the possibility that individuals with different combinations of isozymes have different rates of elimination of ethanol. The presence of more active ADH isozymes was predicted to increase the rates of ethanol metabolism. This has been difficult to demonstrate, in part because a given isozyme constitutes only a fraction of the total capacity of the liver to oxidize ethanol and because the elimination rates of ethanol are rather variable even among individuals of the same *ADH* genotypes, or even twins (Kopun & Propping, 1977; Martin *et al*., 1985). To date, different *ADH1B* genotypes have been related to only a small portion of the intra-individual differences in ethanol elimination rates (Mizoi *et al*., 1994; Thomasson *et al*., 1995; Neumark *et al*., 2004). The *ADH1B*3* polymorphism has been shown to be associated with an approximate 15% increase in the rate of ethanol metabolism. Both *ADH1B*2* and *ADH1B*3* are protective against alcoholism (Edenberg *et al*., 2006). The *ADH1C* polymorphism did not affect the elimination of ethanol (Couzigou *et al*., 1991). It has not been possible to demonstrate increased blood levels of acetaldehyde in individuals with the higher-activity ADH enzymes except in individuals with inactive ADH2 (see below).

The ADH isozymes that have a high K_m for ethanol, e.g. β3, π and σ, are predicted to be more active when blood ethanol concentrations are high or in tissues of the upper gastrointestinal tract that are directly exposed to alcoholic beverages. Increased clearance of ethanol was seen in baboons with high blood ethanol concentrations (Pikkarainen & Lieber, 1980). This has not been tested directly in humans to date because of ethical concerns, but studies of intoxicated individuals indicated a more rapid elimination rate of ethanol when blood ethanol levels were higher (Brennan *et al*., 1995; Jones & Andersson, 1996).

An additional *ADH* genetic variant is a *Pvu* II restriction fragment length polymorphism in an intron of the *ADH1B* gene. It is not known whether the variant alters expression of the gene or is linked to another susceptibility locus; the *B* allele was found at a higher frequency in alcoholics and in patients with alcoholic cirrhosis (Sherman *et al*., 1993b). Single nucleotide polymorphisms (SNPs) that are presumed to influence expression of the *ADH4* gene (*ADH2* in the new nomenclature; Duester *et al*., 1999) have been linked to the risk for alcoholism (Edenberg *et al*., 2006); one polymorphism in the promoter affects gene expression (Edenberg *et al*., 1999). Similarly, sequence variants in the promoter of *ADH1C* may affect its expression (Chen *et al*., 2005a).

Tissue distribution of ADH

In humans, the liver expresses the highest levels of class I, II and III, which is consistent with the role of the liver in the elimination of ethanol. However, the enzymes are expressed in several other tissues, and may play a role in the toxicity or carcinogenicity

Table 4.1 Biochemical properties of human alcohol dehydrogenase (ADH)[a] and acetaldehyde dehydrogenase (ALDH)

Gene locus	Allele	Protein subunit	K_m	$V_{max}=(k_{cat})$	Ethnic/national distribution	References
			K_m ethanol (mM)			
ADH1A	*ADH1A*	α	4.2	27	Europe, Africa	Burnell & Bosron (1989); Ehrig *et al.* (1990)
ADH1B	*ADH1B*1*	β1	0.05	9	Europe, Africa	Bosron & Li (1986); Thomasson *et al.* (1995)
	*ADH1B*2*	β2	0.9	400	Asia	
	*ADH1B*3*	β3	34	300	Africa, Native American	
ADH1C	*ADH1C*1*	γ1	1.0	87	All	
	*ADH1C*2*	γ2	0.63	35	Europe	
	*ADH1C*3*		NR	NR	Native American	Osier *et al.* (2002)
ADH4	*ADH4*1*	π	34	40	All	
	*ADH4*2*		10.6	10.5	Sweden	Strömberg *et al.* (2002)
ADH5		χ	1000		All	
ADH6		NPT	30	NR	All	
ADH7		σ, μ	20	1510	All	

Table 4.1 (continued)

Gene locus	Allele	Protein subunit	K_m	$V_{max}=(k_{cat})$	Ethnic/national distribution	References
			K_m acetaldehyde (μM)			
ALDH1A1			30		All	
ALDH2	*ALDH2*1*		1		All	
	*ALDH2*2*				Asia	Crabb *et al.* (1989)
	*ALDH2*3*				Taiwan, China	Novoradovsky *et al.* (1995a)
ALDH1B1	*ALDH1B1*1*		NR			
(ALDH5)	*ALDH1B1*2*		NR			Sherman *et al.* (1993a)
ALDH9A1	*ALDH9A1*1*		30		All	Kurys *et al.* (1989)
	*ALDH9A1*2*					Lin *et al.* (1996)

k_{cat}, constant of turnover rate of enzyme-substance complex; K_m, Michaelis constant; NR, not reported; NPT, not purified from tissue; Vmax, maximum velocity

[a] For nomenclature of ADHs, see Duester *et al.* (1999); ADH1A, ADH1B and ADH1C are the new nomenclature of ADH1, ADH2 and ADH3 (old nomenclature), respectively. ADH4 is the old nomenclature of ADH2, ADH5 is the old nomenclature of ADH6 and ADH7 is the old nomenclature of ADH4 (see Duester *et al.*, 1999). The kinetic constants are noted for the homodimers of the ADH subunits listed (heterodimers behave as if the active sites were independent). The K_m values are in mM (ethanol) for ADH and μM (acetaldehyde) for ALDH, and the V_{max} values for ADHs are given in terms of turnover numbers (min^{-1}) for comparison. The column labelled ethnic/national distribution indicates which populations have high allele frequencies for these variants. The alleles are not limited to these populations.

of ethanol in those tissues. This has been studied in enzyme assays that use a variety of substrates to distinguish partially the various isozymes, and by use of northern blotting to assess mRNA levels. However, in the two studies, total class I *ADH* mRNA was analysed (i.e. by probing the blots with an *ADH1B* or *ADH1C* cDNA), which thus does not allow an understanding of locus-specific expression (see Table 4.2). Class I *ADH* is expressed in several tissues, in particular in the gastrointestinal tract (Yin *et al.*, 1993; Seitz *et al.*, 1996; Yin *et al.*, 1997), salivary glands (Väkeväinen *et al.*, 2001) and mammary gland (Triano *et al.*, 2003). Breast tissue expresses mRNA that corresponds to class I ADH and contains immunoreactive class I ADH by immunohistochemistry (localized to the mammary epithelial cells) and western blotting. These assays did not differentiate between ADH1A, ADH1B and ADH1C. Activity assays revealed the presence of ADH that is maximally active with 10 mM ethanol and can be inhibited with 4-methylpyrazole (Triano *et al.*, 2003). These characteristics are consistent with the presence of the *ADH1B* gene product, β-ADH (Triano *et al.*, 2003) or the *ADH1C* gene product, γ-ADH. Conversely, Gene Expression Omnibus (GEO) (microarray) profiles (www.ncbi.nih.gov) indicate the presence of *ADH1B* transcripts in breast tissue. Individuals homozygous for *ADH1C*1* had higher levels of acetaldehyde in the saliva after an alcohol challenge (Visapää *et al.*, 2004). Class IV is expressed at highest levels in the gums, tongue, oesophagus and stomach (Yin *et al.*, 1993; Dong *et al.*, 1996). Gastric mucosa contains several ADHs (γ-, σ- and μ-ADH) (Yin *et al.*, 1997), but σ-ADH was absent in the stomach biopsies from about 80% of Asians. Those who lacked this enzyme had a lower first-pass metabolism of ethanol (Dohmen *et al.* 1996), which suggests that σ-ADH is important in the gastric oxidation of ethanol. The mechanism for this deficiency has not been discovered, despite sequencing of exons in various ethnic groups. The human colon expresses ADH1C in the mucosa and, very weakly, ADH1B in the smooth muscle (Yin *et al.*, 1994). The relative expression of various *ADH* mRNAs can be estimated from the frequency of expressed sequence tags detected in cDNA libraries, which permits assessment of the probable level of expression of ADH enzymes in less accessible tissues. Figure 4.1 shows a compilation of data on the expression of *ADH1C, ADH4, ADH6* and *ADH7* transcripts in human tissues. These data may be subject to error due to the presence of repetitive elements. While not of human origin, there is a large mass of microorganisms in the gastrointestinal tract that may contribute to ethanol oxidation and the local formation of acetaldehyde. Microorganisms express numerous forms of ADH, which can contribute to the formation of acetaldehyde in the lower gastrointestinal tract or wherever microbial overgrowth occurs.

Variation of expression of ADH

In humans, the amount of ADH in the liver is not induced by chronic alcohol drinking before the development of liver disease (Panés *et al.*, 1989); however, with fasting, protein malnutrition and liver disease, ADH activity and the rate of ethanol elimination are decreased. Orchiectomy increased rates of ethanol elimination in humans (Mezey *et al.*, 1988). Little is known about the expression of extrahepatic ADH, with

Table 4.2 Distribution of alcohol dehydrogenase (*ADH*) and aldehyde dehydrogenase (*ALDH*) mRNAs in human tissues

Enzyme	mRNA	No mRNA detected	References
Class I (ADH1A, ADH1B, ADH1C)	Liver, lung, stomach, ileum, colon, uterus, kidney, spleen, skin, testis, ovary, cervix, heart, skeletal muscle, pancreas, prostate, adrenal cortex and medulla, thyroid, blood vessels (intima and media: mainly ADH1B detected as isozyme protein and activity)	Brain, placenta, peripheral blood leukocytes	Engeland & Maret (1993); Estonius *et al*. (1996); Allali-Hassani *et al*. (1997)
Class II (ADH4)	Liver, small intestine, pancreas, stomach, testis, kidney		Engeland & Maret (1993); Estonius *et al*. (1996)
Class III (ADH5)	All tissues examined		
Class IV (ADH7)	Stomach (other epithelial tissues not examined); small intestine, fetal liver highest of all		Yokoyama *et al*. (1995); Estonius *et al*. (1996)
ADH5	Liver, small intestine, fetal kidney; fetal liver highest of all		Estonius *et al*. (1996)
ALDH1A1	Liver, lung, kidney, skeletal muscle, pancreas; lower in testis, prostate, ovary, lung, small intestine		Stewart *et al*. (1996a)
ALDH2	Fetal heart, brain, liver, lung, kidney; adult liver, kidney, skeletal and cardiac muscle, lung; lower in pancreas		Stewart *et al*. (1996a)
ALDH1B1 (ALDH5)	Fetal heart, brain, liver, lung, kidney; adult liver, skeletal muscle, kidney; lower in brain, placenta, prostate, gut, lung, pancreas, ovary, testis		Stewart *et al*. (1996a)
ALDH9A1	Liver, skeletal muscle, kidney; low levels in heart, pancreas, placenta, lung, brain		Lin *et al*. (1996)

the exception of gastric ADH, which is reduced in women under 50 years of age who are heavy drinkers according to some investigators (Seitz *et al*., 1993) but not others (Yin *et al*., 1997).

(ii) *Microsomal oxidation pathway*

General description

Ethanol can be metabolized by microsomal ethanol-oxidizing systems, predominantly via CYP2E1. Other cytochrome-associated enzymes, CYP1A2 and CYP3A4, contribute to a lesser extent (Lieber, 2004a). Hamitouche *et al.* (2006) demonstrated that a wide variety of recombinant human CYP isoforms expressed in baculovirus-infected insect cells, with the exception of CYP2A6 and 2C18, can oxidize ethanol to

Figure 4.1. Tissue distribution of alcohol dehydrogenase (*ADH*), cytochrome P450 2E1 (*CYP2E1*) and catalase (*CAT*) transcripts reflected by the abundance of expressed sequence tags

Tissue	*ADH1C*	*ADH4*	*ADH6*	*ADH7*	*CYP2E1*	*CAT*
Adipose tissue	4251	0	0	0	0	144
Adrenal gland	611	0	0	0	0	32
Blood	0	17	0	0	53	367
Bone	13	0	0	0	13	55
Bone marrow	0	0	0	0	0	634
Brain	27	0	1	0	19	47
Cervix	62	0	20	0	0	41
Colon	153	0	14	0	0	84
Connective tissue	74	0	0	0	0	65
Eye	9	0	0	19	0	67
Heart	602	0	55	0	0	100
Kidney	56	0	84	0	0	79
Larynx	32	0	0	32	0	98
Liver	1930	729	252	0	843	319
Lung	169	0	0	40	28	69
Lymph node	10	0	0	0	0	146
Mammary gland	450	29	23	0	29	58
Muscle	122	0	8	17	8	69
Nerve tissue	550	0	0	0	39	118

Figure 4.1. (contd)

Tissue	*ADH1C*	*ADH4*	*ADH6*	*ADH7*	*CYP2E1*	*CAT*
Oesophagus	472	0	52	996	0	0
Ovary	0	0	9	0	28	0
Pancreas	36	4	4	0	0	95
Pharynx	0	0	0	0	0	0
Placenta	16	0	0	0	0	121
Prostate	32	0	0	0	6	51
Salivary gland	0	0	48	0	0	146
Skin	21	0	0	0	0	85
Small intestine	1558	22	90	0	0	22
Spleen	416	0	0	0	0	37
Stomach	254	0	48	9	0	19
Testis	28	0	11	0	8	48
Thymus	135	0	0	0	13	0
Thyroid	0	0	0	0	18	163
Tongue	30	0	15	90	0	30
Trachea	1444	0	0	288	0	20
Urinary bladder	132	0	0	33	0	99
Uterus	217	0	8	0	4	62
Vascular	118	0	0	0	0	157

The number given for each tissue is the abundance of the expressed sequence tag in terms of transcripts/million.
This Figure is compiled from information publicly available at the National Center for Biotechnology Information (NCBI) (see http://www.ncbi.nlm.nih.gov/unigene)

acetaldehyde, with K_ms of approximately 10 mM. CYP2E1 is associated with nicotinamide-adenine dinucleotide phosphate (NADPH)-CYP reductase in the endoplasmic reticulum, and reduces molecular oxygen to water as ethanol is oxidized to acetaldehyde. Its K_m for ethanol is about 10 mM; thus CYP2E1 may assume a greater role in ethanol metabolism at high blood alcohol levels. CYP2E1 is unusually 'leaky' and generates reactive oxygen species including hydroxyl radical, superoxide anion, hydrogen peroxide and hydroxyethyl radical. Thus, CYP2E1 is a major source of oxidative stress (Caro & Cederbaum, 2004).

Microsomal ethanol-oxidizing systems were originally thought to be implicated in the proliferation of the endoplasmic reticulum proliferation in liver biopsies from alcoholics. This was subsequently shown to be due to increased amounts of the enzyme now designated CYP2E1. CYP2E1 can be induced by chronic alcohol drinking, especially in the perivenular zone, and it may contribute to the increased rates of ethanol elimination in heavy drinkers. CYP2E1 is induced during fasting, by diabetes and by a diet high in fat, which may relate to its ability to oxidize the ketone, acetone (Lieber, 2004b). Liver biopsies of recently drinking alcoholics showed a substantial increase in *CYP2E1* mRNA indicating that pre- and post-translational mechanisms are responsible for the induction of this enzyme (Takahashi *et al.*, 1993).

Tissue distribution

CYP2E1 is expressed at high levels in the liver, as well as numerous other tissues, as demonstrated by western blotting, analysis of mRNA, or expressed sequence- tag analyses (Figure 4.1). The organs include kidney, lung, oesophagus, biliary epithelium, pancreas, uterus, leukocytes, brain, colon and nasal mucosa (Ingelman-Sundberg *et al.*, 1994; Crabb, 1995; McKinnon & McManus, 1996; Nishimura *et al.*, 2003). Western blots and activity assays have confirmed expression of CYP2E1 in the oesophagus, pancreas and lung, among other organs. In the brain, CYP2E1 was reported to be expressed in neurons and was induced by administration of ethanol (Tindberg & Ingelman-Sundberg, 1996). CYP2E1 has also been detected in breast tissue (El Rayes *et al.*, 2003)

Genetic variants

An *Rsa* I (−1019C >T) polymorphism (the *Rsa*I^+ allele is also named the *c1* allele) is located in the 5′-flanking region of the *CYP2E1* gene (Hayashi *et al.*, 1991) in a region that interacts with hepatocyte nuclear factor 1 (HNF-1). The *Rsa*I^- allele (*c2*) was more active in in-vitro transcription assays (Watanabe *et al.*, 1994), although a corresponding increase in CYP2E1 activity *in vivo* has not been confirmed unequivocally, based on the clearance of chlorzoxazone. The frequency of this polymorphism depends on continental origin: the *c2* variant is found in 5–10% of Caucasians and in 35–38% of East Asians (Garte *et al.*, 2001). A meta-analysis suggested a possible increased risk for gastric cancer in Asians homozygous for the *c2* allele (Boccia *et al.*, 2007). Another polymorphism, detectable with the DraI restriction enzyme, is located in intron 6 (Uematsu *et al.*, 1991). The distribution of the variant genotype (lacking the *Dra*I site) also depends on continental origin: 40–50% of East Asians carry this genotype, while

only 8–12% of Caucasians lack the *Dra*I site (Garte *et al*., 2001). A recently described polymorphism is the −71G >T polymorphism in the promoter region of the *CYP2E1* gene, which has been associated with enhanced transcriptional activity of promoter constructs in HepG2 cells (Qiu *et al*., 2004). Heterozygosity for this allele occurs in about 10% of Caucasians (Yang *et al*., 2001). The effects of the various genotypes on the pharmacokinetics of ethanol or the risk for alcoholic complications have been inconsistent.

A 96-base-pair insertion polymorphism is known to occur in the regulatory region of the *CYP2E1* gene. The insertion allele is relatively common in Asians (15%) but less so in Caucasians (2%) (Fritsche *et al*., 2000). The polymorphism was shown to increase the inducibility of CYP2E1 activity, as judged from chloroxazone metabolism, in patients who were obese or who had recently consumed alcoholic beverages (McCarver *et al*., 1998). Other polymorphisms have been catalogued by Agarwal (2001).

Since CYP2E1 has a high K_m for ethanol, it generates more acetaldehyde when ethanol concentrations are elevated. There is no evidence that acetaldehyde is a product inhibitor of CYP2E1; in fact, CYP2E1 can oxidize acetaldehyde to acetate, although probably not in the presence of ethanol.

(iii) *Ethanol oxidation by catalase*

Peroxisomal catalase is a tetrameric, haeme-containing enzyme. In addition to converting hydrogen peroxide to water and oxygen, it can oxidize ethanol to acetaldehyde in a hydrogen peroxide-dependent fashion. This pathway is not thought to be a major elimination pathway under most physiological conditions, but it may be important in certain tissues. Acatalasemic mice had longer sleep times than their normal counterparts (Vasiliou *et al*., 2006), which suggests a role of catalase in the effects of ethanol on the brain. It has been suggested that, by inhibiting fatty acid oxidation in the liver, ethanol shunts fatty acids to the peroxisomal pathway, which leads to the formation of hydrogen peroxide, which in turn increases the ability of catalase to oxidize ethanol. This would be particularly important if it occurred in extrahepatic tissues, since plasma fatty acid levels are increased under some circumstances by alcoholic beverage consumption.

There are only few studies on the role of catalase in the oxidation of ethanol. Catalase is expressed in nearly all tissues, as estimated from data on the abundance of expressed sequence tags (Figure 4.1). Catalase is also expressed by microorganisms in the colon and contributes to the formation of acetaldehyde from ethanol in the lower gastrointestinal tract (Tillonen *et al*., 1998). Absence of active catalase (acatalasaemia) is encountered in Asian populations. Several single nucleotide polymorphisms in the 5′ untranslated region and introns have been reported (Jiang *et al*., 2001), but there are no known effects of these variants on the expression or activity of the enzyme, nor on responses to ethanol.

(iv) *Non-oxidative ethanol metabolism*

Ethanol can be non-oxidatively metabolized to form fatty acid ethyl esters (FAEEs) (Laposata & Lange, 1986), which appear in human serum shortly after consumption of ethanol (Doyle *et al.*, 1994). These esters form during the hydrolysis of fatty acid esters (e.g. triglycerides) in the presence of ethanol; they are toxic to cells (Laposata *et al.*, 2002). Fatty acid ethyl ester synthase (FAEES) activity has been attributed to several distinct enzymes: an anionic form of GST (GST-pi-1) was reported by Bora *et al.* (1991) to be the same as FAEES III from human heart muscle. The purified enzyme has a K_m for ethanol of 300 mM, indicating that, *in vivo*, its activity increases in proportion to cellular ethanol concentration (Bora *et al.*, 1996), and it also exhibits carboxylesterase activity. However, the identity of FAEES as a GST was challenged by Board *et al.* (1993). Additional enzymes with FAEES activity include lipoprotein lipase, carboxylesterase ES10 in the liver and cholesterol esterase in the pancreas (Kaphalia *et al.*, 1997). These enzymes are found in several tissues that are affected by ethanol yet do not have high levels of ethanol-oxidizing enzymes (heart, brain, pancreas). In addition, it has been demonstrated that ethanol can be transferred to fatty acyl-coenzyme A (CoA) by an enzyme called acyl-CoA:ethanol *O*-acyltransferase (AEAT) (Diczfalusy *et al.*, 2001). AEAT activity is high in the human duodenum, pancreas and liver. This distribution of AEAT may explain the appearance of FAEEs in lipoproteins: FAEEs may be formed in the duodenum and intestine during absorption of fat in the presence of ethanol. These enzymes all appear to have a high K_m for ethanol, and thus are more active at high concentrations of ethanol (e.g., in the gut and after heavy drinking).

(v) *Other pathways of ethanol oxidation*

Several minor pathways of acetaldehyde formation have been suggested. Nitric oxide synthases 1 and 2 were reported to generate the 1-hydroxyethyl radical from ethanol in the presence of NADPH and arginine, which is to be expected given the presence of a CYP motif within the structure of the enzymes. The 1-hydroxyethyl radical can break down to form acetaldehyde (Porasuphatana *et al.*, 2006). Castro *et al.* (2001a,b) reported that cytosolic xanthine oxidoreductase can oxidize ethanol to acetaldehyde. CYP reductase (in the absence of specific forms of CYP known to be involved in ethanol metabolism, such as CYP2E1) was reported to oxidize ethanol to the 1-hydroxyethyl radical and acetaldehyde, possibly via the semiquinone form of flavine adenine dinucleotide (Díaz Gómez *et al.*, 2000). Other investigators reported the formation of acetaldehyde from ethanol in tissue extracts for which the responsible enzymes have not been identified or only to a limited extent, in studies with different cofactors and inhibitors (Castro *et al.*, 2002, 2003, 2006). It is possible that other oxidant species (hydroxyl radical) that are formed non-enzymatically may be able to oxidize ethanol to acetaldehyde. In addition, acetaldehyde can be formed during the degradation of threonine, putatively by threonine aldolase (Chaves *et al.*, 2002; Crabb & Liangpunsakul, 2007).

(b) Acetaldehyde

(i) *Acetaldehyde oxidation by ALDHs*

General description

Acetaldehyde is metabolized predominantly by nicotinamide-adenine dinucleotide $(NAD)^+$-dependent ALDHs. These enzymes have broad substrate specificity for aliphatic and aromatic aldehydes, which are irreversibly oxidized to their corresponding carboxylic acids (Vasiliou *et al.*, 2004). The ALDHs are expressed in a wide range of tissues, and their nomenclature has recently been revised. The original designations assigned numbers based on electrophoretic mobility, and different laboratories used different systems. Based on kinetic properties and sequence similarities, the ALDHs have been classified into three groups: class I (ALDH1) is present in the cytosol and has a low K_m for aldehydes; class II (ALDH2) is located in the mitochondria, has a low K_m and is the isozyme responsible for the majority of the further oxidation of acetaldehyde that is formed as a result of ethanol oxidation; and class III (ALDH3 or ALDH4) is present in the cytosol and in microsomes of tumours (stomach and cornea) and has a high K_m (Vasiliou *et al.*, 2000, 2004). In addition to these three groups, the human genes that code for ALDHs have been classified into 18 major families; updated information on classification and chromosome location can be found at: http://www.aldh.org/. In this system, *ALDH1* is designated *ALDH1A1* and *ALDH2* retains the same name. *ALDH3* is renamed *ALDH3A1* and *ALDH4* is designated *ALDH4A1*.

The most important enzymes for ethanol metabolism are cytosolic ALDH1A1 and mitochondrial ALDH2. Both are tetrameric enzymes composed of ~55-kDa subunits. ALDH1A1 has a very low K_m for NAD^+ and a low K_m for acetaldehyde (about 50 μM), and is very sensitive to disulfiram (Antabuse) *in vitro*. ALDH1A1 is involved in ethanol detoxification, metabolism of neurotransmitters and synthesis of retinoic acid (Vasiliou *et al.*, 2004). ALDH2 has a K_m for acetaldehyde less than 5 μM, and is less sensitive to disulfiram *in vitro*. These enzymes have high inhibition constants for reduced NAD (NADH), and thus remain active despite the high $NADH/NAD^+$ ratio established in cytosol and mitochondria during ethanol metabolism.

Numerous other ALDH enzymes have been studied. ALDHE3, which is encoded by the *ALDH9A1* gene (Lin *et al.*, 1996), has properties similar to ALDH1A: it is expressed in the cytosol and has a K_m for aliphatic aldehydes of about 30–50 μM (Kurys *et al.*, 1989). It has a low K_m for aminoaldehydes such as 4-aminobutyraldehyde, and hence may play a role in the metabolism of compounds derived from polyamines such as spermine, as well as trimethylaminobutyraldehyde in the synthesis of carnitine. It also oxidizes betaine aldehyde efficiently (Chern & Pietruszko, 1995). A cys115ser variant was reported by Lin *et al.* (1996), who named the alleles *ALDH9A1*1* and **2* (any differences in enzymatic activity are not yet known). *ALDH1B1* (originally designated *ALDH5*; Hsu & Chang, 1991) is unique among the *ALDH* genes as it lacks introns. Its enzyme is closely related to ALDH2 (72% sequence similarity) and its N-terminus may be a mitochondrial leader sequence. The *ALDH1B1* gene is polymorphic at two

different residues: valine or alanine at position 69 and leucine or arginine at position 90 of the protein (Hsu & Chang, 1991; Sherman *et al.*, 1993a), but it is not known if these substitutions alter its enzymatic properties. The highest levels of *ALDH1B1* mRNA are expressed in liver, kidney and skeletal muscle (Stewart *et al.*, 1996a).

ALDH3A1 and ALDH4A1 are widely expressed, but have low affinity for aliphatic aldehydes and higher affinity for aromatic aldehyde substrates. The ALDH3 family includes the cytosolic, tetrachlorodibenzo-*para*-dioxin-inducible ALDH, the hepatoma-associated ALDH, and the corneal and gastric ALDH3 (Vasiliou *et al.*, 1993, 2000, 2004). The gastric form may oxidize acetaldehyde generated during gastric metabolism of ethanol. ALDH4 has been identified as glutamic γ-semialdehyde dehydrogenase (or Δ-1-pyrroline-5-carboxylate dehydrogenase); ALDH6A1 is methylmalonyl semialdehyde dehydrogenase (Kedishvili *et al.*, 1992); the functions of ALDH7 and ALDH8 are not yet known (Hsu *et al.*, 1995; Fong *et al.*, 2006).

The *ALDH1A1* gene has been cloned (Hsu *et al.*, 1989), and the promoter has been studied in transfection and DNA-binding assays. A minimal promoter was shown to bind nuclear factor (NF)-Y/CP1 and octamer factors (Yanagawa *et al.*, 1995). Two polymorphisms, a 17 base-pair deletion (−416/-432; *ALDH1A1*2*) and a 3 base-pair insertion (–524; *ALDH1A1*3*), were discovered in the *ALDH1A1* promoter. *ALDH1A1*2* was observed at frequencies of 0.035, 0.023, 0.023 and 0.012 in Asian, Caucasian, Jewish and African-American populations, respectively. *ALDH1A1*3* was observed only in the African-American population at a frequency of 0.029 (Spence *et al.*, 2003). In an African-American population, a significant association was observed between the *ALDH1A1*3* allele and patients with alcoholism (p=0.03); a trend was also observed that the *ALDH1A1*2* allele was more frequent in the alcoholic group (p=0.12). In Asian populations, *ALDH1A1*3* was not observed and *ALDH1A1*2* yielded no significant association with alcoholism, when controlling for the *ALDH2*2* genotype (Spence *et al.*, 2003). In a population of Indians in Southwest California, it was suggested that the *ALDH1A1*2* allele may be associated with a protective effect against the development of alcohol use disorders (Ehlers *et al.*, 2004). In inhabitants of Trinidad and Tobago of East Indian and African descent, the *ALDH1A1*2* allele was found to be associated with increased risk for the development of alcoholism in those of Indian origin (Moore *et al.*, 2007).

The importance of ALDH2 in ethanol oxidation is emphasized by the alcohol flush reaction (Goedde *et al.*, 1979; Harada *et al.*, 1981). Alcohol-induced facial flushing is common in Japanese, Chinese and Koreans, while these reactions are rare among Caucasians (Wolff, 1972). Flushing correlates with the accumulation of acetaldehyde (Mizoi *et al.*, 1979). In non-flushers, drinking alcoholic beverages elicited a small increase in acetaldehyde levels (to 3–5 μM); in flushers, the levels were variable, but could exceed 80 μM (Enomoto *et al.*, 1991a,b). The activity of ALDH (ALDH1 and ALDH2) in hair roots was examined in individuals who reported flushing (associated with ALDH1-deficiency characterized by electrophoretic assays); about 40% of Japanese had ALDH2 activity (Harada *et al.*, 1982), and most flushed when they

drank, which indicates that ALDH2 plays a crucial role in maintaining low levels of acetaldehyde during ethanol oxidation (Harada *et al*., 1983). The *ALDH2*2* allele deficiency was reported in South American and North American Indians (Novoradovsky *et al*., 1995a) and ALDH2 enzyme deficiency was shown in Chachi Indians of Ecuador (Novoradovsky *et al*., 1995b). However, a new allele, *ALDH2*3*, was detected in North American Indians. The mutation responsible for the deficiency is a G→A substitution that results in a glutamate to lysine substitution at position 487 of the enzyme (Yoshida *et al*., 1984; Crabb *et al*., 1989). The normal allele is *ALDH2*1* and the mutant allele is designated *ALDH2*2*. The *ALDH2*2* heterozygotes, as well as homozygotes, are ALDH2-deficient (Crabb *et al*., 1989), but the homozygotes have much higher acetaldehyde levels after they drink alcoholic beverages than the heterozygotes; consistent with this, the heterozygotes have residual low-K_m ALDH activity in liver biopsies (Enomoto *et al*., 1991a). It is estimated that about 30% of total liver ALDH activity is ALDH2 and 70% is contributed by other forms (ALDH1A1, ALDH9A1 and possibly ALDH1B1) when assayed with 200 μM acetaldehyde (Yao *et al*., 1997).

Studies on the effect of ALDH2-deficiency on ethanol elimination rates are limited by the severity of the flushing reaction. Early studies did not show a difference in ethanol elimination rates between flushers and non-flushers (Mizoi *et al*., 1979; Inoue *et al*., 1984), but a subsequent study detected reduced rates of ethanol elimination in individuals with ALDH2-deficiency when the subjects were stratified by *ADH* genotype (Mizoi *et al*., 1994).

A mutation in the *ALDH2* promoter was simultaneously reported by Harada *et al.* (1999) and Chou *et al.* (1999). This A/G variant occurs at about −360 base-pair distance from the hepatocyte nuclear factor 4 (HNF4) binding site. The A allele is less active than the G allele in reporter-gene transfection assays (Chou *et al*., 1999), and is less common in alcoholics with active ALDH2 (Harada *et al*., 1999). These variants have been found in all ethnic groups. There is also one additional reported variant, designated $ALDH2^{2Taiwan}$, which involves a glutamate to lysine substitution at position 479 in addition to the *ALDH2*2* variant (Novoradovsky *et al*., 1995a). Whether this variant alters the dominant negative effect of *ALDH2*2* is unknown.

Tissue distribution

ALDH1A1 and *ALDH2* mRNAs are expressed in a variety of human tissues in addition to the liver (Stewart *et al*., 1996a); *ALDH2* mRNA was particularly abundant in the kidney, muscle and heart. Low levels of *ALDH1A1* and *ALDH2* mRNAs were found in the placenta, brain and pancreas; these are obviously target organs for alcoholic pathology, consistent with the hypothesis that the presence of ALDHs is protective against the toxicity of acetaldehyde (Table 4.2 and Figure 4.2). Colonic and oesophageal mucosae express low levels of low-K_m ALDH activity (Yin *et al*., 1993, 1994). In the colon, the activity of low-K_m ALDH was similar whether the individual was ALDH2-sufficient or -deficient, which supports the notion that the major enzyme present was ALDH1A1. In the oesophagus, overall low-K_m ALDH activity was low and was predominantly attributable to ALDH1A1. Morita *et al.* (2005) reported the

presence of immunoreactive ALDH2 in the oesophagus of moderate-to-heavy alcoholic beverage drinkers, but no or low expression of ALDH2 in the oesophagus of non-drinkers or light drinkers, and speculated that the difference was related to *ALDH2*2* status; however, this allele has not been associated with the absence of immunoreactive ALDH2 protein in the past. Breast epithelium is reported to express ALDH1A1 and ALDH3 (Sreerama & Sladek, 1997). There are no reports of ALDH2 enzyme activity in the breast, but the expressed sequence tag database suggests that *ALDH2* and *ALDH1B1* transcripts are present (Figure 4.2). Examination of the GEO profiles database (at: http://www.ncbi.nih.gov/geo) suggests that normal breast tissue may express *ALDH1A1* and *ALDH2* mRNA.

4.2.2 *Experimental systems*

(a) Ethanol

(i) *ADH pathway*

Several classes of *Adh* genes are expressed in animals: class VI *Adh* was reported in deer-mouse and rat liver (Höög & Brandt, 1995); and class VII *Adh* was cloned from chicken (Kedishvili *et al.*, 1997), but the human homologues of these have not been found.

Tissue distribution

As in humans, ADHs are expressed in a variety of tissues in rats and mice. High levels of class I ADH activity were found in the liver, lung, small intestine, colon, duodenum, stomach, kidney, testis, epididymis and uterus, and mRNA was detectable in most tissues of rats (Estonius *et al.*, 1993; Table 4.3). Cytosolic ADH has been found in the parotid gland of rats, and chronic alcoholic beverage use was associated with parotid steatosis (Maier *et al.*, 1986). Class IV ADH is found in the blood vessels of rats (Allali-Hassani *et al.*, 1997). ADH activity with octanol was reported to be present in numerous epithelial tissues, which may reflect the presence of either class II or class IV *Adh* (Svensson *et al.*, 1999; Crosas *et al.*, 2000). Haber *et al.* (1998) reported that pancreatic acinar cells metabolize ethanol via class III *Adh* (see Table 4.3) (Julià *et al.*, 1987; Boleda *et al.*, 1989).

Variation in expression

Fasting reduces ADH activity in rats (Bosron *et al.*, 1984), which correlates with ethanol elimination rates (Lumeng *et al.*, 1979), whereas growth hormone induces rat ADH activity (Mezey & Potter, 1979). Chronic ethanol consumption can affect the expression of Adh: ethanol increased hepatic ADH activity in male rats by reducing testosterone levels (Rachamin *et al.*, 1980). The amount of ethanol consumed from conventional liquid diets did not alter liver ADH activity, whereas higher doses achieved by intragastric infusion of ethanol induced this activity. In rats, class I *Adh* mRNA and enzyme activity are inducible by administration of high levels of ethanol by gastric infusion. This leads to cyclic changes in blood ethanol concentrations despite continuous infusion of ethanol. Regulation of rat hepatic *Adh* gene expression by ethanol has

Figure 4.2. Tissue distribution of aldehyde dehydrogenase (*ALDH*) transcripts reflected by the abundance of expressed sequence tags

Tissue	*ALDH1A1*	*ALDH2*	*ALDH1B1*	*ALDH9A1*
Adipose tissue	360	504	72	432
Adrenal gland	1506	384	29	324
Blood	123	53	23	169
Bone	27	55	55	41
Bone marrow	306	0	20	102
Brain	360	119	22	185
Cervix	103	20	0	228
Colon	272	198	59	59
Connective tissue	326	34	6	217
Eye	231	115	14	106
Heart	178	133	33	156
Kidney	648	84	75	338
Larynx	65	65	0	0
Liver	1439	376	14	138
Lung	437	138	8	115
Lymph	0	134	22	22
Lymph node	0	83	10	20
Mammary gland	81	35	23	245

Figure 4.2 (contd)

Mouth	477		57		28		159	
Muscle	78		34		0		95	
Nerve	119		239		0		119	
Oesophagus	156		0		104		156	
Ovary	65		150		0		28	
Pancreas	182		91		9		54	
Pharynx	351		43		0		329	
Placenta	84		40		3		90	
Prostate	135		65		35		175	
Salivary gland	48		0		0		97	
Skin	217		95		74		127	
Small intestine	5103		112		22		474	
Spleen	813		18		18		302	
Stomach	1047		264		48		97	
Testis	733		60		37		266	
Thymus	193		0		0		296	
Thyroid	90		200		54		345	
Tonsil	0		116		0		0	
Trachea	2784		0		20		329	
Urinary bladder	725		65		0		32	
Uterus	928		58		62		150	
Vascular	533		59		19		197	

The number given for each tissue is the abundance of the expressed sequence tag in terms of transcripts/million.
This Figure is compiled from information publicly available at the National Center for Biotechnology Information (NCBI) (see http://www.ncbi.nlm.nih.gov/unigene)

Table 4.3 Alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) enzyme activity and mRNA distribution in rats

Enzyme	Activity	mRNA	References
Class I (ADH3)	Liver, lung, small intestine, colon, kidney, testis, epididymis, uterus	Most tissues in varying amounts	Estonius *et al.* (1993); Boleda *et al.* (1989)
Class II (ADH1)	Eye, ear canal, nasal and buccal mucosa, trachea, lung, tongue, oesophagus, stomach, rectum, vagina; lower in intestine, adrenals, colon, testis, epidiymis, ovary, uterus, urinary bladder, penis, skin	Liver, duodenum, kidney, stomach, spleen, testis	Estonius *et al.* (1993); Boleda *et al.* (1989) Note: Reported studies probably detected both class II and class IV ADH in various tissues, due to overlapping substrate specificities
Class III (ADH2)	Ubiquitous	All tissues	Estonius *et al.* (1993); Boleda *et al.* (1989)
Class IV (σ-ADH)	Skin, ears, eye, nasal and buccal mucosa, tongue, vagina, oesophagus, penis, rectum, blood vessels	Not examined	
ALDH1A1	Liver	Not examined	
ALDH2	Liver, vascular tissue	Not examined	Sydow *et al*. (2004)
ALDH1B1	Liver	Not examined	
ALDH9A1	Liver	Not examined	Kurys *et al.* (1989)

Most of the ADH activity data are from Julià *et al.* (1987); Boleda *et al*. (1989); Allali-Hassani *et al.* (1997) (blood vessels).

been proposed to be due to induction of the transcription factor CCAAT enhancer-binding protein β (C/EBPβ) and suppression of C/EBPγ, a truncated, inhibitory form of C/EBPβ called liver inhibitory protein (He *et al*., 2002), and of sterol regulatory element-binding protein-1 (SREBP-1) (He *et al*., 2004). In addition, chronic intragastric infusion of ethanol increases portal vein endotoxin, which can induce *Adh* mRNA via increased binding of upstream stimulatory factor to the *Adh* promoter (Potter *et al*., 2003).

Role of substrate and product concentrations in controlling ADH activity

Modelling of ethanol oxidation in rat liver indicated that ADH activity was controlled by the total activity of the ADH enzyme as well as by product inhibition by NADH and acetaldehyde; thus ADH operates below its V_{max} at steady-state (Crabb *et al*., 1983). Liver NADH levels are elevated during ethanol oxidation because the first enzyme in the malate–aspartate shuttle, malate dehydrogenase, has a high K_m for NADH, and thus is more active as the level of NADH rises. The high level of NADH does not limit the rate of the shuttle or mitochondrial re-oxidation of NADH, as had been suggested (Crow *et al*., 1982). Flux through the pathway is also dependent on the total activity of

ADH. Reduction in total ADH activity (as occurs during fasting) reduced the ability of the liver to oxidize ethanol in rats. In contrast, increases in ADH activity did not increase the metabolic rate proportionally (Crabb *et al.*, 1983). Metabolism of ethanol can be acutely increased when a large intragastric dose of ethanol (5 g/kg bw) is given to rats. This swift increase in ethanol metabolism is dependent upon activation of the sympathic nervous system, activation of Kupffer cells, depletion of liver glycogen, increased plasma fatty acids and increased provision of cofactors for ADH (NAD^+) and catalase (hydrogen peroxide). This phenomenon may contribute to the hepatotoxicity of heavy alcoholic beverage consumption (Bradford & Rusyn, 2005).

Regulation of *Adh* gene expression *in vitro*

The *Adh1* promoters are all active in the liver. Transfection studies and experiments using nuclear extracts have shown that the *Adh* promoters interact with ubiquitous transcription factors (e.g. TATAA binding factors, upstream stimulatory factor, CCAAT transcription factor/NF-1 and specificity protein 1-like factors), as well as tissue-specific factors (e.g. HNF-1, D box-binding protein and C/EBPα and β; reviewed by Edenberg, 2000). The *Adh5* (class III *Adh*) and *Adh7* (class IV *Adh*) promoters lack TATAA boxes (Edenberg, 2000). The *Adh5* promoter is GC rich, which is a characteristic of housekeeping genes and consistent with its ubiquitous expression. Binding sites for thyroid hormone, retinoic acid and glucocorticoid receptors have been identified in the upstream regions of Class I *Adh* genes. In rats, hypothyroidism increased and hyperthyroidism decreased ADH activity in liver and kidney. It is not clear whether these effects occur at the level of transcription or translation, on the half-life of the ADH protein, or a combination of these (Dipple *et al.*, 1993). Growth hormone increased ADH activity in rats and cultured hepatocytes, while thyroid hormones decreased it (Potter *et al.*, 1993); androgens increased ADH activity in mouse kidney and reduced it in the adrenal glands (in Edenberg, 2000).

No post-translational modifications of the ADH enzyme have been recognized. However, in an in-vitro study peroxynitrite oxidized the active site of yeast ADH, which caused disulfide-bond formation and release of zinc, which inactivated the enzyme (Daiber *et al.* 2002); this could lead to inactivation of ADH at sites where nitric oxide is formed. Whether this is physiologically relevant remains to be shown.

(ii) *Microsomal ethanol-oxidation pathway*

Control of expression of CYP2E1

The human *CYP2E1* gene spans 11 kb, contains 9 exons and a typical TATAA box. HNF1α is critical for its expression (Liu & Gonzalez, 1995).

Expression is also controlled both at the level of mRNA (high concentrations of ethanol can induce transcription of the *CYP2E1* gene; Takahashi *et al.*, 1993) and by stabilization of the protein, as observed for ethanol, acetone and pyrazole derivatives (Takahashi *et al.*, 1993; Lieber, 2004a,b). Other data suggest that additional signals may affect its expression. For instance, CYP2E1 can be induced by interleukin (IL)-4 in human hepatoma cells (Lagadic-Gossmann *et al.*, 2000) and by phorbol ester and other

cellular stress factors, such as ischaemic injury in astrocytes (Tindberg, 2003). Insulin reduced the expression of CYP2E1 post-transcriptionally by destabilizing its mRNA (Woodcroft *et al.*, 2002). Castro *et al.* (2006) reported ethanol-inducible, microsomal ethanol-oxidizing activity in the rat mammary gland. In young female Sprague-Dawley rats, ethanol fed in a liquid diet resulted in a 30–50% increase in ethanol metabolism in mammary tissue extracts. CYP2E1 is also expressed in the kidney (Ronis *et al.*, 1991), lung (Yang *et al.*, 1991), rat colon mucosa (Hakkak *et al.*, 1996), brain (Tindberg & Ingelman-Sundberg, 1996), duodenum and jejunum (Shimizu *et al.*, 1990). After chronic feeding of ethanol, immunoreactive CYP2E1 was found in the buccal mucosa, oesophagus, tongue, forestomach and proximal colon of rats (Shimizu *et al.*, 1990).

CYP2E1 is reported to be a substrate for cAMP-dependent protein kinase A. Phosphorylation of a serine residue inactivates the enzyme (Oesch-Bartlomowicz *et al.*, 1998). Whether this plays a physiological role in controlling the activity of this enzyme is not clear, although, under several conditions in which CYP2E1 activity is low (fasting, diabetes), hepatic protein kinase A activity is high.

(iii) *Oxidation by catalase*

The activity of catalase depends upon the availability of hydrogen peroxide. When fatty acids were perfused through rat liver, peroxisomal β-oxidation generated hydrogen peroxide and stimulated ethanol oxidation. This raises the possibility that, under conditions of increased fatty acid oxidation (fasting, high fat diet) or oxidant stress (and production of hydrogen peroxide), catalase-mediated ethanol oxidation may be increased. Chronic ethanol feeding was reported to increase catalase activity (Orellana *et al.*, 1998). In ADH-deficient deermice, ethanol and methanol oxidation were highly sensitive to inhibition by the catalase inhibitor, aminotriazole (Bradford *et al.*, 1993).

Regulation of catalase gene expression *in vitro*

Little is known regarding transcriptional control of catalase expression in mammalian cells. The rat catalase gene is a single-copy gene that spans 33 kb. The promoter region lacks a TATAA box and an initiator consensus sequence, contains multiple CCAAT boxes and GC boxes, and contains multiple transcription initiation sites, consistent with its housekeeping function (Nakashima *et al.*, 1989). The rat catalase promoter contains a peroxisome proliferator-responsive element (Girnun *et al.*, 2002) and can be induced by peroxisome proliferators. In cells exposed to hydrogen peroxide, the non-receptor protein tyrosine kinases, Abl and Arg, associate with catalase and can activate it by phosphorylating two tyrosine residues. However, at higher concentrations of hydrogen peroxide, phosphorylation of these residues can stimulate ubiquitination and proteasomal degradation of the enzyme (Cao *et al.*, 2003).

(b) Acetaldehyde

Aldehyde dehydrogenase

Ethanol does not induce ALDH2 expression. Dietary restriction and protein deficiency, both common in human alcoholic patients, reduced ALDH2 activity in rats.

A recent report (Moon *et al.*, 2006) suggested that ALDH2 may be inhibited during chronic ethanol feeding through oxidant stress, which leads to the formation of nitric oxide and nitrosylation of the active cysteine site of ALDH2. This was not recognized in earlier studies, partly because thiol reagents such as dithiothreitol, which is used in the preparation of tissue and cell homogenates, reverse the formation of the nitrosylated enzyme. ALDHs are widely distributed in animal tissues (Oyama *et al.*, 2005) (Table 4.3 and Figure 4.2). ALDH was found in the nasal respiratory epithelium (the ciliated epithelial cells) of rats, although the olfactory epithelium lacked ALDH activity. There was low activity in the trachea but the Clara cells of the lower bronchioles exhibited high activity (Bogdanffy *et al.*, 1986). However, it is unknown which class of ALDH this represents. ALDH2 is important in the bioactivation of nitrate vasodilators such as glyceryl trinitrate; the enzyme is present in the muscle layer of the blood vessels (Sydow *et al.*, 2004).

Because of the influence of the *ALDH2* genotype on alcoholic beverage consumption in humans, variations in rat ALDH2 enzyme have been investigated. Several coding region polymorphisms exist. Rats that have a preference for ethanol (ethanol-preferring) express an ALDH2 with glutamine at position 67 (ALDH2Gln), while rats that do not (non-preferring) express an ALDH2 with arginine at that position (ALDH2Arg). However, the enzymatic properties of the purified enzymes are similar, and the different isozymes were not associated with high or low ethanol intake in the F_2 generations of intercrosses of the ethanol-preferring and non-preferring rats (Carr *et al.*, 1995). These variants are also found in rats that accept (ethanol-accepting) ethanol and those that do not (non-accepting). Of interest, the non-accepting rats had higher blood acetaldehyde levels after administration of ethanol; however, rat strains did not differ in the frequencies of the *Aldh2Arg* and *Aldh2Gln* alleles (Koivisto *et al.*, 1993). While there was no reported difference in acetaldehyde levels after ethanol consumption between UChA (low ethanol-drinking) and UChB (high ethanol-drinking) rat strains, 94% of the UChA rats had the *Aldh2Arg* allele, while the UChB rats had either the Sprague-Dawley allele *Aldh2Gln* or the *Aldh2Arg* plus an additional substitution of lysine for glutamine at position 479, i.e. *Aldh2Lys*. Ethanol-drinking patterns in these rats correlated well with the *Aldh2* genotype (Sapag *et al.*, 2003). The K_m for NAD^+ was 4- to 5-fold higher for the ALDH2Arg enzyme than for ALDH2Gln or ALDHLys. It appears that variation in ALDH2 activity in rats may affect their ethanol preference, and that there may be strain differences in acetaldehyde metabolism that are relevant to studies on the carcinogenicity of ethanol and acetaldehyde.

Transgenic mice that lack ALDH2 activity have been created by knockout technology (Isse *et al.*, 2002). These mice have reduced ethanol preference and, when exposed to higher doses of ethanol by gavage, have elevated acetaldehyde levels in the blood, liver and brain (Isse *et al.*, 2005). These animals have been used for toxicological studies of ethanol and acetaldehyde (see Section 4.5).

In-vitro studies

The human and rat recombinant ALDH2*2 enzymes expressed in *Escherichia coli* have a much higher K_m for NAD^+ and a lower V_{max} compared with the wild-type enzyme (Farrés *et al.*, 1994a). Xiao *et al.* (1995, 1996) expressed the two human *ALDH2* alleles in tissue cultures of Hela and CV-1 cells, which do not naturally express ALDH2. *ALDH2*1* directed expression of an active low-K_m ALDH2. The *ALDH2*2* allele directed expression of a functionally inactive but immunoreactive protein (ALDH2Lys). Transduction of *ALDH2*2* into *ALDH2*1*-expressing cells (*Aldh2Glu*) reduced the ALDH2 activity substantially, which suggests that only enzymes with tetramers that contain either three or four wild-type subunits are active (Xiao *et al.*, 1995); the *ALDH2*2*-containing tetramers were less stable and further reduced the activity of heterotetramers (Xiao *et al.*, 1996). The X-ray crystal structure of ALDH2 showed that the mutation occurs in a region of the protein that is involved in subunit–subunit interaction (Steinmetz *et al.*, 1997). Introduction of a positive charge at position 487 (Glu 487 Lys) disrupts ionic bonds with arginines that are normally neutralized by the glutamate; this may suffice to inactivate the adjacent subunits and explain the dominance of the mutation.

The *ALDH2* gene has been studied extensively. It has no TATAA box (Hsu *et al.*, 1988); similarly to *ALDH1A1*, it has a binding site for the ubiquitous NF-Y/CCAAT protein 1 (NF-Y/CP1) near the transcription start site (Stewart *et al.*, 1996b). Pinaire *et al.* (1999) found that, upstream from the CCAAT box, there is a promoter site bound by hepatocyte nuclear factor 4 (HNF-4) and retinoid X receptor, which activate expression, while apolipoprotein A regulatory protein-1, chicken ovalbumin upstream promoter-transcription factor and peroxisome proliferator-activated receptor δ oppose this activation. It is probable that this site integrates the effects of several different transcription factors in different tissues and this regulatory mechanism may explain the tissue specificity of expression.

4.3 Genetic susceptibility

4.3.1 *Humans*

(a) Genes encoding enzymes involved in alcohol metabolism

(i) *ADH-1B*

ADH1B (previously called *ADH2*) is polymorphic, and its superactive *ADH1B*2* allele is highly prevalent among East Asians (i.e. 54–96%; Goedde *et al.*, 1992), but relatively rare among Caucasians (i.e. 1–23%). The less active *ADH1B*1* is a risk factor for alcoholism in both East Asians and Caucasians (Zintzaras *et al.*, 2006). *ADH1B*1/*1* carriers showed an increased risk for upper aerodigestive tract cancer (odds ratio, 1.6–8.2 versus *ADH1B*1/*2* and *ADH1B*2/*2* carriers) in eight case–control studies of Japanese, Taiwanese, Thai and central European populations (reviewed in Yokoyama

& Omori, 2005; see Table 4.4) and in a prospective cohort study in cancer-free Japanese alcoholics (hazard ratio, 2.0; Yokoyama *et al.*, 2006b; Table 4.5), but there was no increased risk found in two Japanese studies, including a study of women that involved a small number of cases (Yang *et al.*, 2005; Yokoyama *et al.*, 2006a).

Two Japanese case–control studies reported overall negative results for an association between *ADH1B* genotype and hepatocellular carcinoma (Takeshita *et al.*, 2000a; Sakamoto *et al.*, 2006; Table 4.6). One Japanese case–control study reported an *ADH1B*1*-associated increased risk for colorectal cancer (odds ratio, 1.9 for **1/*1*; 1.4 for **1/*2*; 1.0 for **2/*2*; Matsuo *et al.*, 2006a). A statistically significant increase in the risk for colorectal cancer was observed for the *ADH1B*1/*1* genotype compared with the *ADH1B*2/*2* genotype, with adjustment for alcoholic beverage intake and other factors. The interaction with alcoholic beverage intake was also examined for the composite genotypes of *ADH1B* and *ALDH2* (see below). A case–control study in Spain reported a statistically non-significant decrease in the risk for the *ADH1B*2/*2* versus *ADH1B*1/*1* genotype (Landi *et al.*, 2005; Table 4.6).

In a large German study (Lilla *et al.*, 2005), a decreased risk for breast cancer for high alcoholic beverage intake (≥12 g ethanol/day versus no intake) was observed in women with the *ADH1B*2* allele, whereas no such association was found in women with the *ADH1B*1/*1* genotype (interaction p=0.05).

ADH1B*1/*1 has an approximately 40 times lower V_{max} than ADH1B*2/*2 (reviewed in Bosron & Li, 1986). Although the *ADH1B* genotype did not affect peak blood acetaldehyde concentration after light alcoholic beverage consumption (Mizoi *et al.*, 1994), a clamping technique with intravenous infusion of ethanol has shown modestly but significantly lower ethanol elimination rates among men who have *ADH1B*1/*1* than among those who have the *ADH1B*2* allele (Neumark *et al.*, 2004). After moderate-to-heavy alcoholic beverage consumption, ethanol may linger in the blood and saliva for longer periods in *ADH1B*1/*1* carriers than in carriers of other genotypes, and lead to prolonged exposure to acetaldehyde in the upper aerodigestive tract as a result of acetaldehyde production by oral bacterial and mucosal ADHs (Homann *et al.*, 2000a).

Individuals with a combination of the *ALDH2*1/*2* and *ADH1B*1/*1* genotypes tend not to experience alcoholic flushing after oral intake of small amounts of alcoholic beverage (Takeshita *et al.*, 1996; Yokoyama *et al.*, 2003), and the diminished intensity of the aversive flushing response among *ALDH2* heterozygotes has been found to be positively associated with higher daily alcoholic beverage consumption (Yokoyama *et al.*, 2003). Japanese who have the *ADH1B*1/*1* genotype are at high risk for heavy drinking (Matsuo *et al.*, 2006b) and for developing alcoholism. Japanese alcoholics who have the *ADH1B*1/*1* genotype are more prone to binge drinking and the withdrawal syndrome earlier in life than those with other genotypes (reviewed in Eriksson *et al.*, 2001). Such *ADH1B*1/*1*-facilitated drinking patterns may affect the risk for alcohol-related cancer.

[The Working Group noted that the available genetic epidemiological data suggest a positive association between *ADH1B*1/*1* and upper aerodigestive tract cancer, but

Table 4.4 Case–control studies of *ALDH2*, *ADH1B* and *ADH1C* genotype-associated risks for cancer (upper aerodigestive tract)

Reference, study location, period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)[a]	Adjustment factors	Comments
Yokoyama *et al*. (1996), Kanagawa, Chiba, Japan, 1991–95	Oesophageal cancer	29 male daily drinkers from Ichikawa General Hospital, 40 alcoholic men from Kurihama National Hospital, aged 44–80 years, Japanese	28 male daily drinkers recruited from the staff Kurihama National Hospital and their acquaintances and 55 alcoholic men from the hospital, aged 41–77 years, Japanese	Structured interview	*ALDH2* Daily drinkers Alcoholics	 12.1 (3.4–42.8) 7.6 (2.8–20.7)	None	
Hori *et al*. (1997), Tokyo, Japan	Oesophageal squamous-cell carcinoma	94 (78 men) from Tokyo Medical and Dental University, Japanese	70 new healthy subjects (43 men) plus 60 healthy men in an other study, Japanese	Not described	Overall *ALDH2* *ADH1B*	 4.4 (2.5–7.7) 6.2 (2.6–14.7)	None	
Yokoyama *et al*. (1998a), Kanagawa, Japan, 1987–97	Oesophageal cancer	87 alcoholic men (71 incident cases, 16 prevalent cases) from Kurihama National Hospital, aged 55±7 years, Japanese	487 cancer-free alcoholic men from the hospital, aged 53±8 years, Japanese	Structured interview	*ALDH2* Alcoholics	 12.5 (7.2–21.6)	Age, drinking, smoking	Because the differences in odds ratio between the incident cases and the prevalent cases were slight, the cases were combined.
	Oropharyngo-laryngeal cancer	34 alcoholic men (19 incident cases, 15 prevalent cases) from the hospital, aged 55±8 years, Japanese				11.1 (5.1–24.4)		
Katoh *et al*. (1999), Kitakyushu, Japan, 1992–98	Oral squamous-cell carcinoma	92 (56 men) from UOEH Hospital, aged 62±12 years, Japanese	147 hospital-based (91 men) from another hospital in Kitakyushu, aged 70±11 years, Japanese	Interview	Overall *ALDH2*	 1.2 (0.7–2.1)	Age, sex, drinking	Alcoholic beverage drinking not significantly associated with the risk for oral cancer

Table 4.4 (continued)

Reference, study location, period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)[a]	Adjustment factors	Comments
Tanabe *et al*. (1999), Hokkaido, Japan, 1994–97	Oesophageal squamous-cell carcinoma	19 patients (17 men) from Asahikawa Medical College Hospital, aged 64±10 years, Japanese	25 patients with head and neck squamous-cell carcinoma (21 men) from the hospital, aged 61±10 years, Japanese	Questionnaire	*ALDH2*	Significantly increased (p<0.009)	None	Alcohol consumption and smoking did not differ between the cases and controls.
Chao *et al*. (2000), Taipei, Taiwan, China, 1997–99	Oesophageal cancer	59 alcoholic men (56 squamous-cell carcinoma , 3 adenocarcinoma) from Tri-Service General Hospital and Veterans General Hospital, aged 65±12 years, Chinese	222 alcoholics (208 men; pancreatitis in 87, cirrhosis in 116, both in 19) from the hospitals, aged 41±11–51±13 years, Chinese	Not described	Alcoholics *ALDH2* *ADH1B*	 Significantly increased (p<0.001) Significantly increased (p<0.025)	None	
Nomura *et al*. (2000), Chiba, Japan, 1996–98	Oral squamous-cell carcinoma	191 (121 men) from Tokyo Dental College, aged 24–94 years, Japanese	121 hospital-based (69 men), aged 40–70 years, Japanese	Not described	Habitual drinkers *ALDH2*	 2.9 (1.1–7.8)	None	Habitual drinking increased the risk for oral cancer (odds ratio, 3.9 [2.4–6.3]).
Matsuo *et al*. (2001), Aichi, Japan, 1984–2000	Oesophageal cancer	102 (86 men) from Aichi Cancer Center, aged 40–76 years, Japanese	241 hospital-based (118 men) from the Center, aged 39–69 years, Japanese	Self-administered questionnaire	*ALDH2* Heavy drinkers (75 mL ethanol/day, ≥5 days/week) Others	 16.4 (4.4–61.2) 1.7 (0.8–3.6)	Age, sex, drinking, smoking	

Table 4.4 (continued)

Reference, study location, period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)[a]	Adjustment factors	Comments
Yokoyama *et al.* (2001), Kanagawa, Japan, 1993–2000	Oesophageal squamous-cell carcinoma	112 alcoholic men from Kurihama National Hospital, aged 56±7 years, Japanese	526 cancer-free alcoholic men from the hospital, aged 53±8 years, Japanese	Structured interview	Alcoholics *ALDH2* *ADH1B*	 13.5 (8.1–22.6) 2.6 (1.6–4.3)	Age, drinking, smoking, *ALDH2* and *ADH1B* genotypes	
	Oropharyngo-laryngeal squamous-cell carcinoma	33 alcoholic men from the hospital, aged 54±8 years, Japanese			*ALDH2* *ADH1B*	18.5 (7.7–44.5) 6.7 (2.8–15.9)		Odds ratios for oral/oro-pharyngeal squamous-cell carcinoma, 20.8 (95% CI; 6.6–65.5); and for hypo-pharyngeal/ epilaryngeal squamous-cell carcinoma, 28.9 (95% CI; 8.7–96.6)
Yokoyama *et al.* (2001) (contd)	Multiple primary oesophageal squamous-cell carcinoma	45 alcoholic men with multiple primary intraoesophageal squamous-cell carcinoma	67 alcoholic men with solitary intraoesophageal squamous-cell carcinoma		*ALDH2* *ADH1B*	3.4 (1.5–7.9) 0.8 (0.3–1.7)		
	Multi-organ primary cancer with oesophageal squamous-cell carcinoma	22 alcoholic men with both oesophageal squamous-cell carcinoma and either oropharyngo-laryngeal squamous-cell carcinoma or gastric adenocarcinoma	90 alcoholic men with oesophageal squamous-cell carcinoma alone		*ALDH2* *ADH1B*	4.0 (1.2–13) 1.2 (0.4–3.4)		

Table 4.4 (continued)

Reference, study location, period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)[a]	Adjustment factors	Comments
Boonyaphiphat *et al*. (2002), Songkhla, Thailand, 1997–2000	Oesophageal squamous-cell carcinoma	202 (172 men) from Songklanagarind Hospital, aged 64±10 years, Thai	261 hospital-based (225 men) from the hospital who had no alcohol- or tobacco-related diseases, aged 65±12 years; matched by age, sex, ethnicity	Structured interview	Overall *ALDH2* *ADH1B* *ALDH2*1/*1* 0 ≤60 g/day >60 g/day *ALDH2*1/*2* 0 ≤60 g/day >60 g/day *ADH1B*1/*1* 0 ≤60 g/day >60 g/day *ADH1B*1/*2* 0 ≤60 g/day >60 g/day	 1.6 (0.9–2.8) 1.6 (1.01–2.4) Interaction p=0.064 1 2.2 (1.1–4.2) 5.3 (2.7–10.3) 1.6 (0.7–3.7) 2.5 (0.9–7.5) 10.8 (3.4–34.7) Interaction p=0.031 0.9 (0.4–1.9) 2.3 (1.1–5.1) 11.5 (5.2–25.5) 1 2.0 (1.0–4.1) 3.4 (1.5–7.0)	Age, sex, smoking, betel chewing, (drinking, *ALDH2* and *ADH1B* genotypes for overall)	Unlike Japanese and Chinese studies, frequency of inactive *ALDH2* is low in Thais: 20% in cases, 18% in controls.
Itoga *et al*. (2002), Chiba, Japan	Oesophageal cancer	82 men (65 habitual drinkers) from Chiba University Hospital, aged 65±10 years, Japanese	192 healthy controls (151 habitual drinkers), aged 51±9 years, Japanese	Questionnaire	Habitual drinkers *ALDH2*	 4.9 (p<0.0001)	None	
Yokoyama *et al*. (2002a), Tokyo, Chiba, Japan, 1998–99	Multiple primary cancer with oesophageal squamous-cell carcinoma	26 men from National Cancer Center Hospital and National Cancer Center Hospital East, aged 61±8 years, Japanese	48 men with solitary intra-oesophageal squamous-cell carcinoma alone from the hospitals, aged 63±9 years, Japanese	Structured questionnaire	Overall *ALDH2*	 5.3 (1.1–51.1) **2/*2* or **1/*2* versus **1/*1*	Age, sex, drinking, smoking	Multiple cancers included both multi-organ cancer and multiple intra-oesophageal squamous-cell carcinoma
	Multi-organ primary cancer with head and neck squamous-cell carcinoma	17 men from National Cancer Center Hospital and National Cancer Center Hospital East, aged 61±10 years; Japanese	29 men with solitary head and neck squamous-cell carcinoma alone from the hospitals, aged 61±13 years, Japanese		*ALDH2*	7.4 (1.3–80.1) **2/*2* or **1/*2* versus **1/*1*		

Table 4.4 (continued)

Reference, study location, period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)[a]	Adjustment factors	Comments
Yokoyama *et al*. (2002b), Tokyo, Chiba, Kanagawa, Osaka, Japan, 2000–01	Oesophageal squamous-cell carcinoma	234 men from Tokyo, Chiba, Kanagawa and Osaka hospitals, aged 40–79 years, Japanese; response rate, 99%	634 cancer-free men who underwent an annual medical check-up at one of two Tokyo clinics, aged 40–79 years; Japanese; response rate, 86%	Structured questionnaire	Overall *ALDH2* *ADH1B* *ADH1C* *ALDH2*1/*1* <22 g/week 22–197 g/week 198–395 g/week ≥396 g/week Former drinker *ALDH2*1/*2* <22 g/week 22–197 g/week 198–395 g/week *ALDH2*2/*2* <22 g/week *ADH1B*1/*1* <22 g/week 22–197g/week 198–395 g/week ≥396 g/week Former drinker *ADH1B*1/*2 or *2/*2* <22 g/week 22–197g/week 198–395 g/week ≥396 g/week Former drinker	7.5 (4.7–11.8) 4.1 (2.1–8.1) 0.9 (0.5–1.7) 0.0 (not calculable) 1 5.6 (1.5–20.3) 10.4 (2.9–37.8) 8.8 (1.5–50.8) 0.8 (0.1–4.1) 5.8 (1.6–21.4) 50.5 (9.2–278) 1.4 (0.2–9.5) 4.3 (0.4–44) 4.0 (1.0–15.5) 33.3 (11.1–99.5) 38.6 (13.3–112.5) 19.6 (1.7–233) 0.2 (0.06–0.7) 1 4.1 (2.3–7.4) 7.0 (3.8–13.0) 5.7 (2.0–16.2)	Age, strong alcoholic beverage, smoking, green-yellow vegetables and fruit (drinking, *ALDH2*, *ADH1B* and ADH1C genotypes for overall)	Multivariate odds ratio for *ALDH2*2/*2* in comparison with *ALDH2*1/*1* was 7.8 (1.3–46.1); however, most men with **2/*2* genotype drank rarely or never and the risk was evaluated based on a small sample size (2 cases/43 controls). For *ADH1C* genotype, the relative risk is associated with less active *ADH1C*1/*1* versus active **1/*2* or **2/*2*. When the linkage disequilibrium between *ADH1B* and *ADH1C* was taken into consideration, the *ADH1C* genotype did not significantly affect the risk for cancer.

Table 4.4 (continued)

Reference, study location, period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)[a]	Adjustment factors	Comments
Muto *et al.* (2005), Kashiwa, Japan, 1999–2001	Multiple primary squamous-cell carcinoma in both the oesophagus and head and neck	40 (37 men) from National Cancer Center Hospital East, aged 29–86 years, Japanese	163 (140 men, 23 women) with single-organ squamous-cell carcinoma of the oesophagus or head and neck from the hospital, aged 29–86 years, Japanese	Structured interview	Overall *ALDH2*	 5.5 (2.4–12.6)	Age, sex	
Wu *et al.* (2005), Kaohsiung, Taiwan, China, 2000–03	Oesophageal squamous-cell carcinoma	134 men from Kaohsiung Veterans General Hospital and Kaohsiung Medical University Hospital, aged 59±13 years, Chinese	237 hospital-based healthy men from the hospitals, aged 58±12 years; matched by age	Structured interview	Overall *ALDH2* *ADH1B* *ALDH2*1/*1* *ADH1B*1/*1* ≤1500 g/year >1500 g/year *ALDH2*1/*1* *ADH1B*1/*2* or **2/*2* 0 ≤1500 g/year >1500 g/year *ALDH2*1/*2* *ADH1B*1/*1* 0 ≤1500 g/year	 5.3 (2.5–11.2) 7.1 (2.7–18.5) versus **2/*2* 14.9 (1.9–116) 33.5 (3.5–320) 1 3.8 (0.7–21.7) 6.1 (1.5–25.3) 18.6 (2.7–129) 139 (10.1–∞)	Age, smoking, education, areca chewing, (drinking, *ALDH2* and *ADH1B* genotypes for overall)	

Table 4.4 (continued)

Reference, study location, period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)[a]	Adjustment factors	Comments
Wu *et al*. (2005) (contd)					*ALDH2*1/*2 ADH1B *1/*2* or **2/*2*			
					0	2.9 (0.7–12)		
					≤1500 g/year	26.6 (6.1–118)		
					>1500 g/year	39.3 (7.1–218)		
					*ALDH2*2/*2 ADH1B*1/*2 or *2/*2*			
					0	2.2 (0.3–14.5)		
Yang *et al*. (2005), Aichi, Japan, 2001–04	Oesophageal cancer	165 (148 men; 159 squamous-cell carcinoma, 6 adenocarcinoma) from Aichi Cancer Center Hospital, aged 61±1 years; Japanese	495 hospital-based (444 men) from the hospital, matched by age and sex, aged 61±0 years, Japanese; response rate, approximately 60%	Structured questionnaire	Overall		Age, smoking, (drinking for overall)	
					ALDH2	6.4 (4.0–10.3)		
					ADH1B	0.62 (0.2–1.7) versus **2/*2*		
					*ALDH2*1/*1*			
					0 g/week	1		
					≤250 g/week	1.9 (0.4–8.4)		
					>250 g/week	4.6 (0.9–23.1) Interaction $p<0.01$		
					*ALDH2*1/*2*			
					0 g/week	1		
					≤250 g/week	9.6 (3.2–28.8)		
					>250 g/week	95.4 (28.7–317)		
Cai *et al*. (2006), Taixing City, China, 2000	Oesophageal squamous-cell carcinoma	218 (141 men) from the Taixing Tumor Registry, aged ≥20 years, Chinese; response rate, 68%	415 population-based, Chinese; matched by age, sex, village; response rate, 90%	Structured interview	*ALDH2*1/*1*	1	Age, sex, drinking, smoking, education, body mass index	Taixing City has a very high incidence rate (65/100 000) of oesophageal cancer; alcohol drinking was not significantly associated with the cancer risk; *ALDH2* genotype may modify the low-selenium intake-associated risk.
					*ALDH2*1/*2*	0.8 (0.5–1.2)		
					*ALDH2*2/*2*	1.7 (0.9–3.5)		
					*ALDH2*1/*1 or *1/*2*	1		
					*ALDH2*2/*2*	1.91 (0.96–3.80)		

Table 4.4 (continued)

Reference, study location, period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)[a]	Adjustment factors	Comments
Chen *et al.* (2006), Taipei, Kaohsiung, Taiwan, China, 2000–04	Oesophageal squamous-cell carcinoma	330 men from National Taiwan University Hospital, Kaohsiung Veterans General Hospital and Kaohsiung Medical University Hospital, aged 60±12 years, Chinese	592 men from the hospitals, aged 59±11 years; matched by age	Structured interview	Overall *ALDH2*1/*1* *ALDH2*1/*2* *ALDH2*2/*2* *ADH1B*1/*1* *ADH1B*1/*2* *ADH1B*2/*2* *ALDH2*1/*1* 0 <1200 g/year ≥1200 g/year *ALDH2*1/*2* 0 <1200 g/year ≥1200 g/year *ALDH2*2/*2* 0 ≥1200 g/year *ADH1B*1/*1* 0 <1200 g/year ≥1200 g/year *ADH1B*1/*2* 0 <1200 g/year ≥1200 g/year *ADH1B*2/*2* 0 <1200 g/year ≥1200 g/year	 1 5.0 (3.1–8.0) 4.2 (1.5–11.8) 4.0 (2.1–7.5) 1.2 (0.8–1.9) 1 1 3.1 (1.3–7.5) 7.2 (3.0–17) 1.3 (0.6–3.0) 42.5 (16.9–107) 30.5 (12.0–77.6) 1.4 (0.4–4.6) 39.8 (2.4–654) 1.7 (0.4–6.6) 26.3 (9.2–74.8) 147 (41.4–525) 0.8 (0.3–1.6) 14.3 (6.2–33.0) 20 (8.5–47) 1 12.0 (5.5–26.2) 9.7 (4.4–21.3)	Age, ethnicity, smoking, education, areca chewing, *ALDH2* or *ADH1B* genotypes (drinking for overall)	The effect of *ALDH2*2/*2* was evaluated based on a small sample size of drinkers. Non-drinkers: 7 cases/40 controls; <1200 g/year: 1 case/0 control; ≥1200 g/year: 2 cases/1 control

Table 4.4 (continued)

Reference, study location, period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)[a]	Adjustment factors	Comments
Hashibe *et al.* (2006), Czech Republic, Poland, Romania, Russia, Slovakia, 2000–02	Upper aerodigestive tract squamous-cell carcinoma	811 (713 men; 168 oral, 113 pharyngeal, 326 laryngeal, 176 oesophageal), from multiple centres; Romania, 142; Poland, 206; Russia, 365; Slovakia, 40; Czech Republic, 58; response rate, 90%	1083 multicentre hospital-based (831 men); Romania, 173; Poland, 209; Russia, 319; Slovakia, 84; Czech Republic, 298; matched by age, sex	Structured interview	*ADH1B* Overall Oral Pharynx Larynx Oesophagus	 2.1 (1.4–3.1) 2.0 (0.96–4.3) 1.7 (0.7–4.2) 1.8 (1.04–2.9) 5.2 (1.9–14.3)	Age, sex, country, drinking, smoking	*ALDH2* +82A>G, +348C>T and –261C>T showed linkage disequilibrium and were associated with risk for overall and oesophageal squamous-cell carcinoma.
Hashimoto *et al.* (2006), Yamaguchi, Japan, 2002–04	Head and neck cancer	192 (146 men; 98 oral, 41 pharyngeal, 47 laryngeal, 6 nasal and sinuses) from Yamaguchi University Hospital, aged 24–91 years, Japanese; response rate, 96%	192 hospital-based (146 men), aged 24–91 years, Japanese; matched by age, sex	Interview, from cases only	Cases versus controls *ALDH2* Case drinkers *ALDH2*	Not significantly different Significantly increased (p<0.009) in cases <66 years compared with cases ≥66 years	None	More cases <66 years were drinkers than cases ≥66 years.
Yokoyama *et al.* (2006a) Tokyo, Chiba, Kanagawa, Osaka, Japan 2000–04	Oesophageal squamous-cell carcinoma	52 women from Tokyo, Chiba, Kanagawa and Osaka hospitals, aged 40–79 years, Japanese; response rate, 100%	412 cancer-free women who underwent an annual medical check-up at one of two Tokyo clinics, aged 40–79 years, Japanese; response rate, 82%	Structured questionnaire	*ALDH2*1/*1* <22 g/week 22–197g/week 198–395 g/week ≥396 g/week *ALDH2*1/*2* <22 g/week 22–197 g/week 198–395 g/week ≥396 g/week	 1 0.8 (0.2–2.6) 2.0 (0.5–7.7) 3.2 (0.7–15.5) 0.5 (0.2–1.3) 2.0 (0.5–7.1) 4.7 (0.7–31) 59 (4.7–750)	Age, smoking, green-yellow vegetables and fruit, hot food and beverages	

Table 4.4 (continued)

Reference, study location, period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)[a]	Adjustment factors	Comments
Asakage *et al*. (2007), Tokyo, Chiba, Kanagawa, Osaka, Japan 2000–03	Oral and pharyngeal squamous-cell carcinoma	96 men (43 hypo-pharyngeal, 53 oral/oropharyngeal) from Tokyo, Chiba, Kanagawa, and Osaka hospitals, aged 40–79 years, Japanese	642 cancer-free men who underwent an annual medical check-up at one of two Tokyo clinics, aged 40–79 years; Japanese; response rate, 86%;	Structured questionnaire	Moderate-to-heavy drinkers (22 g/drink, ≥9 drinks/ week) *ALDH2* *ADH1B* *ADH1C*	 3.6 (2.0–6.7) 5.6 (2.3–13.6) 3.2 (1.4–7.5)	Age, drinking, smoking, intake of green-yellow vegetables	When the linkage disequilibrium between *ADH1B* and *ADH1C* was taken into consideration, the *ADH1C* genotype did not significantly affect the risk for cancer.
	Hypopharyngeal squamous-cell carcinoma	43 men			*ALDH2* *ADH1B* *ADH1C*	10.1 (3.8–26.8) 7.2 (2.4–22.1) 2.8 (0.8–10.3)		
	Oral/oro-pharyngeal squamous-cell carcinoma	53 men			*ALDH2* *ADH1B* *ADH1C*	1.8 (0.8–3.9) 4.2 (1.4–12.6) 4.3 (1.7–11.2)		

[a] Associated with inactive heterozygous *ALDH2*1/*2* versus active **1/*1*, less active *ADH1B*1/*1* or *ADH1C*1/*1* versus active **1/*2* or **2/*2* ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CI, confidence interval; UOEH, University of Occupational and Environmental Health

Table 4.5 Cohort studies of *ALDH2* and *ADH1B* genotype-associated risk for cancer (upper aerodigestive tract)

Reference, location	Cohort description	Exposure assessment	Cancer and site	Exposure categories	No. of subjects/ squamous-cell carcinoma	Hazard ratio (95% CI)	Adjustment factors	Comments
Yokoyama *et al.* (1998b), Kanagawa, Japan	34 Japanese alcoholic men who underwent endoscopic mucosectomy for carcinoma *in situ* or mucosal squamous-cell carcinoma of the oesophagus during 1993–97; endoscopic follow-up from 6 to 48 months (mean, 22 months)	*ALDH2* genotyping	Oesophageal squamous-cell carcinoma, metachronous primary	Active *ALDH2*1/*1* Inactive *ALDH2*1/*2*	15/1 19/8	1 7.6 (0.9–61)	Not described	The log-rank test showed a significant effect of *ALDH2* genotype ($p<0.024$).
Yokoyama *et al.* (2006b), Kanagawa, Japan	808 Japanese alcoholic men confirmed cancer-free by endoscopic screening during 1993–2005; endoscopic follow-up from 1 to 148 months (median, 31 months)	*ALDH2*, *ADH1B* genotyping at baseline examination in 556 patients	Upper aerodigestive tract squamous-cell carcinoma	Active *ALDH2*1/*1* Inactive *ALDH2*1/*2* Active *ADH1B*1/*2* and **2/*2* Less-active *ADH1B*1/*1*	484/27 72/26 381/28 175/25	1 11.6 (5.7–23.3) 1 2.0 (1.02–4.0)	Age	

Table 4.5 (continued)

Reference, location	Cohort description	Exposure assessment	Cancer and site	Exposure categories	No. of subjects/ squamous-cell carcinoma	Hazard ratio (95% CI)	Adjustment factors	Comments
Yokoyama *et al.* (2006b) (contd)			Oesophageal squamous-cell carcinoma	Active *ALDH2*1/*1*	484/14	1		
				Inactive *ALDH2*1/*2*	72/19	13.0 (5.2–32.1)		
				Active *ADH1B*1/*2* and **2/*2*	381/18	1		
				Less-active *ADH1B*1/*1*	175/15	1.6 (0.7–3.9)		
			Oropharyngo-laryngeal squamous-cell carcinoma	Active *ALDH2*1/*1*	484/17	1		
				Inactive *ALDH2*1/*2*	72/13	11.7 (4.7–29.5)		
				Active *ADH1B*1/*2* and **2/*2*	381/16	1		
				Less-active *ADH1B*1/*1*	175/14	2.0 (0.8–5.0)		

ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CI, confidence interval

Table 4.6 Case–control studies of *ALDH2*, *ADH1B* and *ADH1C* genotype-associated risk for cancerof the liver, colorectum and breast

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) associated with inactive heterozygous *ALDH2*1/*2* versus active **1/*1* and *ADH1B, ADH1C* genotypes	Adjustment factors	Comments
Hepatocellular carcinoma							
Shibata *et al.* (1998), Kurume, Japan, 1992–95	115 men (15 HBsAg-positive, 96 anti-HCV-positive) from Kurume University Hospital, aged 40–74 years, Japanese	115 hospital- (1 HBsAg-positive, 8 anti-HCV-positive) and 115 population-based men, aged 40–74 years, Japanese; matched by age	Self-administered questionnaire	*ALDH2* Versus hospital controls Versus community controls	**2/*2* or **1/*2* versus **1/*1* 1.1 (0.6–2.5) 0.5 (0.2–1.0)	Not described	The frequency (38%) of *ALDH2*1/*1* in the community controls was lower than that generally reported in Japan.
Yokoyama *et al.* (1998a), Kanagawa, Japan, 1987–97	18 alcoholic men (13 incident cases, 5 prevalent cases) from Kurihama National Hospital, aged 56±7 years, Japanese	487 cancer-free alcoholic men from the hospital, aged 53±8 years, Japanese	Structured interview	Alcoholics *ALDH2*	0.7 (0.1–5.6)	Age, drinking, smoking	

Table 4.6 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) associated with inactive heterozygous *ALDH2*1/*2* versus active **1/*1* and *ADH1B, ADH1C* genotypes	Adjustment factors	Comments
Koide *et al*. (2000), Nagoya, Japan, 1994	84 (64 men; 12 HBsAg-positive, 68 anti-HCV-positive) from Nagoya City University Hospital and its affiliated hospital, aged 46–79 years, Japanese	84 population-based (0 HBsAg-positive, 6 anti-HCV-positive) from the same resident community, Japanese; matched by age, sex	Structured interview	Overall *ALDH2*	0.80 (0.5–1.4)	Age, sex	Alcoholic beverage drinking was not a significant risk factor.
Takeshita *et al*. (2000a), Hyogo, Japan, 1993–96	102 (85 men; 8 HBsAg-positive, 71 anti-HCV-positive) from 20 hospitals, aged 62±8 years (men) and 65±6 years (women), Japanese	125 hospital-based (101 men; 0 HBsAg-positive, 0 anti-HCV-positive) from the same hospitals, aged 60±12 years (men) and 63±13 years (women), Japanese; matched by age, sex	Self-administered questionnaire	Overall *ALDH2* *ADH1B*	1.1 (0.6–2.1) **1/*1* or **1/*2* versus **2/*2* 1.3 (0.7–2.0)	Age, smoking	Alcoholic beverage drinking was a significant risk factor.
Yu *et al*. (2002), Haimen, China, 1995–97	248 (207 men; 91 HBsAg-positive, 7 anti-HCV-positive) from Haimen People's Hospital, aged 25–79 years, Chinese	248 population-based (207 men; 21 HBsAg-positive, 8 anti-HCV-positive), Chinese; matched by age, sex, residence	Structured interview	Overall *ALDH2*	**2/*2* or **1/*2* versus **1/*1* 0.72 (0.5–1.2)	None	Alcoholic beverage drinking was not a significant risk factor.

Table 4.6 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) associated with inactive heterozygous *ALDH2*1/*2* versus active **1/*1* and *ADH1B, ADH1C* genotypes	Adjustment factors	Comments
Kato *et al*. (2003), Tokyo, Japan	99 (82 men; 99 anti-HCV-positive) from Nippon Medical School, aged 42–78 years, Japanese	135 hospital-based (104 men; 0 anti-HCV-positive), aged 32–81 years, Japanese; matched by age, sex	Not described	Overall *ALDH2*	**2/*2* versus **1/*2* or **1/*1* 5.4 (2.1–14.0)	None	20% of patients had *ALDH2*2/*2*; the rate is much higher than that in the other studies (2–10%).
Munaka *et al*. (2003), Fukuoka, Japan, 1997–98	78 (61 men; 14 HBV, 54 HCV, 8 HBV+HCV) from UOEH hospital, aged 47–84 years, Japanese	138 hospital-based unmatched (94 men; 1 HBV, 10 HCV), aged 34–92 years, Japanese	Structured interview	Overall *ALDH2*	**2/*2* or **1/*2* versus **1/*1* 1.5 (0.9–2.7) 9.8 (1.6–58.6)	Age, sex Age, sex, drinking, HCV, HBV	Alcoholic beverage drinking was a significant risk factor.
Covolo *et al*. (2005), Brescia, Pordenone, Italy, 1999–2002	200 (79% men; 22 HBsAg-positive, 92 HCV RNA-positive) from 5 hospitals in northern Italy, mean age, 66.5±8 years; response rate, ≥95%	400 hospital-based (79% men; 10 HBsAg-positive, 19 HCV RNA-positive), matched by age, sex, date, hospital of admission; response rate, ≥95%	Structured interview	Overall *ADH1C*	**1/*1* versus **1/*2* or **2/*2* 0.8 (0.5–1.3)	Age, sex, area of recruitment, HCV, HBV	Alcoholic beverage drinking was a significant risk factor.

Table 4.6 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) associated with inactive heterozygous *ALDH2*1/*2* versus active **1/*1* and *ADH1B, ADH1C* genotypes	Adjustment factors	Comments
Sakamoto *et al*. (2006), Saga, Japan, 2001–04	209 (141 men; 13 HBsAg-positive, 173 anti-HCV-positive, 6 both positive) from Saga Medical School Hospital and Saga Prefectural Hospital, aged 40–79 years, Japanese; response rate, 92%	275 hospital-based (180 men; 6 HBsAg-positive, 21 anti-HCV-positive) from Saga Medical School Hospital, aged 40–79 years, Japanese; response rate, 73% 381 hospital-based chronic liver disease (205 men; 20 HBsAg-positive, 266 anti-HCV-positive, 3 both positive) from the 2 hospitals, aged 40–79 years, Japanese; response rate, 96%	Structured interview	Light-to-moderate drinkers (<69 g ethanol/day *ALDH2* Hospital controls Chronic liver disease controls	 4.4 (1.2–15.4) 1.8 (0.8–3.7)	Age, sex, smoking, HCV, HBV	Alcoholic beverage drinking was a significant risk factor; no *ALDH2*-associated risk observed in non-drinkers or heavy drinkers; there were no significant interactions between current drinking status and *ADH1B* genotype.

Table 4.6 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) associated with inactive heterozygous *ALDH2*1/*2* versus active **1/*1* and *ADH1B, ADH1C* genotypes	Adjustment factors	Comments
Colon cancer							
Yokoyama *et al*. (1998a), Kanagawa, Japan, 1987–97	46 alcoholic men (35 incident cases, 11 prevalent cases) from Kurihama National Hospital, aged 58±9 years, Japanese	487 cancer-free alcoholic men from the hospital, aged 53±8 years, Japanese	Structured interview	Alcoholics *ALDH2*	3.4 (1.5–7.4)	Age, drinking, smoking	
Colorectal cancer							
Murata *et al*. (1999), Chiba, Japan, 1989–95	270 (163 men; 160 colon, 110 rectum) from Chiba Cancer Center Hospital, Japanese	121 hospital-based (60 men), Japanese	Self-administered questionnaire	Male colon cancer *ALDH2*1/*1* (mL ethanol / day) 0 2.7–27 ≥27 *ALDH2*1/*2* 0 0.1–1.0 ≥1.0	 1.0 (reference) 1.3 (0.2–8.6) 1.9 (0.4–8.6) 1.0 (reference) 1.6 (0.3–7.8) 3.1 (0.7–14.0)	Age	The number of *ALDH2*2* alleles was more frequent in colon cancer cases (trend p=0.04), but not rectal cancer cases (trend p=0.21), compared with controls; trend p adjusted for sex only; odds ratios for each genotype not shown.

Table 4.6 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) associated with inactive heterozygous *ALDH2*1/*2* versus active **1/*1* and *ADH1B, ADH1C* genotypes	Adjustment factors	Comments
Murata *et al*. (1999) (contd)				Male rectal cancer *ALDH2 *1/*1* (mL ethanol / day) 0 2.7–27 ≥27 *ALDH2 *1/*2* 0 2.7–27 ≥27	 1.0 (reference) 0.9 (0.1–5.8) 1.4 (0.4–5.1) 1.0 (reference) 0.7 (0.1–3.7) 1.3 (0.2–7.0)		

Table 4.6 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) associated with inactive heterozygous *ALDH2*1/*2* versus active **1/*1* and *ADH1B, ADH1C* genotypes	Adjustment factors	Comments
Matsuo *et al.* (2002), Aichi, Japan, 1999	142 (83 men; 72 colon, 70 rectum) from Aichi Cancer Center Hospital, Japanese	241 (118 men), from the hospital, Japanese	Self-administered questionnaire	Overall *ALDH2* Men **1/*1* **1/*2* **2/*2* Women **1/*1* **1/*2* **2/*2* Alcohol drinking *ALDH2 *1/*1* Low Moderate High *ALDH2 *1/*2* Low Moderate High *ALDH2*2/*2* Low Moderate High	 1.0 (reference) 0.7 (0.4–1.3) 0.4 (0.1–1.5) 1.0 (reference) 1.1 (0.6–2.2) 0.6 (0.2–2.5) 1.0 (reference) 1.2 (0.5-2.6) 1.9 (0.8-4.8) Trend p=0.14 1.0 (ref) 0.8 (0.3–2.0) 3.6 (1.0–13.0) Trend p=0.16 1.0 (reference) 24.5 (0.8–787) Not calculated Trend p=0.07	Age, smoking in the overall analysis; age, sex in the stratified analysis	Alcohol category: low (less than once), moderate (≥1 per week with <50 mL ethanol), high (≥1 per week with ≥50 mL ethanol); increased risk associated with alcohol in *ALDH2*1/*2* was seen for rectal cancer (trend p=0.01), not for colon cancer (trend p=0.44).

Table 4.6 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) associated with inactive heterozygous *ALDH2*1/*2* versus active **1/*1* and *ADH1B, ADH1C* genotypes	Adjustment factors	Comments
Landi *et al.* (2005), Barcelona, Spain	377 from a hospital	326 non-cancer patients at the same hospital	None	Overall *ADH1B* **1/*1* **1/*2* **2/*2*	 1.0 (reference) 1.0 (0.7–1.6) 0.6 (0.1–3.5)	Age, sex	Alcohol beverage intake not ascertained
Otani *et al.* (2005), Nagano, Japan; 1998–2002	107 (66 men) from 4 hospitals in Nagano Prefecture	224 healthy (141 men) from among those receiving medical check-up; matched for hospital, sex, age (±3 years), residence area	Self-administered questionnaire	Overall *ALDH2* **1/*1* **1/*2* **2/*2*	 1.0 (reference) 1.1 (0.7–1.9) 1.2 (0.5–2.9)	Age, sex, residence, hospital	No stratification with alcohol intake
Matsuo *et al.* (2006a), Aichi, Japan, 2001–04	257 (162 men; 123 colon, 131 rectum, 3 both) from Aichi Cancer Center Hospital, aged 59±10 years, Japanese	771 hospital-based (486 men), aged 59±10 years, Japanese; matched by age, sex	Self-administered questionnaire	Overall *ALDH2* **1/*1* **1/*2* **2/*2* *ADH1B* **1/*1* **1/*2* **2/*2*	 1.0 (reference) 1.0 (0.7–1.4) 1.0 (0.5–1.8) 1.9 (1.1–3.5) 1.4 (1.0–1.8) 1.0 (reference)	Age, sex, drinking, smoking, body mass index, family history, estrogen use; conditions with potential use of NSAIDs	A strong interaction between *ALDH2* and *ADH1B* was noted ($p<0.001$); the association with alcohol was examined with the composite genotype stratified (see test).

Table 4.6 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) associated with inactive heterozygous *ALDH2*1/*2* versus active **1/*1* and *ADH1B, ADH1C* genotypes	Adjustment factors	Comments
Breast cancer							
Freudenheim *et al*. (1999), western New York, USA, 1986–91	315 women (134 premenopausal, 181 postmenopausal) from major hospitals in Erie and Niagara counties, aged 40–85 years, Caucasian; 66% of eligible premenopausal cases, 54 % of eligible postmenopausal cases	356 population-based (126 premenopausal, 230 postmenopausal), aged 40–85 years, Caucasian; 62% of eligible premenopausal cases, 44 % of eligible postmenopausal cases	Structured interview	Premenopausal *ADH1C*1/*1* Lower Higher *ADH1C*1/*2* and **2/*2* Lower Higher Postmenopausal *ADH1C*1/*1* Lower Higher *ADH1C*1/*2* and **2/*2* Lower Higher	 1.0 (0.4–2.5) 3.6 (1.5–8.8) Interaction p=0.16 1 0.8 (0.4–1.7) 0.9 (0.5–1.6) 1.2 (1.1–2.2) 1 0.8 (0.5–1.4)	Age, education, body mass index, parity, age at first birth, age at menarche, fruit and vegetable intake, duration of lactation, benign breast disease, age at menopause	The cut-off between lower and higher alcoholic beverage intake was 6.5 and 4.5 drinks per month on average over the past 20 years for the pre- and postmetnopausal women, respectively.

Table 4.6 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) associated with inactive heterozygous *ALDH2*1/*2* versus active **1/*1* and *ADH1B, ADH1C* genotypes	Adjustment factors	Comments
Hines *et al*. (2000), 11 states, USA, 1989–94	465 women of 32 826 cohort members in 11 states, 85% Caucasian	621 population-based from the cohort, Caucasian; 85% matched by birth years, menopausal status, hormone use	Self-administered questionnaire	*ADH1C*1/*1* 0 g ethanol/day ≤10 g/day >10 g/day *ADH1C*1/*2* 0 g/day ≤10 g/day >100 g/day *ADH1*2/*2* 0 g/day ≤10 g/day >100 g/day	 1 0.8 (0.5–1.3) 0.8 (0.4–1.5) Interaction p=0.15 0.7 (0.4–1.2) 1.1 (0.7–1.8) 0.8 (0.4–1.4) 0.6 (0.3–1.2) 0.6 (0.3–1.2) 1.1 (0.5–2.4)	Age of birth, drinking, body mass index, parity, age at menarche, family history, benign breast disease	
Choi *et al*. (2003), Seoul, Republic of Korea, 1995–2001	346 women (226 premenopausal, 120 postmenopausal) from 3 hospitals in Seoul, aged 47±10 years, Korean	377 hospital-based women (209 premenopausal, 168 postmenopausal), aged 47±14 years, Korean	Structured interview	Overall *ALDH2*	 0.8 (0.6–1.2)	Age, family history	

Table 4.6 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) associated with inactive heterozygous *ALDH2*1/*2* versus active **1/*1* and *ADH1B, ADH1C* genotypes	Adjustment factors	Comments
Coutelle *et al*. (2004), Heidelberg, Germany	117 women from the University Hospital of Heidelberg, aged 53±12 years, Caucasian	111 alcoholics (74 cirrhosis, 22 pancreatitis, 15 heavy drinkers), aged 57±11 years, Caucasian; matched by age	Interview	Overall *ADH1C* **1/*1*, **1/*2* or **2/*2*	 1.8 (1.4–2.3) 1	Not described	Alcohol intake: cases, 17±22 g/day; alcoholic controls, 110±89 g/day
Lilla *et al*. (2005), southern Germany, 1992–95	613 women aged ≤50 years, from 38 hospitals; 61% of eligible cases, aged 42±6 years	1082 population-based; 48% of eligible controls, aged 43±6 years	Self-administered questionnaire	*ADH1B*1/*1* 0 g ethanol/day ≥12 g/day *ADH1B*1/*2* and **2/*2* 0 g/day ≥12 g /day	 1 1.1 (0.8–1.6) 1 0.3 (0.1–1.0) Interaction p=0.05	Age, education, smoking, family history, menopausal status, breast-feeding	Interactions between other drinking categories and *ADH1B* genotype not significant

Table 4.6 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) associated with inactive heterozygous *ALDH2*1/*2* versus active **1/*1* and *ADH1B*, *ADH1C* genotypes	Adjustment factors	Comments
Terry *et al.* (2006), New York, USA, 1996–97	1047 women, from the Long Island Breast Cancer Study Project; 70% of eligible cases; English speakers	1101 population-based; 70.7% of eligible controls; English speakers	Structured interview	Lifetime intake *ADH1C*1/*1* 0 g ethanol/day 15–30 g/day ≥30 g/day *ADH1C *1/*2* 0 g/day 15–30 g/day ≥30 g/day *ADH1C *2/*2* 0 g/day 15–30 g/day ≥30 g/day	 1 2.0 (1.1–3.5) 0.8 (0.4–1.7) Interaction p=0.20 1 1.5 (0.9–2.4) 0.8 (0.4–1.5) 1 1.3 (0.5–3.5) 0.9 (0.2–3.4)	Age, education, race, caloric intake, smoking, body mass index, history of benign breast disease, parity, age at first birth, age at menarche, menopausal and lactation status	The association for *ADH1C*1/*1* carriers who drank 15–30 g/day was more pronounced among premenopausal women (odds ratio, 2.9; 95% CI, 1.2–7.1) versus postmenopausal women (odds ratio, 1.8; 95% CI, 0.9–3.8).

ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CI, confidence interval; HbsAg, hepatits B virus surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; NSAIDS, non-steroidal anti-inflammatory drugs

the mechanisms by which the functional polymorphism affects cancer susceptibility has not been fully explained. The evidence of a relationship between the *ADH1B* genotype and cancer in other organs is inconclusive because of the small number of studies.]

(ii) *ADH1C*

ADH1C (previously called *ADH3*) gene polymorphism is a major polymorphism among Caucasians. The homodimer encoded by the *ADH1C*1* allele catalyses the production of acetaldehyde from ethanol at a rate 2.5 times faster than the homodimer encoded by the *ADH1C*2* allele (reviewed in Bosron & Li, 1986). In a follow-up study of Australian twins the *ADH1C* genotype showed a considerably weaker effect on drinking behaviour than did the *ADH1B* genotype; however, among *ADH1B*1/*1* men, *ADH1C*1/*1* carriers were less likely to become alcoholics (Whitfield *et al.*, 1998). A meta-analysis of 11 case–control studies of alcoholics failed to show such an *ADH1C*-associated risk in Caucasians (Zintzaras *et al.*, 2006). Two alcohol-challenge tests reported inverse results: higher salivary concentrations of acetaldehyde were found in healthy Caucasians with *ADH1C*1/*1* than in those with *ADH1C*2* (Visapää *et al.*, 2004) and lower breath concentrations of acetaldehyde were measured in *ADH1C*1/*1* carriers than in *ADH1C*2* carriers among Japanese cancer patients with an inactive *ALDH2*2* allele (Muto *et al.*, 2002).

Fourteen case–control studies in populations exclusively or mainly composed of Caucasians have investigated associations between *ADH1C* genotype and upper aerodigestive tract cancer, but showed no consistent pattern of association (Table 4.7). A higher *ADH1C*1/*1*-associated risk was shown in five studies: for laryngeal cancer in a small population of alcoholics (Coutelle *et al.*, 1997), for oral and pharyngeal squamous-cell carcinoma in heavy alcoholic beverage drinkers (Harty *et al.*, 1997), for upper aerodigestive tract cancer in comparison with control patients with alcoholic cirrhosis, alcoholic pancreatitis or alcoholism (Visapää *et al.*, 2004; Homann *et al.*, 2006) and for upper aerodigestive tract squamous-cell carcinoma in a large central-European population (811 cases, 1083 controls; Hashibe *et al.*, 2006). However, the same central-European study (Hashibe *et al.*, 2006) yielded no association when the linkage disequilibrium between *ADH1B*2* and *ADH1C*1* was taken into consideration. Negative results were reported in six other studies (Bouchardy *et al.*, 2000; Olshan *et al.*, 2001; Sturgis *et al.*, 2001; Zavras *et al.*, 2002; Risch *et al.*, 2003; Wang *et al.*, 2005a). A pooled analysis of data from seven case–control studies with a total of 1325 cases and 1760 controls confirmed the negative results (Brennan *et al.*, 2004), but three others reported an interaction between *ADH1C*2 /*2* and alcoholic beverage drinking (Schwartz *et al.*, 2001; Nishimoto *et al.*, 2004; Peters *et al.*, 2005). The direction and magnitude of interaction may have differed because of differences in alcohol consumption, ethnicity and linkage disequilibrium between *ADH1C* and *ADH1B* among the study populations.

East Asian case–control studies have consistently demonstrated an *ADH1C*2*-associated risk for alcoholism (Zintzaras *et al.*, 2006). Two Japanese case–control studies reported that the *ADH1C*2* allele increases the risk for oral/oropharyngeal cancer,

Table 4.7 Case–control studies of *ADH1C*-genotype-associated risk for cancer of the upper aerodigestive tract (non-Asians)

Reference, study location, and period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) by *ADH1C* genotype (*1, fast V_{max}; *2, slow V_{max})	Adjustment factors	Comments
Coutelle *et al*. (1997), Bordeaux, France	Oropharyngeal and laryngeal cancer	39 alcoholic cancer patients (21 oropharynx, 18 larynx), mean age, 54 yrs, Caucasian.	37 alcoholic men from an alcoholism clinic, mean age, 42 years, Caucasian.	Not described	*ADH1C *1/*1* vs **1/*2+*2/*2* Overall Oropharyngeal Laryngeal	 3.6 (0.7–10.0) 2.6 (0.7–10.0) 6.1 (1.3–28.6)	Age	All subjects consumed more than 100 g ethanol/ day for more than 10 years.
Harty *et al*. (1997), Puerto Rico, 1992–95	Oral and pharyngeal squamous-cell carcinoma	137 (123 men), from the Puerto Rico Cancer Registry, aged 21–79 years, 48 % response rate, white 91, black 15, mestizo 18, other 13	146 population-based controls (112 men), 57% response rate, white 102, black, 10, mestizo 24, other 10	Structured interview	Heavy drinkers *ADHIC* **1/*1* **1/*2 + *2/*2* Risk elevation per additional drink/week **1/*1* **1/*2 +*2/*2*	 5.3 (1.0–28.8) 1 3.6% (1.9–5.4%) 2.0% (0.9–3.0%)	Age, sex, tobacco, fruit and vegetable consumption	Heavy drinkers ≥57 drinks/ week: 46% cases, 9% controls
Bouchardy *et al*. (2000), France, 1988–92	Oral, pharyngeal, and laryngeal squamous-cell carcinoma	121 (113 men; 67 oral, 50 pharyngeal, 4 unspecified), aged 54±10 years, 129 (127 men, 2 women; 129 laryngeal), aged 55±9 years, Caucasian	172 hospital-based controls (163 men), regular smokers, matched by age, sex and hospital, aged 55±11 years	Structured interview	*ADH1C* Oral/ pharynx **1/*1* **1/*2* **2/*2* Larynx **1/*1* **1/*2* **2/*2*	 1.1 (0.6–2.2) 0.7 (0.4–1.4) 1 0.7 (0.4–1.4) 1.0 (0.5–1.8) 1	Age, sex, drinking, smoking	Heavy drinkers >80 g/day: 59% oral/ pharyngeal cases, 60% laryngeal cases, 37% controls

Table 4.7 (continued)

Reference, study location, and period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) by *ADH1C* genotype (*1, fast V_{max}; *2, slow V_{max})	Adjustment factors	Comments
Olshan *et al*. (2001), North Carolina, USA, 1994–97	Head and neck squamous-cell carcinoma	182 (76% men; 93 oral, 37 pharyngeal, 52 laryngeal) from University of North Carolina Hospital, aged >17 years, 88% response rate, 62% white, 38% black	202 hospital-based controls (56% men), matched by age and sex, 86% response rate, 86% white, 14% black	Structured interview	*ADH1C* **1/*1* **1/*2* **2/*2*	 0.9 (0.4–1.9) 0.8 (0.4–1.7) 1	Age, sex	Heavy drinkers ≥60 drinks/ week: 23% cases, 3% controls. No interaction between alcohol drinking and *ADH1C* genotype
Sturgis *et al*. (2001), Houston, USA, 1995–2000	Oral and pharyngeal squamous-cell carcinoma	229 (145 men), from Anderson Cancer Center, 90% response rate, non-Hispanic white	575 hospital-based controls (340 men), from a multispecialty managed-care institute, matched by age, sex and smoking, 73% response rate, non-Hispanic white	Questionnaire	*ADH1C* **1/*1* **1/*2* **2/*2*	 1 1.0 (0.7–1.4) 1.2 (0.8–1.9)	Age, sex, drinking, smoking	

Table 4.7 (continued)

Reference, study location, and period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) by *ADH1C* genotype (*1, fast V_{max}; *2, slow V_{max})	Adjustment factors	Comments
Schwartz *et al.* (2001), Washington, USA, 1985–89, 1990–95	Oral squamous-cell carcinoma	333 (237 men; 141 tongue, 76 tonsils/ oropharynx, 50 oral floor, 16 gum, 13 soft palate, 37 miscellaneous), from residents of the counties, aged 18–65 years, 54–63 % response rate, white 312, black 12, other 9	541 population-based controls (387 men), from residents of the counties, aged 18–65 years, 61–63% response rate, white 511, black 14, other 16	Structured interview	*ADHIC* **1/*1* **1/*2* **2/*2* Risk elevation per additional drink/week **1/*1* **1/*2* **2/*2*	 1.0 (0.7–1.5) 1.3 (1.0–1.2) 1 1.2% (0.0–2.4%) 2.5% (1.5–2.6%) 5.3% (2.1–8.5%)	Age, sex, race Age, sex, race, smoking	Heavy drinkers ≥43 drinks/ week: 17% cases, 4% controls
Zavras *et al.* (2002), Athens, Greece, 1995–98	Oral SCC	93 from 3 hospitals in Athens, Caucasian	99 hospital-based controls, matched by age and sex, Caucasian	Structured interview	Overall *ADH1C* **1/*1* **1/*2* **2/*2*	 1 0.8 (0.4–1.6) 0.9 (0.3–2.5)	Sex, drinking, smoking	
Risch *et al.* (2003), Southwest Germany, 1998–2000	Laryngeal squamous-cell carcinoma	245 (226 men) from the Rhein-Neckar Larynx Case–Control Study, aged 38–80 years, Caucasian	251 population-based controls (232 men), matched by age and sex, aged 38–80 years, Caucasian	Structured interview	*ADHIC* **1/*1* **1/*2*+**2/*2*	 1.1 (0.7-1.6) 1	Drinking, smoking	Heavy drinkers >75 g/day: 35% cases, 17% controls

Table 4.7 (continued)

Reference, study location, and period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) by *ADH1C* genotype (*1, fast V_{max}; *2, slow V_{max})	Adjustment factors	Comments
Nishimoto *et al*. (2004), São Paulo, Brazil, 1995–2001	Oral, pharyngeal, and laryngeal squamous-cell carcinoma	141 (110 men; 63 oral, 49 pharyngeal, 29 laryngeal) from Hospital do Câncer A.C. Camargo, aged 17–90 years, white 119, non-white 22	134 hospital-based unmatched controls (91 men), aged 22–90 years, white 110, non-white 24	Structured interview	*ADH1C* Lifetime alcohol intake <100 kg **1/*1+*1/*2 *2/*2* ≥100 kg **1/*1+*1/*2 *2/*2*	 1 3.8 (1.5–9.7) 1 0.52 (0.2–1.2)	Age, sex, family history	Heavy drinkers ≥100 kg: cases 74%, controls 28%. Opposite ADH1C effects between those with lifetime alcohol intake <100 kg and ≥100 kg
Visapää *et al*. (2004), Mannheim, Heidelberg, Germany	Upper aerodigestive tract cancer	107 (89 men; 16 oral, 8 oropharyngeal, 22 hypo-pharyngeal, 41 laryngeal, 20 oesophageal), from ENT Hospital Mannheim, aged 59±11 yrs, 99 smokers, Caucasian	103 hospital-based controls (67 men; 39 alcoholic cirrhosis, 38 alcoholic pancreatitis, 26 alcoholics), from Salem Medical Centre, matched by age, aged 58±9 yrs, 95 smokers, Caucasian	Structured interview	*ADH1C* **1* allele	1.7 (1.1–2.6) *vs *2* allele	Age, sex, drinking, smoking	Heavy drinkers >80 g/day: 53% cases, 100% controls; >20 g/day: 100% cases, 100% controls

Table 4.7 (continued)

Reference, study location, and period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) by *ADH1C* genotype (*1, fast V_{max}; *2, slow V_{max})	Adjustment factors	Comments
Wang *et al.* (2005a), Iowa, USA, 1994–97, 2000–02	Head and neck squamous-cell carcinoma	348 (226 men; 223 oral, 125 oropharyngeal), from the University of Iowa Hospitals & Clinics and the Iowa City Veterans Affairs Medical Center; 64% >55 yrs; 87% response rate, white 333, black 15	330 hospital-based controls (194 men), from the Iowa hospitals; 62% >55 yrs; 92% response rate, white 314, black 16	Self-administered questionnaire	*ADH1C* **1/*1* **1/*2* **2/*2*	 0.7 (0.4–1.1) 0.8 (0.5–1.2) 1	Age, drinking, smoking	Drinkers >21 drinks/ week: 41% cases, 17% controls
Peters *et al.* (2005), The greater Boston area, USA, 1999–2003	Head and neck squamous-cell carcinoma	521 (375 men; 256 oral, 149 pharyngeal, 106 laryngeal), from 9 hospitals, aged >17 years, mean age 60 yrs, 71% response rate, Caucasian 446, black 23, other 50	599 population-based controls (430 men), matched by age, sex, and town, aged >17 years, mean age 61 yrs, 41% response rate, Caucasian 540, black 21, other 37	Self-administered questionnaire	*ADH1C* **1/*1+*1/*2* Non-drinkers Light drinkers Heavy drinkers (>30 drinks/ wk) **2/*2* Non-drinkers Light drinkers Heavy drinkers (>30 drinks/ wk)	 1 0.9 (0.6–1.3) 2.3 (1.4-3.8) 0.8 (0.4–1.8) 0.9 (0.6–1.6) 7.1 (2.3–22) Interaction (p=0.05)	Age, sex, race, smoking	Heavy drinkers >30 drinks/ week: 27% cases, 9% controls

Table 4.7 (continued)

Reference, study location, and period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) by *ADH1C* genotype (*1, fast V_{max}; *2, slow V_{max})	Adjustment factors	Comments
Hashibe *et al.* (2006), Romania, Poland, Russia, Slovakia, Czech Republic, 2000–02	Upper aerodigestive tract squamous-cell carcinoma	811 (713 men; 168 oral, 113 pharyngeal, 326 laryngeal, 176 oesophageal), from multiple centres, response rate 90%; Romania 142, Poland 206, Russia 365, Slovakia 40, Czech Republic 58; 80% current smokers	1083 multi-centre hospital-based controls (831 men), matched by age and sex, Romania 173, Poland 209, Russia 319, Slovakia 84, Czech Republic 298; 40% current smokers	Structured interview	*ADH1C I350V *1/*1* (Val/Val) *ADH1C R272Q *1/*1* (Gln/Gln) *ADH1C*1* (350 Val) + *ADH1C*1* (272 Gln) + *ADH1B*1* (Arg)	1.4 (1.01–1.9) *vs *2/*2* (Ile/Ile) 1.5 (1.1–2.1) *vs *2/*2* (Arg/Arg) 1.1 (0.97–1.3) *vs* the combined slow haplotypes ADHC*1 (350 Ile) + ADHC*2 (272 Arg) + ADHB*1 (Arg)	Age, sex, country, drinking, smoking	Daily drinkers: 17% cases, 13% controls. *ADH1B* and *ADH1C* showed linkage disequilibrium.

Table 4.7 (continued)

Reference, study location, and period	Cancer site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) by *ADH1C* genotype (*1, fast V_{max}; *2, slow V_{max})	Adjustment factors	Comments
Homann *et al*. (2006), Lübeck, Erlangen-Nürnberg, Freiburg, Regenburg, Heidelberg, Germany, 1999–2003	Upper aerodigestive tract cancer, hepatocellular carcinoma	123 oesophageal cancer (100 men; 85 squamous-cell carcinoma, 38 adeno-carcinoma), age 63±10 years, 86 head and neck cancer (73 men; 23 oral, 26 pharyngeal, 37 laryngeal), age 57±9 years, 86 alcohol-associated hepatocellular carcinoma (79 men), age 66±8 years, Caucasian	525 hospital-based controls (387 men): 217 alcoholic cirrhosis, age 57±12 years; 117 alcoholic pancreatitis, age 49±11 years, 17 cirrhosis + pancreatitis, age 53±12 years; 174 heavy drinkers, age 53±12 years, Caucasian	Interview	ADH1C 1*1 Head and neck Oesophagus Alcohol-associated hepatocellular carcinoma	 2.2 (1.1–4.4) *vs* 1*2 +2*2 2.9 (1.8–4.7) *vs* 1*2 + 2*2 3.6 (1.3–9.5) *vs* 1*2 + 2*2	Age, sex, smoking	All subjects consumed more than 40 g ethanol/day for more than 10 years.

ADH, alcohol dehydrogenase; CI, confidence interval; V_{max}, maximum velocity: activity of the enzyme encoded by the gene; *vs*, versus

hypopharyngeal cancer (Asakage *et al.*, 2007) and oesophageal cancer (Yokoyama *et al.*, 2002b) (Table 4.4). However, when the linkage disequilibrium between *ADH1B* and *ADH1C* was taken into consideration, no relationship was found between *ADH1C* genotype and cancer risk or between *ADH1C* genotype and alcoholism (Chen *et al.*, 1999). Haplotype analyses revealed that the apparent effect of the *ADH1C*2* allele reflects its linkage with the *ADH1B*1* allele, which has a true effect on the risk for cancer as well as on the risk for alcoholism. [The Working Group noted that the evidence of a contribution of the *ADH1C* polymorphism to the development of cancer in the upper aerodigestive tract is inconclusive.]

Two European case–control studies investigated associations between *ADH1C* genotype and hepatocellular carcinoma. One reported no association (Covolo *et al.*, 2005; Table 4.6), and the other found a positive association between *ADH1C*1/*1* and the risk for alcohol-associated hepatocellular carcinoma in comparison with control patients with alcoholic cirrhosis, alcoholic pancreatitis, or alcoholism (Homann *et al.*, 2006; Table 4.7). [The Working Group noted that the evidence of a relationship between *ADH1C* genotype and hepatocellular carcinoma is inconclusive because of the small number of studies.]

Four case–control studies conducted in Germany and the USA investigated the relationship between *ADH1C* genotype and the risk for breast cancer (Table 4.6). Three of them addressed an effect of the combination of *ADH1C* genotype and alcoholic beverage intake on the risk for breast cancer. Freudenheim *et al.* (1999) showed an increased risk associated with higher lifetime alcoholic beverage intake for AD*H1C*1/*1* carriers *vs ADH1C*1/*2* and *ADH1C*2/*2* carriers in both pre- and postmenopausal women, the increase being more evident in premenopausal women. Terry *et al.* (2006) reported an increased risk for breast cancer with moderate lifetime alcoholic beverage intake (15–30 g/day), but not with high intake (≥30 g/day), in women with *ADH1C*1/*1* only, and the association was more pronounced among premenopausal women. Such an interaction was not observed for any categories of current alcoholic beverage intake. There was no increase in the risk for any combination of *ADH1C* genotypes and alcoholic beverage intake in the third study (Hines *et al.*, 2000). A fourth study used patients with alcoholic cirrhosis, alcoholic pancreatitis or alcoholism as controls and showed an increased risk for *ADH1C*1/*1* compared with *ADH1C*1/*2* or *ADH1C**2/*2 (Coutelle *et al.*, 2004). [The Working Group noted that the evidence of a relationship between *ADH1C* genotype and breast cancer is inconclusive because of the small number of studies, but a few reports suggested an increased risk associated with moderate lifetime alcoholic beverage intake for the *ADH1C*1/*1* genotype in premenopausal women.]

(iii) *CYP2E1*

The enzyme CYP2E1 is induced by chronic alcoholic beverage consumption and plays a role in ethanol oxidation and the metabolic activation of many carcinogens, including *N*-nitrosamines, benzene and aniline. *CYP2E1* has various polymorphisms, and the *Pst*1- and *Rsa*1-cleavage site polymorphism (*c1/c2*) in the 5′-transcriptional

region has been the most intensively investigated. However, its functional consequence has been a matter of controversy. Early studies showed increased CYP2E1 expression and activity associated with the *c2* allele (Hayashi *et al.*, 1991; Tsutsumi *et al.*, 1994), but this finding has not been confirmed in other studies (Carrière *et al.*, 1996; Kim *et al.*, 1996; Powell *et al.*, 1998; Kato *et al.*, 2003), and contrary results have been reported (Huang *et al.*, 2003). A meta-analysis of case–control studies showed no association between the *CYP2E1* genotype and risk for either alcoholism or alcoholic liver disease (Zintzaras *et al.*, 2006). The results for cancer were inconsistent. Although two case–control studies showed that the *c1* allele increased the risk for oesophageal cancer (Tan *et al.*, 2000; Lu *et al.*, 2005), negative results were reported in eight other case–control studies (Lucas *et al.*, 1996; Hori *et al.*, 1997; Morita *et al.*, 1997; Tanabe *et al.*, 1999; Chao *et al.*, 2000; Gao *et al.*, 2002; Li *et al.*, 2005a; Yang *et al.*, 2005) and a *c2* allele-associated risk was found in yet another study (Lin *et al.*, 1998). A *c2* allele-associated risk for oropharyngolaryngeal cancer was reported in four case–control studies (Hung *et al.*, 1997; Bouchardy *et al.*, 2000; Gattás *et al.*, 2006; Sugimura *et al.*, 2006), and no association was observed in four (Lucas *et al.*, 1996; González *et al.*, 1998; Matthias *et al.*, 1998; Katoh *et al.*, 1999). A *c2* allele-associated risk for hepatocellular carcinoma was reported in three case–control studies (Ladero *et al.*, 1996; Koide *et al.*, 2000; Munaka *et al.*, 2003) and no increased risk in four others (Lee *et al.*, 1997; Wong *et al.*, 2000; Yu *et al.*, 2002; Kato *et al.*, 2003), a *c1/c1* genotype-associated risk was observed in another (Yu *et al.*, 1995). [The Working Group noted that the evidence of a contribution of the *CYP2E1* polymorphism to the development of cancer is inconclusive.]

(iv) *ALDH2*

The variant allele *2 that encodes an inactive subunit of ALDH2 is dominant and highly prevalent among East Asians (28–45%; Goedde *et al.*, 1992), but is not found in most other populations. The inactivity of ALDH2 inhibits persons from drinking heavily by causing acetaldehydaemia and alcoholic flushing responses. Most homozygotes for inactive *ALDH2*2/*2* are non-drinkers or occasional drinkers, but substantial percentages of East Asians who are habitual drinkers, including alcoholics, are heterozygous for inactive *ALDH2*1/*2* (Table 4.8).

Cancers of the upper aerodigestive tract

All case–control studies that involved 13 independent Japanese and Taiwanese (Chinese) alcoholic beverage drinking populations have shown that heterozygosity for inactive *ALDH2* is a strong risk factor for oesophageal cancer, mainly squamous-cell carcinoma (odds ratios, 4.4–16.4; reviewed in Yokoyama & Omori, 2003; see Wu *et al.*, 2005; Yang *et al.*, 2005; Chen *et al.*, 2006; Yokoyama *et al.*, 2006a; Table 4.4). A case–control study conducted in a Thai population, in which only 18% of the controls had inactive *ALDH2*, showed a marginally significant positive association (odds ratio, 1.6; Boonyaphiphat *et al.*, 2002). However, a case–control study conducted in Taixing City, China, where the incidence rate of oesophageal cancer is extremely high (65/100

Table 4.8 Relationship between *ALDH2* genotype and alcohol consumption in Japanese men

Alcoholic beverage consumption	*ALDH2* genotype		
	Homozygous active **1/*1* (*n*=341)	**Heterozygous inactive **1/*2* (*n*=250)**	**Homozygous inactive **2/*2* (*n*=43)**
Never or <22 g/week	6.2%	32.0%	95.3%
22–197 g/week	28.2%	41.2%	4.7%
198–395 g/week	39.6%	14.0%	0%
≥396 g/week	22.9%	10.8%	0%
Former drinkers	3.2%	2.0%	0%

From Yokoyama *et al.* (2002b) ALDH, aldehyde dehydrogenase

000 population), did not show a significant association between the risk for this type of cancer and inactive heterozygous *ALDH2* or with alcoholic beverage drinking (Cai *et al*., 2006). This study reported a marginally significant increased risk in inactive *ALDH2* homozygotes (odds ratio, 1.9) and suggested that inactive homozygous *ALDH2* may modify the cancer susceptibility associated with low selenium intake, an important risk factor in this high-risk population.

ALDH2-related susceptibility to oesophageal squamous-cell carcinoma in Japanese and Taiwanese (Chinese) may include light-to-moderate as well as heavy alcoholic beverage drinkers (Yokoyama *et al*., 2002b; Lewis & Smith, 2005; Wu *et al*., 2005; Yang *et al*., 2005; Chen *et al*., 2006) and female drinkers (Yokoyama *et al*., 2006a). Two prospective studies of Japanese alcoholics showed an increased risk for oesophageal squamous-cell carcinoma in heterozygotes for inactive *ALDH2* (relative hazards, 7.6 and 13.0; Yokoyama *et al*., 1998b, 2006b; Table 4.5). [The Working Group noted that the available genetic epidemiological data provide ample evidence of a strong contribution of the heterozygous *ALDH2* genotype to the development of alcohol-related cancer in the oesophagus.]

Inactive *ALDH2* has consistently been reported to be a strong risk factor for synchronous and metachronous multiple cancers in the oesophagus and oropharyngolarynx, both in Japanese alcoholics and in the general population (odds ratio, 3.4–7.4; reviewed in Yokoyama & Omori, 2003; Muto *et al*., 2005; Table 4.4). Oesophageal dysplasia is also associated with inactive heterozygous *ALDH2*, which serves as a predictor of squamous-cell carcinoma in the oesophagus and oropharyngolarynx in Japanese alcoholics (Yokoyama *et al*., 2006b); the presence of multiple areas of oesophageal dysplasia increases the risk for multiple cancers in Japanese patients with squamous-cell carcinoma of the oesophagus and oropharyngolarynx (Muto *et al*., 2002, 2005).

Other Japanese case–control studies of the *ALDH2*-associated risk for cancer of the oropharyngolarynx have reported different patterns of association according to

anatomical site and drinking habit. A study of oral cancer in which alcoholic beverage consumption was not a risk factor showed that the *ALDH2* genotype had no effect (Katoh *et al.*, 1999), but another study of oral cancer, in which alcoholic beverage consumption was a risk factor, reported a relatively weak but significantly increased risk (odds ratio, 2.9) associated with inactive heterozygous *ALDH2* (Nomura *et al.*, 2000). A case–control study of head and neck cancer, which lacked information on anatomical subsites, showed no difference in *ALDH2* genotype between cases and controls (Hashimoto *et al.*, 2006). However, the study also lacked information on the drinking status of the controls, and analysis of the association with *ALDH2* without consideration of drinking status is misleading. More cases <66 years of age were alcoholic beverage drinkers than those ≥66 years of age, and more drinking cases <66 years of age were heterozygotes for inactive *ALDH2* than drinking cases ≥66 years of age, which suggests an interaction between *ALDH2* and alcoholic beverage drinking in cases <66 years of age. A more sophisticated case–control study of oral and pharyngeal cancer showed that inactive heterozygous *ALDH2* is a strong risk factor for squamous-cell carcinoma in the hypopharynx (odds ratio, 10.1) among moderate-to-heavy drinking men, but not for squamous-cell carcinoma in the oral cavity and oropharynx (Asakage *et al.*, 2007). Although the number of cases size was small, inactive heterozygous *ALDH2* strongly increased the risk for cancer among alcoholic men in both the oral cavity/oropharynx (odds ratio, 20.8) and hypopharynx/epilarynx (odds ratio, 28.9; Yokoyama *et al.*, 2001). A prospective study of cancer-free Japanese alcoholic men showed a hazard ratio of 11.7 for oropharyngolaryngeal squamous-cell carcinoma in inactive *ALDH2* heterozygotes (Yokoyama *et al.*, 2006b; Table 4.5). [The Working Group noted that, while it is often difficult to differentiate clearly between exact locations of tumours in the oropharyngolaryngeal area based on the available published data, there is strong evidence for a contribution of heterozygous *ALDH2* genotype to the development of alcohol-related cancer in the oropharyngolarynx as a whole, and especially in the hypopharynx. However, the Group noted that epidemiological studies provide suggestive but inconclusive evidence of an association of the heterozygous *ALDH2* genotype with alcohol-related cancers in the individual oropharyngolaryngeal subsites of the oral cavity, oropharynx and larynx.]

Liver cancer

One Chinese and seven Japanese case–control studies of *ALDH2*-associated risk for hepatocellular carcinoma yielded conflicting results (Table 4.6). Most of the cases of hepatocellular carcinoma had HCV or HBV infection. Four of the Japanese studies and the Chinese study did not show an increased risk (Shibata *et al.*, 1998; Yokoyama *et al.*, 1998a; Koide *et al.*, 2000; Takeshita *et al.*, 2000a; Yu *et al.*, 2002). However, except for a study of Japanese alcoholics, all the null results were based on analyses that did not consider drinking status. One of the studies reported that the heterozygosity or homozygosity for inactive *ALDH2* was associated with a high risk for hepatocellular carcinoma by multiple regression analysis (odds ratio, 9.8; Munaka *et al.*, 2003); another study reported an interaction between inactive heterozygous *ALDH2* and

light-to-moderate alcoholic beverage drinking when using hospital controls, but not when using other controls with chronic liver disease, and that no interaction between *ALDH2* and heavy alcoholic beverage drinking was observed (Sakamoto *et al.*, 2006). A further study reported that inactive homozygous *ALDH2*2/*2* genotype was associated with an increased risk for HCV antibody-positive hepatocellular carcinoma (odds ratio, 5.4 versus other genotypes; Kato *et al.*, 2003). However, the percentage of hepatocellular carcinoma patients with the *ALDH2*2/*2* genotype in that study (20%) was much higher than that in the other studies (2–10%). Very few Japanese heavy drinkers who had hepatocellular carcinoma with negative markers for viral hepatitis were heterozygous for inactive *ALDH2* (0–12.5%; Ohhira *et al.*, 1996; Yamagishi *et al.*, 2004). [The Working Group noted that available epidemiological studies provide suggestive but inconclusive evidence of an association between heterozygous *ALDH2* genotype and hepatocellular carcinoma.]

Colorectal cancer

Five Japanese case–control studies investigated the association between *ALDH2* genotype and colorectal cancer (Table 4.6). A small study in alcoholics reported an increased risk for colon cancer in inactive *ALDH2*2* heterozygotes compared with those homozygous for the active *ALDH2*1* allele (Yokoyama *et al.*, 1998a). The other four studies reported no overall association between *ALDH2* genetic polymorphism and colorectal cancer (Murata *et al.*, 1999; Matsuo *et al.*, 2002; Otani *et al.*, 2005; Matsuo *et al.*, 2006a), but one suggested that heterozygosity for inactive *ALDH2* increased the risk for colon cancer associated with alcoholic beverage consumption (Murata *et al.*, 1999), and another suggested that heterozygosity for inactive *ALDH2* increased the risk for rectal cancer associated with alcoholic beverage consumption (Matsuo *et al.*, 2002). One study examined the relationship between the composite *ALDH2* and *ADH1B* genotype and colorectal cancer (Matsuo *et al.*, 2006a). In this study, the combination of the *ALDH2*1/*1* and *ADH1B*1/*2* genotype as well as that of the *ALDH2*2* and *ADH1B*2/*2* allele was associated with a substantial decrease in the risk compared with *ALDH2*1/*1* and *ADH1B*2/*2*; adjusted odds ratios for individuals harbouring the *ALDH2*1/*1* genotype and the *ADH1B*1* allele, the *ALDH2*2* allele and the *ADH1B*2/*2* genotype, and the *ALDH2*2* allele and the *ADH1B*1* allele were 0.10 (95% CI, 0.04–0.21), 0.10 (95% CI, 0.06–0.19) and 1.36 (95% CI, 0.94–1.97), respectively. [The Working Group noted that interpretation of the findings was difficult with respect to etiological significance.] The associations with composite genotypes did not differ greatly by alcoholic beverage intake (Matsuo *et al.*, 2002). Two studies examined the relationship between *ALDH2* genotype and colorectal adenomas based on independent data sets in the Self Defence Forces Health Study (Takeshita *et al.*, 2000b; Hirose *et al.*, 2005). The first study was small in size (69 cases and 131 controls) and showed no difference in the distribution of genotypes between cases and controls. The second study was based on 452 cases of colorectal adenoma and 1050 controls; odds ratios for *ALDH*1/*1*, *ALDH*1/*2* and *ALDH*2/*2* were 1.00 (reference), 0.81 (95% CI, 0.62–1.05) and 0.67 (95% CI, 0.35–1.27), respectively, with adjustment for

age, hospital, rank, cigarette smoking and alcoholic beverage use (categorized as life-long non-use, former use and current use of <30, 30–59 or >60 mL alcohol per day). No clear interaction between alcoholic beverage intake and *ALDH2* genotype was noted; high alcoholic beverage intake was associated with an approximately 1.5-fold increase in the risk (odds ratio, 1.53; 95% CI, 1.01–2.32) regardless of *ALDH2*1/*2* genotype. [The Working Group noted that the available epidemiological evidence was rather suggestive of the lack of an effect of the heterozygous *ALDH2* genotype to increase the risk for colorectal cancer. This may reflect the fact that acetaldehyde levels in the colon are high due to microbial metabolism of ethanol, and *ALDH2* plays only a small role in controlling this concentration (see Section 4.1.2).]

Breast cancer

A case–control study of female breast cancer in the Republic of Korea did not show any *ALDH2*-associated risk, but drinking status was not described in detail and no adjustment was made for alcoholic beverage drinking (Choi *et al*., 2003). [The Working Group noted that the epidemiological evidence was insufficient to support an association between heterozygous *ALDH2* genotype and breast cancer.]

Effects of ALDH2 deficiency on acetaldehyde levels

An alcohol-challenge test showed 10–20 times higher acetaldehyde levels in saliva than in blood (Homann *et al*., 1997), and the same and subsequent studies showed that oral microflora forms acetaldehyde from ethanol and largely contributes to acetaldehyde levels in saliva (Homann *et al*., 1997, 2000a). After a moderate oral dose of ethanol, the salivary acetaldehyde levels of individuals with inactive *ALDH2* were two to three times those of individuals with active *ALDH2* (Väkeväinen *et al*., 2000). *ALDH2* activity in the upper aerodigestive tract is extremely weak (Yin *et al*., 1997), and inefficient degradation of acetaldehyde in the upper aerodigestive tract may increase the risk for acetaldehyde-associated carcinogenesis. Higher levels of acetaldehyde–DNA adducts have been demonstrated in Japanese alcoholics with inactive heterozygous *ALDH2* than in those with active *ALDH2* (Matsuda *et al*., 2006). Also, sister chromatid exchange (Morimoto & Takeshita, 1996) and micronuclei (Ishikawa *et al*., 2003) are more frequent in the lymphocytes of habitual alcoholic beverage drinkers with inactive heterozygous *ALDH2* than in those of habitual drinkers with active *ALDH2*. More data on the genotoxic effects of acetaldehyde are discussed in Section 4.7.

(b) Genes involved in folate metabolism

(i) *Folate metabolism and genetic polymorphisms*

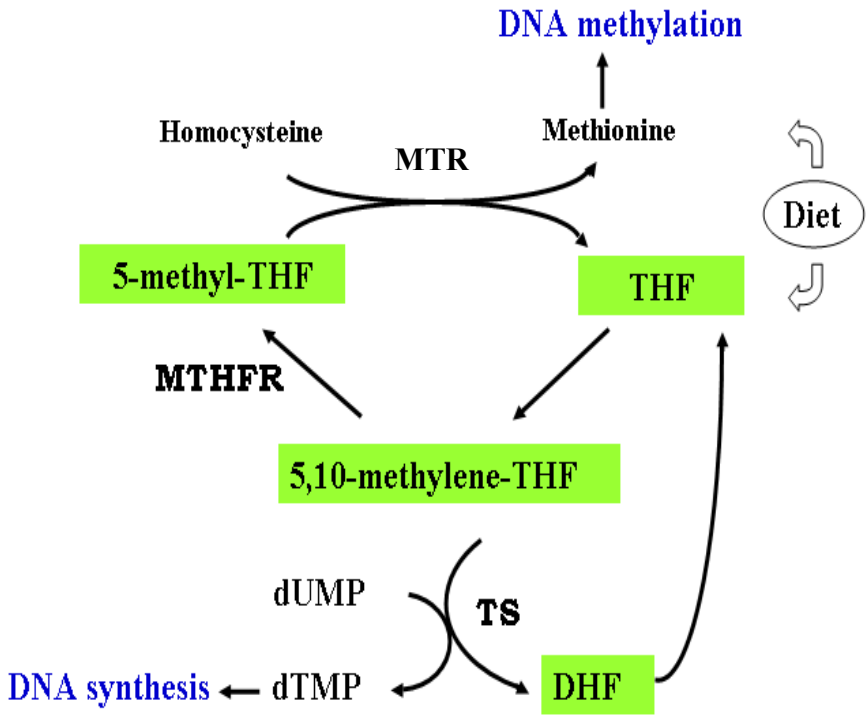
Excessive alcoholic beverage consumption causes folate deficiency, as exemplified by megaloblastic anaemia among alcoholics, and multiple effects of alcoholic beverages on folate metabolism have been described (Halsted *et al*., 2002; Mason & Choi, 2005). Alcoholic beverage consumption leads to folate depletion by decreasing its intestinal absorption and hepatic uptake and by increasing renal excretion through a reduction in tubular re-absorption; acetaldehyde also cleaves folate as shown *in vitro* by Shaw *et al*.

(1989). Acetaldehyde, rather than ethanol *per se*, was responsible for folate cleavage, although no such direct effect has been demonstrated in animals or humans (Mason & Choi, 2005). In a study of Japanese men in a rural community (Yokoyama *et al*., 2005), the amount of alcoholic beverage intake was not correlated with serum folate levels. An inverse correlation was found in carriers of the *ALDH2*1/*2* genotype, which renders the enzyme inactive, but not in those homozygous for the *ALDH2*1/*1* genotype.

Folate metabolism is linked to DNA methylation and synthesis, which are two crucial steps in carcinogenesis (Figure 4.3). Methylenetetrahydrofolate reductase (MTHFR), 5-methyltetrahydrofolate-homocysteine *S*-methyltransferase (MTR) and thymidylate synthase (TS) are key enzymes in folate metabolism (Lucock, 2000; Mason & Choi, 2005), and genetic polymorphisms of these enzymes have been investigated widely, particularly in relation to the risk for colorectal cancer (Sharp & Little, 2004; Kono & Chen 2005). MTHFR irreversibly converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which provides the methyl group for the conversion of homocysteine to methionine, the precursor of *S*-adenosylmethionine, the universal methyl donor for methylation of a wide variety of biological substrates including DNA. MTR is a vitamin B12-dependent enzyme that catalyses the conversion of homocysteine to methionine. Depletion of methionine results in global genomic hypomethylation and aberrant methylation of CpG clusters in the promoters of tumour-suppressor and DNA-repair genes. The substrate of MTHFR, 5,10-methylenetetrahydrofolate, is required for TS-catalysed conversion of deoxyuridylate to thymidylate. An adequate supply of thymidylate is required for DNA synthesis and repair, and depletion of the thymidylate pool results in uracil misincorporation into DNA, leading to single- and double-strand breaks. Ethanol inhibits the reaction catalysed by MTR, resulting in a decrease in *S*-adenosylmethionine and genomic hypomethylation. Inhibition of the conversion of homocysteine to methionine also causes accumulation of 5-methyltetrahydrofolate (a substrate for MTR), i.e. the so-called 'methylfolate trap', and thereby depletes folate in the forms necessary for thymidylate synthesis (Mason & Choi, 2005).

Two functional common polymorphisms in the *MTHFR* gene have been determined. One is the *C677T* polymorphism, with an alanine-to-valine substitution at codon 222, which results in reduced activity of the enzyme, and the other is the *A1298C* polymorphism, which results in a substitution of glutamate with alanine at codon 429 (Frosst *et al*., 1995; van der Put *et al*., 1998). Lower activities of the enzyme are also noted in relation to the *MTHFR A1298C* polymorphism, although the extent of reduction is less evident (Weisberg *et al*., 1998). With regard to the *MTR* gene, the *A2756G* polymorphism that comprises a change from aspartate to glycine at codon 919 has been deemed functional in terms of serum homocysteine and folate levels (van der Put *et al*., 1997). A tandem-repeat polymorphism exists in the enhancer region of the *TS* promoter, which contains triple (*TS*3R*) or double (*TS*2*R) repeats of a 28-base-pair sequence (Horie *et al*., 1995); rare alleles containing larger repeats have also been documented (Matsuo *et al*., 2005). The expression of mRNA is enhanced in individuals who are homozygous for the triple repeats (*TS 3R/3R*) over those with the *TS 2R/2R*

Figure 4.3. Abbreviated scheme of folate metabolism in relation to DNA methylation and thymidylate synthesis



From Kono & Chen (2005)
dTMP, deoxythymidine monophosphate (deoxythymidylate); dUMP, deoxyuridine monophosphate (deoxyuridylate); MTHFR, methylenetetrahydrofolate reductase; MTR, 5-methyltetrahydrofolate-homocysteine S-methyltransferase (also called methionine synthase); THF, tetrahydrofolate; TS, thimidylate synthase

genotype (Trinh *et al.*, 2002). A second *TS* polymorphism, a 6-base-pair deletion in the 3′ untranslated region (*TS 1494del6*), is assumed to be associated with decreased mRNA stability (Ulrich *et al.*, 2000; Mandola *et al.*, 2004; Ulrich *et al.*, 2005).

(ii) *Cancers associated with folate metabolism status*

Colorectal cancer

Two case–control studies nested in the Health Professionals Follow-up Study and the Physicians' Health Study in the USA first reported a decreased risk for colorectal cancer associated with the *MTHFR 677TT* genotype (Chen *et al.*, 1996; Ma *et al.*, 1997). Several studies have replicated this initial finding in different populations, although some have failed to find such an association, as reviewed elsewhere (Sharp & Little, 2004; Kono & Chen, 2005). In a meta-analysis of 16 studies (Kono & Chen, 2005), the combined odds ratio for the *677TT* versus *677CC* genotype was 0.82 (95% CI, 0.72–0.93), while the corresponding value for the *677CT* genotype was 0.97 (95% CI: 0.90–1.04). Results from more recent studies are also consistent with the above estimates (Le Marchand *et al.*, 2005; Matsuo *et al.*, 2005). Thus, the *MTHFR 677TT* genotype has the potential to protect against colorectal cancer.

Results on the *MTHFR A1298C* polymorphism and colorectal cancer are variable across and within studies (Kono & Chen, 2005). In case-control studies in the USA, a decreased risk for colorectal cancer for *MTHFR 1298CC* versus *1298AA* was observed in whites, but not in blacks (Keku *et al.*, 2002), and in women, but not in men (Curtin *et al.*, 2004). No clear association between the *MTHFR 677TT* genotype and colorectal cancer was seen in these studies. The *MTHFR C677T* and *A1298C* polymorphisms are in linkage disequilibrium, and an independent effect of *1298CC* (or *677TT*) is only examined in individuals with the *677CC* (or *1298AA*) genotype. Decreased risk associated with the *677TT* genotype in those with the *1298AA* genotype is more consistent than decreased risk for the *1298CC* genotype in those with the *677CC* genotype (Kono & Chen, 2005). As only few studies are available, the role of the *MTHFRA 1298C* polymorphism in colorectal cancer is uncertain.

Decreased risk for colorectal cancer associated with *MTHFR 677TT* is typically observed in individuals with high folate intake (Giovannucci, 2004; Kono & Chen, 2005). Similarly, an evident decrease in the risk for colorectal cancer associated with the *MTHFR 677TT* genotype was seen more frequently in individuals with no or light consumption of alcoholic beverages (Table 4.9). Part of the inconsistency in the findings may be due to differences in the overall folate status among study populations. Alcoholic beverage intake is an important determinant of folate status in populations with folate-replete diets such as health professionals and physicians in the USA (Giovannucci, 2004). Because the production of 5-methyltetrahydrofolate (a substrate for MTR) is reduced in individuals with *MTHFR 677TT*, an increased rather than a decreased risk due to DNA hypomethylation is expected in carriers of this allele. It is now considered that low activity of MTHFR or the *677TT* genotype is probably advantageous as it ensures a thymidylate pool for DNA synthesis when folate status is replete

Table 4.9 Odds ratios (and 95% confidence intervals [CI]) for colorectal cancer for the *MTHFR 677TT* genotype in combination with alcoholic beverage consumption

Reference, study location and period	Sex	Alcohol intake	Odds ratio (95% CI)	*p* for interaction
Chen *et al.* (1996), USA, 1986–94	Men	Low (≤1 drinks/week) Medium High (≥5 drinks/week)	0.11 (0.01–0.85) 0.55 (0.18–1.64) 1.56 (0.65–3.81)	0.02
Ma *et al.* (1997), USA, 1982–95	Men	Low (0–0.14 drinks/day) Medium (0.15–0.8 drinks/day) High (≥0.9 drinks/day)	0.12 (0.03–0.57) 0.42 (0.15–1.20) 1.31 (0.48–3.58)	<0.01
Slattery *et al.* (1999), USA, 1991–94	Both	Low (≤1 g/day) Medium High (>20 g/day)	1.0 (0.7–1.4) 0.5 (0.3–0.8) 1.0 (0.6–1.6)	Not reported
Keku *et al.* (2002), USA, 1996–2000	Both	Never Ever	1.0 (0.5–2.1) 0.7 (0.3–1.4)	
Yin *et al.* (2004), Japan 2000–03	Both	None Medium (<1 unit/day) High (≥1 unit/day)	0.58 (0.36–0.93) 0.73 (0.40–1.33) 0.89 (0.53–1.47)	0.62
Le Marchand *et al.* (2005), USA, 1995–99	Both	≤ Median (0.01 g ethanol/day) > Median	0.53 (0.34–0.82) 1.06 (0.74–1.56)	0.02
Matsuo *et al.* (2005), Japan 2001–04	Both	None Medium High (≥5 drinks/week, 50 g ethanol/drink)	1.48 (0.70–2.78) 0.51 (0.24–1.09) 0.43 (0.12–1.57)	Not reported

MTHFR, methylene tetrahydrofolate reductase The reference category is the *MTHFR 677CC* or *CC/CT* genotype with the lowest level of alcoholic beverage consumption. The *CC* and *CT* genotypes were combined in studies by Chen *et al.* (1996), Yin *et al.* (2004) and Le Marchand *et al.* (2005).

(Chen *et al.*, 1996; Giovannucci, 2004). Studies of colorectal adenoma have generally failed to showed an inverse association between the *MTHFR C677T* polymorphism and overall risk, but suggested that risks associated with the *MTHFR 677TT* genotype were differential according to folate or alcoholic beverage intake; the risk was elevated in those who had high alcoholic beverage or low folate intake and was decreased in those with low alcohol or high folate intake (Levine *et al.*, 2000; Ulvik *et al.*, 2001; Giovannucci *et al.*, 2003; Marugame *et al.*, 2003). In the case of folate depletion, the *MTHFR 677TT* genotype may diminish DNA methylation due to a decrease in methionine synthesis (Friso *et al.*, 2002; Giovannucci, 2004).

The variant homozygote (*GG*) of the *MTR A2576G* polymorphism was related to a decreased risk for colorectal cancer, especially in subjects with low alcoholic beverage consumption (<1 drink/day), in the combined analysis of the Physicians' Health

Study and the Health Professionals Follow-up Study (Ma *et al.*, 1999). A decreased risk for colorectal cancer associated with *2576GG* was also noted in Norway (Ulvik *et al.*, 2004), but not in other studies in the USA (Le Marchand *et al.*, 2002; Ulrich *et al.*, 2005) or Japan (Matsuo *et al.*, 2005). There was even an increased risk associated with the *2576GG* genotype in alcoholic beverage drinkers in the Japanese study (Matsuo *et al.*, 2005). A study of colorectal adenoma suggested an increased risk in women, but not in men, who had the *2576G* allele and high alcoholic beverage consumption (Goode *et al.*, 2004).

Individuals homozygous for double repeats of the *TS* enhancer region (*TS 2R/2R*) consistently show a decreased risk for colorectal cancer compared with those with the *TS 3R/3R* genotype (Chen *et al.*, 2003; Ulrich *et al.*, 2005; Matsuo *et al.*, 2005). While the *TS*-repeat polymorphism was unrelated to the overall risk for colorectal adenoma (Ulrich *et al.*, 2002; Chen *et al.*, 2004), those with high *TS* expression (*TS 3R/3R*) showed a threefold increase in risk only when they had high alcoholic beverage consumption (Chen *et al.*, 2004). Similarly, the risk for adenoma for the *TS 3R/3R* versus *2R/2R* genotype was elevated when folate intake was low, but was lowered when folate intake was high (Ulrich *et al.*, 2002). No clear association was observed for the *TS 1494del6* polymorphism in relation to colorectal cancer and adenoma (Ulrich *et al.*, 2002; Chen *et al.*, 2003; Ulrich *et al.*, 2005).

Other cancers

Studies on the *MTHFR C677T* polymorphism and the risk for breast cancer have produced rather mixed results. In a meta-analysis of 15 cases–control studies and two cohort studies (Lewis *et al.*, 2006), the authors reported an odds ratio of 1.04 (95% CI, 0.96–1.16) for the *677TT* versus the *677CC* genotype. In the Shanghai Breast Cancer Study (Shrubsole *et al.*, 2004) and the Long Island Breast Cancer Study (Chen *et al.*, 2005b), the authors found an increased risk associated with the *MTHFR 677TT* genotype among women with low folate intake. In a case–control study nested within the Multiethnic Cohort Study (Le Marchand *et al.*, 2004), the *MTHFR 677TT* genotype was associated with a decreased risk for breast cancer in women who had ever used hormone replacement therapy. In this subgroup, a decreased risk for the *677TT* genotype was noted in women with low alcoholic beverage consumption. The *MTHFR A1298C* polymorphism itself does not seem to be associated with risk for breast cancer (Shrubsole *et al.*, 2004; Le Marchand *et al.*, 2004; Chen *et al.*, 2005b; Justenhoven *et al.*, 2005). Justenhoven *et al.* (2005) examined the association of the *MTR A2756G* and *TS 1494del6* polymorphisms and found no clear association with the risk for breast cancer.

In a recent meta-analysis of the relationship between the *MTHFR C677T* polymorphism and the risk for oesophageal, gastric and pancreatic cancer (Larsson *et al.*, 2006), the investigators reported combined odds ratios associated with the *677TT* genotype compared with the *677CC* genotype of 1.90 (95% CI, 1.38–2.60) for gastric cardia adenocarcinoma based on four studies in China and one study in Italy and of 1.68 (95% CI: 1.29–2.19) for gastric cancer at all sites based on three studies in China and

one study each in Italy, Mexico and the Republic of Korea. Results for oesophageal squamous-cell carcinoma in seven populations (five in China and one each in Japan and Germany) and for pancreatic cancer in three studies were highly heterogeneous, and combined odds ratios were not estimated for these cancers. A limited number of studies suggested a greater increase in risk associated with the *MTHFR 677TT* genotype for gastric cardia carcinoma (Stolzenberg-Solomon *et al.*, 2003) and for pancreatic cancer (Li *et al.*, 2005b; Wang *et al.*, 2005b) among alcoholic beverage drinkers. In contrast, the *MTHFR 677CC* genotype was associated with an increased risk for hepatocellular carcinoma in patients with alcoholic liver cirrhosis (Saffroy *et al.*, 2004). Defective DNA synthesis may also play an important role in alcohol-related carcinogenesis in a folate-deficient state.

(c) Genes involved in DNA repair

Several studies have investigated the possible role of DNA-repair gene variants in carcinogenesis associated with alcoholic beverage consumption. In contrast to the strong effects of *ADH* and *ALDH* variants, the reported effects of DNA-repair gene variants have been quite modest and of borderline significance. In a recent review, Boffetta and Hashibe (2006) reported "small but insignificant differences in risk between current drinkers and non-drinkers for sequence variants in *XRCC1, OGG1, XPC* and *ERCC2*".

Below is a summary of the studies, divided by the repair pathway and directly related to alcoholic beverage drinking.

(i) *Direct repair by O^6-methylguanine methyltransferase (MGMT)*

Genetic variation in *MGMT* is of interest in view of earlier findings that exposure to ethanol decreases the activity of this repair enzyme in rats (Garro *et al.*, 1986; Wilson *et al.*, 1994). Two *MGMT* polymorphisms have been studied primarily: *Leu84Phe* and *Ile143Val*. Huang *et al.* (2005) found that *Phe84* and *Val143* alleles were protective against head and neck cancers. Notably, the protective effect of *Val143* was particularly pronounced in alcoholic beverage drinkers who consumed more than 21 drinks per week. However, these authors had noted that the same allele was associated with an increased risk for lung cancer in an earlier, smaller study. Tranah *et al.* (2006) investigated the relationship between the same *MGMT* variants and colorectal cancer. These authors found that the *Leu84* allele interacted with alcoholic beverage consumption, but only in women. They suggested that this effect involves an interaction of MGMT with the estrogen receptor rather than an effect on DNA repair. Studies by Teo *et al.* (2001) have shown that, following the removal of an O^6-methylguanine adduct, the modified MGMT enzyme can prevent the estrogen receptor-stimulated gene expression that is important for cell proliferation. Indeed, the *MGMT 84 Phe/Phe* genotype is associated with an increased risk for breast cancer in postmenopausal women (Han *et al.*, 2006), although until now there is no evidence of an interaction with alcoholic beverage drinking.

(ii) *Base-excision repair*

The *Ser321Cys* variant of the 8-oxoguanine DNA glycosylase 1 (*OGG1*) gene has been identified in the human population. *OGG1* encodes a DNA glycosylase that is responsible for the first step in the repair of the oxidative DNA lesion 8-oxo-deoxyguanine. One study suggests that the Cys-containing enzyme is significantly less active than the Ser-containing form (Kohno *et al.*, 1998). Takezaki *et al.* (2002) observed no effect of the *OGG1* genotype on the overall odds ratio for stomach cancer; however, in individuals who drank more than two drinks per week, the odds ratio for the *Cys/Cys* genotype was 6.55 (95% CI, 1.21–35.5). Elahi *et al.* (2002) also found that the *OGG1 Cys* allele was associated with an increased risk for orolaryngeal cancer. Stratifying by drinking behaviour, they found no association between genotype and cancer in never drinkers, but an increased risk for cancer in alcoholic beverage drinkers homozygous for the *Cys* allele.

(iii) *Nucleotide-excision repair*

The nucleotide-excision-repair pathway may play a role in the repair of several types of DNA lesion that could result from alcoholic beverage consumption or acetaldehyde, such as the malondialdehyde–deoxyguanine and crotonaldehyde–deoxyguanine adducts (Brooks & Theruvathu, 2005; Theruvathu *et al.*, 2005; Matsuda *et al.*, 2006). Shen *et al.* (2001) found that individuals who carry the +/+ genotype for a xeroderma pigmentosum (XP) complementation group C-biallelic poly(AT) insertion/deletion (*XPC-PAT)* intronic polymorphism had a slightly increased risk for head and neck cancer, and that this genotype was associated with an increased risk in never drinkers and former drinkers, but not in current drinkers. Sturgis *et al.* (2000) focused on the *XPD* polymorphism *Gln751Lys*, and found that the *Lys/Lys* genotype was associated with an increased risk for head and neck cancers, and that the risk for this genotype was higher in current tobacco smokers and current alcoholic beverage drinkers. [It should also be pointed out that, although the *XPD Lys751Gln* is commonly considered to be a functional polymorphism, there is little direct evidence to support this, and both functional and evolutionary evidence suggest that this polymorphism is in fact benign (Clarkson & Wood, 2005).]

Cui *et al.* (2006) studied the relationship between the *XPG His1104Asp* polymorphism and lung cancer and squamous-cell carcinomas of the larynx and oesophagus in relation to alcoholic beverage drinking and smoking. They found an increased risk for squamous-cell carcinomas in heavy drinkers who had at least one copy of the *His* allele. [In contrast to the *Gln751Lys* polymorphism, the *His1104Asp* polymorphism is probably functional, based on evolutionary considerations.]

(iv) *Single-strand break repair*

The single-strand break-repair pathway may be particularly important in protecting against DNA damage that results from alcoholic beverage intake, because several studies with the comet assay have shown that exposure of cells to ethanol *in vitro*

can cause single-strand breaks (Blasiak *et al*., 2000; Eysseric *et al*., 2000; Lamarche *et al*., 2003, 2004). However, the relationship between single-strand breaks and cancer is obscured by the fact that patients with a defect in the repair of single-strand breaks develop neurological disease, but are not at significantly increased risk for cancer (Caldecott, 2003).

Kietthubthew *et al*. (2006) found a marginally significant risk for oral cancer with the X-ray repair cross-complementing group 1 *(XRCC1) 194Trp* allele, and reported that this allele interacted with alcoholic beverage and tobacco consumption to increase this risk. With regard to the *XRCC1 Arg399Gln* variant, Sturgis *et al*. (1999) observed a significantly increased risk associated with the *Gln/Gln* genotype among current users of tobacco and alcoholic beverages. In contrast, Lee *et al*. (2001) observed that the *Arg/Arg* genotype was associated with an increased risk for oesophageal cancer in alcoholic beverage drinkers, but not in non-drinkers. Finally, Hong *et al*. (2005) determined the genotypes for three *XRCC1* polymorphisms (*Arg194Trp*, *Arg399Gln* and *Arg280His*) in colorectal cancer patients and non-cancer controls. Certain combinations of these genotypes altered the risk for colorectal cancer in subjects who drank >80 g ethanol per week.

4.3.2 *Experimental systems*

Błasiak (2001) found that exposure of human lymphocytes to 30 mM ethanol inhibited the repair of DNA strand breaks generated by the radiomimetic drug bleomycin. Pool-Zobel *et al*. (2004) used the comet assay to study DNA damage and repair in cells obtained from rectal biopsies from human alcoholic beverage abusers and controls. They found that DNA damage in these cells correlated with DNA damage in lymphocytes. Male alcoholic beverage abusers had significantly less damage than controls, and their cells showed greater repair than those of controls following exposure of the cells to hydrogen peroxide. The authors proposed that this may be the result of an induction of repair as a result of the alcoholic beverage abuse.

Asami *et al*. (2000) exposed rats to increasing concentrations of ethanol (12–70%) in the drinking-water over a 20-week period. When concentrations of ethanol reached 50%, one group of rats was switched from a standard diet to an autoclaved diet to simulate nutrient deficiency. Groups of rats were killed at various time points, and the levels of 8-oxo-deoxyguanine and the activity of its repair enzyme in oesophageal mucosa were assayed. Levels of both 8-oxo-deoxyguanine and repair-enzyme activity were increased by feeding the autoclaved diet. Ethanol had no effect alone, but potentiated the effect of the autoclaved diet. [As this is a very unusual experimental model, it is difficult to draw any conclusions from this study.]

Bradford *et al*. (2005) found that rats and mice exposed to ethanol (35% of calorie intake) via intragastric feeding showed increased levels of oxidative DNA damage, as well as an increased expression level of base excision-repair in the liver, which suggested a compensatory induction of base excision repair by ethanol. These effects

were not seen in *CYP2E1* knockout mice, and were blocked by a CYP2E1 inhibitor. Navasumrit *et al.* (2001a) observed a decrease in hepatic MGMT activity after a single intragastric dose of ethanol (5 g/kg), which is consistent with earlier findings that either acute or chronic treatment with ethanol reduced the activity of this enzyme (Garro *et al.*, 1986; Wilson *et al.*, 1994). The activities of other base excision-repair enzymes, alkylpurine-DNA–*N*-glycosylase and OGG1, were also modulated by treatment with ethanol. Four weeks of feeding a liquid diet (36% ethanol-derived calories) decreased alkypurine-DNA-*N*-glycosylase activity, whereas OGG1 activity was elevated after 1 week of ethanol in liquid diet, but decreased after 4 weeks (Navasumrit *et al.*, 2001a).

4.4 Modifying effects of ethanol consumption on metabolism and clearance

4.4.1 *Humans*

The metabolism and clearance of ethanol are relevant to tumorigenesis in several regards: effects on the level and time course of exposure of target tissues to ethanol; the generation of toxic by-products, particularly reactive oxygen species, during metabolism; and the derangement of other metabolic pathways as a result of co-factor depletion and alteration of intracellular and extracellular signalling.

(a) Effects of ethanol on ethanol metabolism

Ethanol is metabolized by ADH, CYP2E1, -1A2 and -3A4, catalase and, in certain tissues, the non-oxidative free fatty acid ethyl ester synthases (FAEES). ADHs have a higher affinity for ethanol than the CYPs, and are present in substantial quantities in the liver; they provide the major route for catabolism of low-to-moderate concentrations of ethanol (reviewed in Crabb, 1995; Lieber, 1999; Agarwal, 2001; Lieber, 2004a; Gemma *et al.*, 2006). ADH is induced in rat liver *in vivo* by intoxicating concentrations of ethanol (Badger *et al.*, 2000; Wang *et al.*, 2002), but this has not been confirmed for humans.

Hepatic microsomal CYP2E1 plays an increasingly important role as blood ethanol concentrations rise, and degrades a significant percentage (up to 10%) of ingested ethanol (reviewed in Fraser, 1997; Gemma *et al.*, 2006). Regulation of CYP2E1 by ethanol is complex and may involve transcriptional, post-transcriptional, translational and post-translational mechanisms (reviewed in Lieber, 1999; Novak & Woodcroft, 2000; Lieber, 2004a; Gonzalez, 2007). CYP2E1 is induced by ethanol in human liver and in cultured liver cells (reviewed in Crabb, 1995; Novak & Woodcroft, 2000; Cederbaum, 2006; Gonzalez, 2007). Induction may occur with a single, moderately high dose (0.8 g/kg bw) (Loizou & Cocker, 2001). In recently drinking alcoholics, CYP2E1 in liver samples was increased fourfold compared with the level in non-drinkers (Tsutsumi *et al.*, 1989), which is in line with an about threefold higher rate of clearance of chlorzoxazone, a CYP2E1 substrate, in alcoholics. The half-life of CYP2E1 was reported to be 2.5 days in abstaining alcoholics (Lucas *et al.*, 1995). Immunohistochemistry

revealed that the hepatic induction of CYP2E1 was primarily perivenous (centrilobular). In the livers of alcoholics, midzonal as well as perivenular CYP2E1 protein was increased and this increase was strongly correlated with elevated *CYP2E1* mRNA (Takahashi *et al.*, 1993).

There is evidence that the isoenzymes, CYP1A2 and CYP3A4 may be induced by alcohol *in vivo*. In alcoholics, the metabolism of certain drugs that are metabolized by CYPs other than CYP2E1 showed increased clearance, although the complexity of factors and conditions do not allow firm conclusions to be drawn (reviewed by Klotz & Ammon, 1998; Sinclair *et al.*, 1998). With the use of midazolam as an indicator of CYP3A activity, individuals with moderate alcoholic beverage consumption (2–3 drinks/day) did not show a difference in systemic clearance, but maximum serum concentration and oral availability differed; there was evidence of induction of CYP3A in the small bowel (Liangpunsakul *et al.*, 2005).

(b) Effects of ethanol on clearance of ethanol from tissues and organisms

The clearance of ethanol is determined primarily by ADH (see Section 4.1). Of the purified ADH alloenzymes, all but ADH1B3, ADH3 and ADH4 are inhibited by ethanol (Lee *et al.*, 2006), which could impede the clearance of ethanol by either the stomach or liver. In addition, ADH in the stomach is decreased in instances of gastritis and gastric atrophy (Brown *et al.*, 1995), such as those induced by alcohol intoxication. ADH was reduced in the gastric mucosa of young male alcoholics (Seitz *et al.*, 1993) and in men of various ages as a function of daily alcoholic beverage intake (Parlesak *et al.*, 2002). The increase in gastric ADH in alcoholics during abstinence from alcohol was interpreted as evidence of its suppression during alcoholic beverage use (Watanabe, 1997). In addition, young women had lower levels of gastric ADH compared with men of the same age (Seitz *et al.*, 1993). Gastric ADH was lower in alcoholic men and women than in non-alcoholics and correlated with reduced first-pass clearance of ethanol in one study (Frezza *et al.*, 1990). In other investigations no correlation was found between first-pass metabolism of ethanol and gastric ADH (Brown *et al.*, 1995) or gastritis in elderly subjects (Pedrosa *et al.*, 1996).

In addition to inducing CYP2E1, ethanol is a very effective competitive inhibitor of CYP2E1 in humans, as assessed by clearance of chlorzoxazone, a CYP2E1 substrate: an acute dose of 0.8 g/kg bw ethanol reduced chlorzoxazone metabolism by 94% (Loizou & Cocker, 2001). Ethanol may also reduce CYP2E1 indirectly as a result of alcoholic liver disease (Dilger *et al.*, 1997). There is evidence that alcoholism reduces first-pass clearance of ethanol (reviewed in Caballería, 1992). When non-alcoholics and alcoholics consumed 150 mg/kg bw ethanol, the first-pass metabolism accounted for 73% and 23% in these groups, respectively (DiPadova *et al.*, 1987). It is probable that part of this effect can be attributed to the direct or indirect actions of ethanol.

Polymorphisms in *ADH* and *CYP2E1* did not relate to gastrointestinal symptoms in alcoholics (Laheij *et al.*, 2004). *ADH* polymorphisms were investigated in the context

of first-pass ethanol metabolism and levels of gastric ADH; individuals who were homozygous for ADH_3^1 (*ADH1C*1*) presented greater ADH activity in gastric biopsies and more rapid clearance than those who were homo- or heterozygous for ADH_3^2 (*AHD1C*2*) (Oneta *et al*., 1998). Although these differences were not statistically significant due to small group-sizes, they were consistent with the higher V_{max} for the *ADH1C*1* form (reviewed in Crabb, 1995).

The rate of gastric emptying also has a major effect on first-pass clearance by the liver (Oneta *et al*., 1998), since a slow rate of delivery of ethanol to the low-K_m hepatic ADHs favours more complete metabolism. Alcoholic beverages as well as various drugs may alter the bioavailability of ethanol via their effects on gastric emptying (Pfeiffer *et al*., 1992; Fraser, 1997); pure ethanol and whisky caused a delay and beer accelerated the process. Mixed findings were reported for white wine. Variations in ethanol concentration, osmolarity and caloric content are thought to contribute to this discrepancy (Pfeiffer *et al*., 1992). Gastric emptying was accelerated by the consumption of ethanol during a meal (Wedel *et al.,* 1991). In contrast, among 46 chronic alcoholics, 11 (23.9%) showed delayed gastric emptying in association with high ethanol consumption and dyspeptic symptoms, and all alcoholics showed an increased mouth-to-caecum transit time (Wegener *et al*., 1991).

In summary, ethanol and/or the constituents of alcoholic beverages may influence the metabolism of ethanol in humans by specific induction of CYP2E1 and -3A4 and possibly -1A2; by competitive inhibition of CYP2E1 activity in the liver, direct inhibition of ADHs in the liver and gastric mucosa, toxic effects on the gastric mucosa that cause loss of ADH, possible induction of hepatic ADH at high doses and by effects on gastric emptying, which may be variable and complex.

(c) Effects of ethanol on the metabolism of xenobiotics

Ethanol interacts with the metabolism of xenobiotics, mainly through the CYP enzymes, in at least two distinct ways: by the induction of metabolic activation leading to enhanced formation of proximate reactive chemical species; and by competitive inhibition of metabolism and clearance, such that central hepatic and gastointestinal clearance is reduced, which results in increased dose delivery to peripheral target tissues (reviewed in Meskar *et al*., 2001). Alteration of phase II conjugation/detoxification enzymes by ethanol may also occur, but this has been studied less extensively.

(d) Effects of ethanol via the induction of CYP2E1

As noted above, ethanol induces CYP2E1 in human liver. Among more than 70 substrates of CYP2E1 (Raucy *et al*., 1993; Guengerich *et al*., 1994; Djordjević *et al*., 1998; Klotz & Ammon, 1998; Cederbaum, 2006) are known carcinogens such as benzene, butadiene and vinyl chloride, as well as many other compounds, e.g. acrylonitrile, azoxymethane, chloroform, carbon tetrachloride, methylazoxymethanol and trichloroethylene. Increased toxicity results from the metabolism of many of these

chemicals induced by CYP2E1. For example, pyridine, a constituent of tobacco smoke, is a substrate of CYP2E1 that generates redox cycling, which leads to DNA damage (reviewed in Novak & Woodcroft, 2000).

In humans, in addition to the prominent expression of CYP2E1 in the perivenous (centrilobular) regions of the liver, the enzyme is also detectable in the kidney cortex and, at lower levels, in the oropharynx, nasal mucosa, ovary, testis, small intestine, colon, pancreas, endothelial cells of the umbilical vein and in lymphocytes (reviewed in Ingelman-Sundberg *et al.*, 1994; Lieber, 1999, 2004a). This enzyme may thus participate in the genesis of cancers at several important target sites. In the liver, induction of CYP2E1 by ethanol has been demonstrated both *in vivo* and in primary hepatocytes (see below). Levels of hepatic CYP2E1 in humans vary at least 50-fold, which is assumed to be due to various inductive influences that possibly interact with polymorphisms in gene regulatory regions (reviewed in Ingelman-Sundberg *et al.*, 1994). Induction of CYP2E1 in extrahepatic tissues has not been studied extensively in humans. Levels of *CYP2E1* mRNA and protein in the lymphocytes of heavy alcohol drinkers correlated well with clearance rates for chlorzoxazone, a marker for hepatic CYP2E1 (Raucy *et al.*, 1997, 1999). This correlation was not seen in a study of moderate alcoholic beverage drinkers (Liangpunsakul *et al.*, 2005).

(e) Effects of induction of other xenobiotic-activating CYPs by ethanol

As noted above, several CYPs in addition to CYP2E1 may be induced by ethanol. Of particular interest are CYP1A2, which activates heterocyclic amines (Oda *et al.*, 2001), and the enzymes in the CYP3A family, which have wide substrate specificity and have been implicated in the activation of several known or suspected human carcinogens, including aflatoxin (IARC, 2002; Kamdem *et al.*, 2006). Although the affinity is low, both isoforms metabolize the tobacco carcinogen, NNK (Jalas *et al.*, 2005). In humans with moderate alcoholic beverage consumption, the possible induction of CYP3A in the intestine was inferred from the reduced oral bio-availability of midazolam (Liangpunsakul *et al.*, 2005).

(f) Effects of inhibition of CYPs by ethanol

Ethanol is a competitive inhibitor of CYP2E1 (Anderson, 1992). At a concentration of 1%, it inhibits the activities of CYP1A1, -2B6 and -2C19 expressed from transfected genes in cultured human lymphoblastoid cells. In this system, ethanol (1%) did not inhibit the activity of CYP1A2, -2C8, -2C9 or -3A4 (Busby *et al.*, 1999). Other studies also showed no inhibition of CYP3A by ethanol (Feierman *et al.*, 2003). There is indirect evidence that ethanol can inhibit the first-pass hepatic metabolism of the environmental carcinogen NDMA in humans, allowing release of this compound into the blood: individuals with chronic renal failure showed detectable blood and urine levels of NDMA, which were increased by consumption of ethanol (Dunn *et al.*, 1990).

4.4.2 *Experimental systems*

Most studies on the in-vivo effects of ethanol in animals have used rats. These experiments involved either pair-feeding of liquid diet with ethanol as 35% of the caloric intake (Lieber-DiCarli model) or gastric infusion of a liquid diet (total enteric nutrition) to achieve blood levels of ethanol comparable with those in human alcoholics, and to induce hepatotoxicity. These modes of exposure are hereafter referred to as LDC and TEN diets, respectively. The TEN model has been shown to maintain normal body weights of the animals, whereas general health effects, including weight loss, may result from feeding the LDC-type diet (Badger *et al*., 1993).

(a) Effects of ethanol on ethanol metabolism

Similarly to humans, involvement of ADH and CYP2E1 in the metabolism and clearance of ethanol has been confirmed in animals (Gonzalez, 2007). During continuous feeding of rodents with ethanol via intragastric infusion, the blood ethanol levels vary in a cyclic manner (Tsukamoto *et al*., 1985), which suggests that rates of metabolism change independently of the uptake of ethanol. Recent data (reviewed by French, 2005) suggest that this phenomenon is directly linked to the liver toxicity of ethanol and depends on the proper functioning of the intact hypothalamic–pituitary–thyroid axis (Li *et al*., 2000), the release of norepinephrine (Li *et al*., 2003) and the availability of cofactors such as NAD to support the oxidation of ethanol by ADH (Bardag-Gorce *et al*., 2002). Changes in hepatic ADH and in the expression of CCAAT/enhancer-binding proteins and of sterol regulatory element-binding protein 1 (SREBP-1) as a result of continuous infusion of ethanol-containing diets into rats have also been studied (Badger *et al*., 2000; He *et al*., 2002, 2004). Induction of hepatic ADH was demonstrated in a rat model that involved repeated intragastric treatment with acute doses of ethanol, which resulted in progressive pathological changes in both the liver and gastric mucosa. A reduction in gastric ADH occurred concomitantly with an increase in hepatic ADH (Wang *et al*., 2002). However, with an LDC-type diet, gastric ADH did not change, although microsomal ethanol metabolism increased significantly (Pronko *et al*., 2002). ADH may also be influenced indirectly by ethanol suppression of testosterone, which reduces the expression of hepatic ADH in spontaneously hypertensive rats (Rachamin *et al.,* 1980).

In rats and rabbits, CYP2E1 contributed 10% and 40–50% of ethanol clearance at 10 mM and 100 mM ethanol, respectively (Fujimiya *et al*., 1989; Matsumoto *et al*., 1994; Matsumoto *et al*., 1996; Matsumoto & Fukui, 2002). Dietary composition can influence the induction of CYP2E1 in rat liver, and high-fat/low-carbohydrate diets produce the greatest induction, especially with unsaturated fat (Yoo *et al*., 1991; Lieber, 1999, 2004b; Cederbaum 2006). In rats given ethanol in a liquid diet, CYP2E1 was increased ninefold in liver microsomes and accounted for about 50% of CYP-dependent microsomal oxidation of ethanol (Johansson *et al*., 1988). Increased transcription of the *CYP2E1* gene appears to occur only at high doses: when rats received continuous

intragastric infusion with ethanol in a TEN liquid diet, hepatic CYP2E1 protein was induced at most doses tested, but mRNA increased only at urinary alcohol concentrations above 3 g/L (65 mM) (Ronis *et al.*, 1993). *CYP2E1* gene transcription in the liver is controlled by the HNF 1α transcription factor, as well as at least one other pathway that involves β-catenin (reviewed in Gonzalez, 2007). *CYP2E1* mRNA can also be destabilized and its rate of translation affected by insulin (De Waziers *et al.*, 1995).

CYP2E1 protein may be increased via enhanced transcription but also by upregulation of protein synthesis or by enhanced stability of the protein to degradation by the lysosomal or proteasomal pathways, which are influenced by substrate binding (reviewed in Gonzalez, 2007). Chronic administration of high doses of ethanol suppressed proteasome activity (Fataccioli *et al.*, 1999; Cederbaum, 2006). With an LDC diet, increased CYP2E1 protein was shown to be due to enhanced enzyme synthesis (Tsutsumi *et al.*, 1993) or protein stabilization by reduced ubiquitin–proteasome-catalysed degradation (Roberts *et al.*, 1995a). These effects are possibly dependent on the difference in age and/or size of the male Sprague-Dawley rats in these two studies (150–170 g and 100–120 g, respectively), because the hormonal status of rats changes markedly over this range.

CYP2E1 induction has also been studied in primary cultures of rat-liver hepatocytes and in FGC-4 rat hepatoma cells (McGehee *et al.*, 1994). A five- to sixfold maximal induction was observed at 10 mM ethanol, which was due to increased protein stability, with no increase in mRNA, as was also reported for human hepatoma cells. It was suggested that the increase in *CYP2E1* mRNA seen *in vivo* with high concentrations of ethanol may involve effects of hormones and other factors that are not present in cell cultures (reviewed in Novak & Woodcroft, 2000; Raucy *et al.*, 2004).

Ethanol also induced CYP3A in rat-liver cells and in intact rats (Feierman *et al.*, 2003), and CYP2B was induced both at the RNA and at the protein level in intact rats. However, the latter enzyme did not appear to contribute to the oxidation of ethanol (Johansson *et al.*, 1988; Sinclair *et al.*, 1991).

The relative contribution of catalase to the overall metabolism of ethanol is not fully resolved and may be more important in the brain than in the liver. The effects of catalase are greatest at high levels of ethanol and are dependent on concentrations of hydrogen peroxide. Rat hepatic catalase is increased moderately by chronic exposure to ethanol (Quertemont, 2004).

(b) Effects of ethanol on clearance of ethanol from tissues and organisms

Studies with baboons, rats and mice have engendered a debate on the relative importance of gastric and hepatic ADH in the first-pass clearance of ethanol. In baboons, the oesophageal mucosa contains higher ADH activity than the stomach, and the upper gastrointestinal tract provides the greatest contribution to first-pass metabolism (Baraona *et al.*, 2000). In rodents, different studies have concluded that first-pass metabolism of ethanol is predominately gastric (Lim *et al.*, 1993) or that gastric first-pass metabolism

is negligible (Pastino *et al*., 1996; Levitt *et al*., 1997b). Physiologically-based pharmacokinetic modelling indicated that gastric clearance was not important in mice (Pastino *et al*., 1996), but in rats the gastric first-pass metabolism cleared 26% and the hepatic metabolism cleared 12% of a 500-mg/kg dose of ethanol (Pastino & Conolly, 2000). At higher doses of ethanol, the relative importance of gastric clearance increased.

(c) Effects of ethanol via induction of CYP2E1

Regulation of CYP2E1 expression by ethanol is complex, and, as shown in rodent studies, may involve increased gene transcription, mRNA stability, translational efficiency or protein degradation (reviewed in Novak & Woodcroft, 2000). In-vitro studies of molecular regulation in humans have been limited to the use of primary hepatocytes and human hepatoma (HepG2) cells that stably express transfected CYP2E1. The induction of *CYP2E1* mRNA was increased twofold in cultured primary human hepatocytes by 50 mM ethanol, but no significant increase in protein was observed (Raucy *et al*., 2004). However, in HepG2 cells, ethanol induced CYP2E1 protein but not mRNA (reviewed in Lieber, 1999; Cederbaum, 2006). Inductive effects were maximal over a concentration range of 5–100 mM ethanol (Carroccio *et al*., 1994) and apparently involved inhibition of CYP2E1 protein degradation by the proteasome pathway (Cederbaum, 2006).

Ethanol is metabolized *in vitro* by human CYP1A2 and -3A4, as well as by CYP2E1, although with a somewhat lower catalytic efficiency (Salmela *et al*., 1998). The use of specific inhibitors in 18 human liver samples indicated that CYP2E1 contributed most to the oxidation of ethanol, while CYP1A2 and CYP3A4 together equalled CYP2E1 in activity (Salmela *et al*., 1998).

In cultured human HepG2 hepatoma cells, ethanol induced the expression of CYP3A4 from a transfected vector (Feierman *et al*., 2003). Isopentanol, which is a major higher-chain alcohol in beverages, synergized with ethanol to induce CYP3A in rats *in vivo* (Louis *et al*., 1994). In primary cultures of human hepatocytes, isopentanol induced CYP2E1 and particularly CYP3A4 (Kostrubsky *et al*., 1995). In addition, ethanol caused proliferation of the smooth endoplasmic reticulum, so that the levels of all CYP isoforms expressed there were increased (reviewed in Lieber, 2004a).

In addition to its well established effects in the liver, ethanol also induces CYP2E1 in extrahepatic tissues of animals. This may be particularly relevant to the activation of xenobiotics. In rats given ethanol in an LDC-type liquid diet, CYP2E1, as indicated by immunohistochemical staining, was increased in duodenal and jejunal villi and, in contrast to controls, could be detected in the squamous epithelium of the cheek mucosa, tongue, oesophagus and forestomach and in the surface epithelium of the proximal colon. The epithelium of the fundic and antral mucosa of the stomach, the ileum, the distal colon and the rectum remained negative for CYP2E1 (Shimizu *et al*., 1990). In the same model, CYP2E1 protein, but not its encoding RNA was induced in the kidney, brain and intestine as well as the liver, with a rapid decline after

removal of ethanol (Roberts *et al.*, 1994). Ethanol given in the drinking-water to rats induced CYP2E1 protein and nitrosodimethylamine (NDMA) demethylase activity in the brain, especially in neuronal cells in several regions (Anandatheerthavarada *et al.*, 1993). CYP2E1 protein induction by inhaled ethanol was demonstrated in Wistar rats in the centrilobular region of the liver, in alveolar cells of the lung and in proximal convoluted kidney tubules (Zerilli *et al.*, 1995). Ethanol at 5% in liquid diet (LDC-type) caused a marked increase in CYP2E1 and CYP1A2 protein and a small increase in CYP2B protein in rat lung, together with increased metabolism of the tobacco carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (Ardies *et al.*, 1996). Ethanol in an LDC diet induced a 3.6-fold increase in CYP2E1 in rat pancreas (Kessova *et al.*, 1998). Induction of CYP2E1 was seen in peripheral blood lymphocytes of rabbits that received ethanol (10 or 15%) in the drinking-water for up to 24 days (Raucy *et al.*, 1995).

Enhancement of the activation of pro-carcinogens by treatment with ethanol was observed in several earlier experiments, and is presumed to be due to the induction of CYP2E1 in target tissues, although this induction was not demonstrated directly. In rats fed ethanol in an LDC diet, significantly enhanced capacity for the activation of *N*-nitrosopyrrolidine to a mutagen was observed in tissue extracts of the lung, liver and oesophagus but not the stomach: in this study mutagenicity was determined in a bacterial mutation assay with *Salmonella typhimurium* strain TA1535 (Farinati *et al.*, 1985). Treatment of rats with ethanol in an LDC-type liquid diet caused increased metabolism of inhaled benzene by hepatic microsomes, resulting in more rapid clearance of this compound *in vivo*. The treatment also enhanced the haemotoxicity of benzene, as was evident from a marked decrease in the number of peripheral white blood cell cells (Nakajima *et al.*, 1985). In C57Bl/6J mice, administration of 5 or 15% ethanol in the drinking-water for 13 weeks resulted in an enhancement of the toxic effects of inhaled benzene in the bone marrow, spleen and peripheral blood cells (Baarson *et al.*, 1982).

Recently, the role of CYP2E1 in the toxicity of xenobiotics was demonstrated more directly in *Cyp2e1*-deficient mice: azoxymethane caused fewer DNA adducts and colonic aberrant crypt foci compared with controls, consistent with the need for CYP2E1 to activate azoxymethane to the proximal carcinogen, methylazoxymethanol. The latter metabolite, however, was more active in *Cyp2e1*-deficient mice compared with controls; it was postulated that the lack of hepatic clearance resulted in greater dose delivery to the colon. In view of the very low level of CYP2E1 in the colon, the methylazoxymethanol produced from azoxymethane in the livers of normal mice would be transported to the colon, where it could damage DNA and initiate neoplasms (Sohn *et al.*, 2001).

(d) Effects of ethanol on expression of other CYPs

Ethanol in an LDC diet induced not only CYP2E1 (fivefold increase) in rat liver, but also CYP1A1, -2B1 and -3A (two- to fourfold); the latter activities persisted for several

days after withdrawal of ethanol (Roberts *et al.*, 1995b). Induction of CYP3A by chronic feeding of ethanol was confirmed in rat liver and hepatocytes by immunoblot analysis and by assessment of metabolism of fentanyl, a specific CYP3A substrate (Feierman *et al.*, 2003). Repeated acute oral treatment of rats with ethanol resulted in induction of CYP2B1 in the liver, but not in the brain (Schoedel *et al.*, 2001). Isopentanol, which is also present in alcoholic beverages, was a weak inducer of rat liver CYP2B and CYP3A when given in a liquid LDC diet, but synergized with ethanol to further increase the levels of these CYPs (Louis *et al.*, 1994).

High doses of ethanol administered to rats by the total enteric nutrition (TEN) method suppressed *Cyp3a2* mRNA and testosterone 6β-hydroxylation, but induced CYP3A9 in the liver; the latter, but not the former, effect was modulated by the fat/carbohydrate ratio of the liquid diet (Rowlands *et al.*, 2000). In the same model, CYP2C11 was suppressed in male rat liver and kidney, concomitant with a reduction in the amount and phosphorylation of the transcription factor STAT5b (Badger *et al.*, 2003). CYP2C11 is a growth hormone-regulated, male-specific steroid hydroxylase that may be involved in xenobiotic activation (Ozawa *et al.*, 2000). CYP2C7 and CYP2E1 were induced by ethanol in the colonic epithelium of rats (Hakkak *et al.*, 1996). Xenobiotics that are substrates for these members of the CYP2 and CYP3 families may be affected by such ethanol-induced changes.

(e) Effects of ethanol through alterations in detoxification

A single oral dose of ethanol given to rats enhanced the hepatotoxicity of 1,2-dibromoethane (IARC, 1999), a soil fumigant and animal carcinogen, due to ADH-dependent suppression of GST activity (Aragno *et al.*, 1996). In contrast, chronic treatment of rats with a diet containing ethanol led to small but significant increases in GST in the oesophagus (Farinati *et al.*, 1989).

(f) Effects of inhibition of CYPs by ethanol

Direct inhibition of CYPs by ethanol in peripheral target tissues may prevent metabolic activation of xenobiotics and hence reduce local toxic and tumorigenic effects. In contrast, inhibition of CYPs, especially CYP2E1, in the liver may reduce the clearance rate of CYP2E1 substrates and result in increased dose delivery to peripheral targets (reviewed in Anderson, 1992; Anderson *et al.*, 1995; Chhabra *et al.*, 1996). In early examples of this effect, intragastric administration of NDMA, a CYP2E1 substrate, in an alcoholic solution twice weekly to C57BL mice resulted in the development of olfactory neuroblastomas in 36% of the mice; this type of tumour was not seen with ethanol or NDMA alone. The percentage of mice with malignant liver tumours was reduced by the NDMA–ethanol treatment, which possibly reflects reduced NDMA activation and ensuing DNA damage in the liver (Griciute *et al.*, 1981). Ethanol as a solvent also enhanced the ability of NDEA and *N*-nitrosodipropylamine (NDPA) to cause malignant forestomach tumours and of NDPA to initiate lung tumours in C57BL mice

(Griciute *et al.*, 1982, 1987). However, the frequency of lymphomas induced by NDEA was significantly reduced when ethanol was used as a solvent (Griciute *et al.*, 1987). When dissolved in ethanol, NNN reduced the latency and increased the aggressiveness of olfactory tumours in BDVI rats (Griciute *et al.*, 1986). Because of the multiple-dose protocol in these experiments, several mechanisms for the effect of ethanol were possible, including altered disposition of the carcinogen within the organs, induction of CYP2E1 or other activating enzymes in the target tissue and/or tumour promotion.

The first hypothesis that ethanol influences the risk for nitrosamine-induced carcinogenesis through alterations in disposition resulted from a study by Swann *et al.* (1984). After acute administration, NDMA induced DNA-adduct formation in rat kidney only when given with ethanol, and ethanol increased alkylation of oesophageal DNA by NDEA. Inhibition of NDMA metabolism by liver slices from ethanol-treated Wistar-derived rats was demonstrated. In a later study in Fischer 344 rats, acute administration of ethanol (up to 20% v/v) by gavage with NMBzA resulted in increased DNA-adduct formation by the nitrosamine in the oesophagus (threefold), lung (twofold) and nasal mucosa (eightfold) (Yamada *et al.*, 1992). Various alcoholic beverages that are associated with risk for human cancer had similar or greater effects.

The interaction of ethanol with the metabolism and disposition of nitrosamines as illustrated above has been further studied in mice and monkeys, and showed effects of considerable magnitude. At concentrations of ~1 mM, ethanol completely inhibits the hepatic metabolism of NDMA *in vivo*, in hepatocytes and in hepatic microsomes (Tomera *et al.*, 1984; Anderson *et al.*, 1992a). The pharmacokinetic effects were studied in detail in mice (Anderson *et al.*, 1994) and patas monkeys (Anderson *et al.*, 1992b) *in vivo*. In mice given 0.5 mg/kg NDMA orally, pharmacokinetic parameters including clearance rate, residence times and AUC values, were increased 30-fold and 450-fold by simultaneous doses of 0.08 and 0.8 g/kg ethanol, respectively. In monkeys, 1.2 g/kg ethanol given orally before a 1-mg/kg intravenous dose of NDMA inhibited the clearance of the nitrosamine completely during 6 h, increased the mean residence time in the blood by about fourfold and the AUC by an average of 10-fold.

The effects of ethanol on NDMA clearance were associated with marked enhancement of toxic effects in peripheral tissues. Strain A mice treated with NDMA at several doses in the presence of 10 or 20% ethanol in the drinking-water for 12 weeks developed a greater number of lung tumours than mice given NDMA only (Anderson, 1988). Increased numbers of kidney tumours were also noted (Anderson *et al.*, 1992a). Similar results were obtained in these mice with a single intragastric dose of 5 mg/kg NDMA; inclusion of ethanol with the NDMA caused a dose-dependent increase in the incidence of lung tumours, with a ninefold enhancement at 20% ethanol (Anderson, 1992). This single-dose experimental design made it less likely that the effects of ethanol were due to the induction of CYP2E1 in the lung or to tumour promotion. Such effects were also ruled out by the observation that 10% ethanol in the drinking-water had no effect on the lung tumorigenicity of NDMA given by other routes: ethanol had to be delivered to the liver as a bolus with NDMA to have a significant effect. Mechanistic

relationships were further confirmed by the observation that the effects of ethanol on the NDMA AUC, on the O^6-methylguanine–DNA adducts levels in the lung and on the average numbers of lung tumours were of the same magnitude (Anderson *et al.*, 1992a).

Similar effects were seen with 6.8 ppm NDEA in strain A mice; inclusion of 10% ethanol in the drinking-water resulted in a fourfold increase in multiplicity of lung tumours and a 16-fold enhancement of the incidence of forestomach tumours. Inclusion of 10% ethanol with 40 ppm NPYR resulted in a 5.5-fold increase in lung tumour multiplicity (Anderson *et al.*, 1993).

In patas monkeys, the toxic and possibly pre-tumorigenic effects of NDMA were studied by use of O^6-methylguanine–DNA adducts as markers after an oral dose of 0.1 mg/kg NDMA, with or without a preceding dose of 1.6 g/kg ethanol (Anderson *et al.*, 1996). These DNA adducts were detected in all tissues, and were increased by co-exposure to ethanol in all tissues except the liver. Particularly striking effects were seen in the oesophagus (17-fold increase), colonic mucosa (12-fold), pancreas (sixfold), urinary bladder (11-fold), ovary (ninefold), uterus (eightfold), brain (ninefold) and spleen (13-fold). The large increase in DNA adducts in the oesophagus and in other peripheral organs as a result of the suppression of clearance of carcinogens may provide a mechanistic explanation for the enhancement of the risk for cancer from smoking by alcoholic beverage consumption (Tuyns, 2001).

The modulating effect of ethanol on nitrosamine clearance has also been studied in reproductive and perinatal studies. In a study with Sprague-Dawley rats, 1.6 g/kg ethanol was given by gavage to nursing dams followed by 5 mg/kg NDMA or 50 mg/kg NNK (Chhabra *et al.*, 2000). Ethanol resulted in a 10-fold increase in O^6-methylguanine–DNA adducts in maternal mammary glands after administration of NDMA and a smaller but significant increase in adduct levels after administration of NNK. Adducts in maternal blood cells also increased. In the suckling infants, DNA adducts were detected in the lungs and kidneys after maternal exposure to NDMA. The adduct levels increased about fourfold after maternal co-treatment with ethanol; maternal exposure to NNK did not result in DNA adducts in the infant tissues. In rats, NNK is not metabolized by CYP2E1 but rather by CYP1A2, -2A3, -2B1 and -2C6 (Jalas *et al.*, 2005). The effects of ethanol on NNK-derived DNA adducts in the maternal tissues suggests that inhibition by ethanol of one or more of these CYP isoforms could impact NNK clearance.

In pregnant patas monkeys, 1.6 g/kg ethanol given orally before an intragastric dose of 1 mg/kg NDMA resulted in a 50% reduction in O^6-methylguanine–DNA adducts in placenta and fetal liver, where adducts were relatively high. In contrast, a 1.5–2.5-fold increase in these adducts was observed in 11 other fetal tissues (Chhabra *et al.*, 1995). These results are consistent with the blockage of both metabolic activation in and clearance of NDMA from placenta and fetal liver by ethanol, which results in increased dose delivery to downstream target organs.

Inhibition of the clearance of carcinogens as a mechanism by which ethanol enhances carcinogenesis by these chemicals leads to the prediction that the enhancing

effects should not be seen if animals are treated with the same concentrations of ethanol and chemical carcinogen, but at different times and/or by different routes, which minimizes co-exposure. Several studies have confirmed this hypothesis. When NDEA was given to rats orally five times a week, followed each day by 25% ethanol (5 mL/rat/day), enhancement of oesophageal carcinogenesis in rats was not observed (Habs & Schmähl, 1981). In contrast, chronic exposure to ethanol in a liquid diet, which ensures constant and persistent concentrations in the blood, increased the incidence of nasal cavity and tracheal tumours in hamsters given NPYR intraperitoneally (McCoy *et al.*, 1981); however, when ethanol was given in the drinking-water (which would have provided primarily nocturnal exposure) no effect was seen on the incidence of tracheal tumours (McCoy *et al.*, 1986). Inclusion of ethanol in a liquid diet also led to an increased incidence of nasal cavity tumours in rats when NNN was co-administered in the liquid diet, but not when the carcinogen was given subcutaneously (Castonguay *et al.*, 1984). Ethanol in the drinking-water at 10% or given intrapharyngeally as a 50% solution did not alter the incidence of rat oesophageal tumours induced by *N*-nitrosopiperidine in the diet (Konishi *et al.*, 1986). In mice, 10% ethanol given with NDMA in the drinking-water resulted in a fivefold increase in the number of lung tumours, but had no significant effect on these numbers when NDMA was given by other routes (intragastrically, intraperitoneally, subcutaneously or intravenously) (Anderson *et al.*, 1992a). These findings support the hypothesis that direct inhibition of carcinogen clearance by ethanol is the operative mechanism. It is unlikely that hormonal change, tumour promotion or various cellular alterations give rise to the effects of ethanol. Alcohol-mediated facilitation of cellular penetration by the carcinogens remains a possible alternative.

Finally, if inhibition of CYP2E1 is responsible for the enhancement of the effects of these various nitrosamines by ethanol, then other CYP2E1 inhibitors should have a similar effect. This has indeed been shown for the CYP2E1 inhibitor disulfiram, which caused an increase in the incidence of paranasal sinus tumours after administration of NDMA, and of oesophageal tumours after administration of NDEA to rats (Schmähl *et al.*, 1976).

This toxicokinetic-based enhancement of genotoxic and tumorigenic effects, which is seen so clearly for nitrosamines, does not necessarily apply consistently to other substrates of CYP2E1. Urethane is activated and metabolized by CYP2E1 (Hoffler & Ghanayem, 2005; Ghanayem, 2007) and this metabolism is inhibited by ethanol (Waddell *et al.*, 1987; Yamamoto *et al.*, 1988; Carlson, 1994; National Toxicology Program, 2004). However, the effects of ethanol on urethane carcinogenicity have been mixed. In a chronic administration model, 10 or 20% ethanol given to A/Ph female mice in the drinking-water together with 200, 500 or 1000 ppm urethane resulted in a reduced multiplicity of lung tumours (Kristiansen *et al.*, 1990).

In B6C3F1 mice, 5% ethanol given with 10, 30 or 90 ppm urethane decreased the incidence of lung tumours in males, whereas 5% ethanol with 10 ppm urethane increased the incidence of these tumours in females. The incidence of Harderian gland

tumours was also decreased by ethanol in males, but only at the 30-ppm urethane dose, and that of haemangiosarcomas of the heart was increased in females, but only at the 90-ppm urethane dose. Interpretation of these results is somewhat hindered by effects of the chemicals on body weights (National Toxicology Program, 2004).

In contrast to low-molecular-weight nitrosamines, which are completely degraded in the liver, urethane is metabolized to an epoxide as proximate carcinogen, with sufficient stability to be carried from the liver to downstream targets (Park *et al.*, 1993). This may explain the reduced carcinogenicity of urethane plus ethanol in some situations.

4.4.3 *Comparison of humans and animals*

(a) Ethanol

Most studies of ethanol metabolism in experimental animals have employed rats, which appear to be a reasonably good model for humans. A few comparative studies have included both species. Localization of ethanol-induced CYP2E1 in the liver (Tsutsumi *et al.*, 1989) and the effect of concentration of ingested ethanol on its pharmacokinetics (Roine *et al.*, 1991) were similar in humans and rats. There is evidence from both humans and rats that chronic exposure to high levels of ethanol, with damage to the gastric mucosa, results in a reduction in gastric ADH (see earlier sections). There have been varying conclusions about the relative importance of gastric versus hepatic first-pass clearance of ethanol for both humans and animals. According to recent physiologically based pharmacokinetic modelling data, gastric metabolism may play a greater role in rats than in humans. In rats, gastric ADH is the high-K_m class IV isoform, ADH7. In the human stomach, three isoforms may be represented from classes I, II and IV, but again ADH7 accounts for most of the activity. Human and rat ADH7 are 88% homologous, but affinities of human and rat ADH7 for ethanol are markedly different: the K_m is 2.4 M for rats and 37 mM for humans (Farrés *et al.*, 1994b). This difference is consistent with greater first-pass metabolism of ethanol in the rat versus the human stomach.

Levels of ADH activity (V_{max}) were found to be about sixfold lower in human than in rat liver (Sinclair *et al.*, 1990) and varied with body weight, as is usual for metabolic parameters (Matsumoto *et al.*, 1999). Possibly as a consequence of this slower ethanol degradation by ADH, the in-vivo induction in the liver of the gene encoding CYP2E1 may occur at lower concentrations of ethanol in humans than in rats. In the latter, blood concentrations >3 g/L were required to increase hepatic *CYP2E1* mRNA (Badger *et al.*, 1993), whereas the alcohol drinkers who showed a marked increase in hepatic *CYP2E1* mRNA in the study of Takahashi *et al.* (1993) must have had lower levels of blood ethanol. Ethanol and isopentanol were more effective in inducing CYP3A in human than rat hepatocytes in culture (Kostrubsky *et al.*, 1995). As noted above, primary hepatocytes from humans, but not from rats, responded to ethanol with an increase in *CYP2E1* mRNA. These results together suggest that the interaction of ethanol with CYPs is more prominent and important in humans than in rats.

(b) Xenobiotics

Both the inductive and the inhibitory effects of ethanol on several CYPs that act on xenobiotics have been observed in humans and animals, although the human data are limited in scope. The marked effects of ethanol on induction of pro-mutagenic DNA adducts by NDMA in a non-human primate (Anderson *et al.*, 1996) indicate that the relationships between inhibition of hepatic clearance of NDMA (and other nitrosamines) by ethanol and the induction of DNA adducts and tumours in extrahepatic targets, which are seen so clearly in rodents, may also pertain to humans. The magnitude of these effects in rodents has often been large (commonly five- to 10-fold), and greater than the tumour-enhancing effects of ethanol in other rodent-based mechanistic models. This comparison suggests that the toxicokinetic hypothesis should be considered to be important, especially in view of the tobacco–alcohol synergisms that are seen with respect to cancer incidence in smokers who consume alcohol.

(c) Interaction of ethanol and tobacco

The combined effects of alcoholic beverages and tobacco on cancer incidence and mortality have been widely studied in many populations. In the more recent studies on multiplicative and additive interactions, synergistic effects of alcoholic beverages and tobacco have been found, especially for oropharyngeal and oesophageal cancers (Castellsagué *et al.*, 2004; Lee *et al.*, 2005).

Although high alcoholic beverage consumption by itself may increase the risk for human head and neck cancers, the effect is much smaller than that of tobacco alone. It seems probable that the synergism between tobacco and alcoholic beverages in the causation of these cancers is due to the enhancement of the effects of tobacco carcinogens by ethanol.

There are data to support at least three possible mechanisms for the enhancing effects of alcoholic beverages on the risk for oropharyngeal and oesophageal cancer due to tobacco.

First, alcohol may have a local permeabilizing effect on penetration of the oral mucosa by tobacco carcinogens (Du *et al.*, 2000).

Additional possible mechanisms may involve CYP2E1 and other enzymes that both activate and detoxify carcinogens present in tobacco, including NDMA, NDEA, NNK, benzene and others. As noted above, ethanol induces CYP2E1 in all species tested, CYP3A4 and probably CYP1A2 in humans and CYP1A1, -2B1 and -3A in rat liver. In rats, ethanol in a liquid diet induced CYP2E1 in epithelia of the cheek, tongue, oesophagus and forestomach (Shimizu *et al.*, 1990); similar inductive events probably occur in humans. Treatment of rats with ethanol using this model resulted in an increased capacity of oesophageal tissue to activate NPYR to a mutagen (Farinati *et al.*, 1985). [The Working Group noted that the induction of CYP2E1 in this study was presumed but not actually measured.] Thus, the induction of CYPs that bring about the

metabolic activation of tobacco carcinogens in target tissues could explain part of the enhancing effects of alcoholic beverages.

A third mechanistic possibility for the enhancing effect of alcohol consumption on tobacco-related cancers arises from the fact that ethanol competitively inhibits hepatic metabolism by CYP2E1 in all species tested, as well as human CYP1A1, -2B6 and -2C19 (see previous sections). This inhibition could result in increased exposure of tissues other than liver and genotoxicity in those tissues induced by tobacco carcinogens that are substrates for these enzymes. Ethanol caused a nearly fivefold increase in oesophageal DNA adducts in rats treated with NDEA (Swann *et al.*, 1984). In monkeys treated with NDMA, alcohol caused a 17-fold increase in oesophageal DNA adducts and a fivefold increase in nasal cavity tissue adducts (Anderson *et al.*, 1996). In each of these studies, ethanol treatment was acute, so that enzyme induction was unlikely. Also, the oesophagus was not directly exposed to either ethanol or carcinogen, which indicates that a systemic interaction, presumably inhibition of hepatic carcinogen clearance, was responsible for the observed effects in the oesophagus and nasal cavity.

The relevance of these findings to tumorigenesis is confirmed by the results of several studies with experimental animals. Daily treatment of rats with NDEA in 30% ethanol caused more oesophageal papillomas than NDEA without ethanol (Gibel, 1967). Repeated oral dosing of mice with NDMA in 40% ethanol resulted in the appearance of nasal cavity tumours that were not seen with NDMA or ethanol alone (Griciute *et al.*, 1981). Inclusion of 10% ethanol in the drinking-water led to a fivefold increase in the incidence of oesophageal tumours in rats caused by NDEA (Aze *et al.*, 1993). Ethanol given in a liquid diet resulted in a significant increase in the incidence of nasal cavity and tracheal tumours in hamsters caused by intraperitoneal injection of NPYR (McCoy *et al.*, 1981). In these studies, CYP enzyme induction was possible, as well as tumour promotion and other effects of the chronic administration of ethanol, but, in view of the marked effects of acute exposures on DNA adducts, inhibition of carcinogen clearance by ethanol may be the best supported interpretation at present.

4.5 Major toxic effects

4.5.1 *Humans*

(a) Alcohol

(i) *Liver*

Chronic ethanol ingestion results in steatosis, steatohepatitis, fibrosis and cirrhosis of the liver. The risk for cirrhosis increases with daily alcoholic beverage intake of >60–80 g per day in men and >20 g per day in women (reviewed in Mandayam *et al.*, 2004). Dose-dependent increases in risk for alcoholic liver disease are observed in both genders (Becker *et al.*, 1996a). Hispanics and blacks have higher cirrhosis-related mortality rates than non-Hispanic whites in the USA, but it is unclear whether the differences

are attributable to genetic differences or are influenced by lifestyle or socioeconomic status (reviewed in Mandayam *et al.*, 2004). The super-active *ADH1B*2* allele and the inactive *ALDH2*2* allele are preventive factors against alcoholism (Harada *et al.*, 1985; Mulligan *et al.*, 2003). These alleles are less frequent in patients with alcoholic liver disease than in general populations (Chao *et al.*, 1994; Tanaka *et al.*, 1996). However, a recent review and a meta-analysis have shown that polymorphisms of genes encoding alcohol-metabolizing enzymes (ADH1B, ADH1C, ALDH2 and CYP2E1) are unlikely to make a significant contribution to the development of alcoholic liver disease among drinkers who consumed the same amounts of alcoholic beverages (reviewed in Stickel & Österreicher, 2006; Zintzaras *et al.*, 2006). Alcoholics are frequently infected HCV (10% in the USA, 14% in Europe, 45–80% in Japan), and numerous studies have found that alcoholic beverage consumption is detrimental to HCV patients (reviewed in Jamal *et al.*, 2005). Alcohol and HCV infection independently increase the risk for HCC, and there may be synergism between the two factors, with HCC occurring at an earlier age and being more advanced in patients who consume alcohol (reviewed in Morgan *et al.*, 2004).

The interaction between alcoholic beverages and HBV is not completely understood. Several studies have reported a positive interaction, but others have shown negative results (reviewed in Mandayam *et al.*, 2004).

(ii) *Pancreas*

Acute and chronic pancreatitis is a well documented alcohol-related disease. Excessive alcohol use accounts for 70–90% of chronic pancreatitis in western countries (Gullo, 2005). The risk for chronic pancreatitis increases in proportion to dose and duration of alcoholic beverage consumption. Ethanol is metabolized in the pancreas to produce toxic metabolites such as acetaldehydes and FAEEs. According to the estimate by Apte and Wilson (2003), the average alcoholic beverage consumption in patients who develop chronic pancreatitis is 150 g ethanol per day for a period of 10–15 years. Alcoholic pancreatitis begins as an acute process and progresses to a chronic condition with recurrent episodes of acute attack, which show endocrine and exocrine dysfunction (*diabetes mellitus* and steatorrhoea). Tobacco smoking and a diet rich in protein and fat are suspected to be contributing factors (Gullo, 2005). The histopathological features of alcoholic pancreatitis are reviewed in more detail elsewhere (Apte & Wilson, 2003; Gullo, 2005).

While moderate alcoholic beverage consumption has generally been related to a decreased risk for type-2 *diabetes mellitus* (Koppes *et al.*, 2005), high alcoholic beverage consumption was associated with an increased risk for this disease (Tsumura *et al.*, 1999) and for glucose intolerance (Sakai *et al.*, 2006) in Japanese, who may have a lower capacity for insulin secretion than Caucasians (Fukushima *et al.*, 2004).

(iii) *Gastrointestinal tract*

Tissue-specific alcohol metabolism

Ethanol concentrations in the colonic lumen as well as in saliva are similar to blood levels in the post-distribution phase (15–120 min after an ethanol challenge), and ethanol in the saliva and colonic lumen is largely derived from the blood stream (Halsted *et al.*, 1973; Salaspuro, 1996). Microbial oxidation of ethanol contributes to the majority of acetaldehyde formation in the saliva and colonic contents. Fairly high levels of acetaldehyde have been measured in human saliva after a moderate dose of ethanol (0.5 g/kg bw). The production of acetaldehyde was reduced after antiseptic mouth rinsing (Homann *et al.*, 1997). Acetaldehyde levels in saliva after ethanol intake were nine times higher in individuals with partially defective ALDH2 than in those with normal activity of this enzyme, but the in-vitro capacity of saliva to produce acetaldehyde from ethanol was the same in both groups. It was concluded that acetaldehyde is also produced in the salivary glands (Väkeväinen *et al.*, 2000).

Histopathology

Ethanol causes a diversity of morphological and functional alterations along the gastrointestinal tract, which differ somewhat in different segments (Siegmund *et al.*, 2003; Rajendram & Preedy, 2005). The consumption of strong alcoholic beverages directly causes local mucosal injury in the oropharynx, oesophagus, stomach and upper part of small intestine (Simanowski *et al.*, 1995). A typical example is haemorrhagic erosion of the gastric and duodenal mucosa. Chronic administration of ethanol results in toxic damage to the gastrointestinal mucosa followed by epithelial regeneration. Hyperproliferation of epithelial cells is a histological feature that is typical of the regeneration process. Highly proliferative cells have a greater chance of DNA replication errors that result in genetic alterations (Simanowski *et al.*, 1995). The toxic effects of ethanol in the upper gastrointestinal tract may be ascribed in part to acetaldehyde that is generated through oxidation of ethanol in the saliva, as is the case in the large intestine where acetaldehyde is mostly generated by colonic microbes (Salaspuro, 2003).

In a comparative study of alcoholics with a mean intake of >100 g ethanol per day and non-alcoholics with a mean intake of <30 g ethanol per day (Simanowski *et al.*, 2001), increased rectal cell proliferation, as determined by histochemical staining, was reported among the alcoholics. The investigators also noted expansion of the proliferative compartment in the rectal mucosa. Alcohol-related histological and molecular changes in the gastrointestinal tract are summarized in detail elsewhere (Simanowski *et al.*, 1995; Siegmund *et al.*, 2003; Rajendram & Preedy, 2005).

Other pathophysiological effects

Sparse literature concerning humans indicates that alcoholic beverage consumption is related to decreased cellular immunity in the small intestine (MacGregor, 1986; Rajendram & Preedy, 2005). Malabsorption of macronutrients and micronutrients

and inadequate dietary intake are known to occur in alcoholics (Bode & Bode, 2003; Manari *et al.*, 2003), and folate is one of the most common nutrients that are deficient. Chronic alcoholic beverage consumption is associated with reduced absorption of water and sodium in the jejunum and ileum, which gives rise to the diarrhoea seen among alcoholics (reviewed in Bode & Bode, 2003).

(iv) *Endocrine organs*

Ethanol affects the function of endocrine organs such as the gonads, anterior and posterior pituitary glands, pancreas, thyroid and adrenal glands (reviewed by Adler, 1992). Some studies also suggest that ethanol may affect gonadotropin secretion at the hypothalamus and/or anterior pituitary (Iranmanesh *et al.*, 1988). The effects of ethanol on sex hormones are of particular interest with regard to the potential mechanism of breast cancer.

Effects on sex hormones in women

In women, chronic consumption of alcoholic beverages may result in estrogen deficiency, anovulation and amenorrhea (Mendelson & Mello, 1988). In particular, alcoholic beverage intake in very large amounts has been associated with menstrual cycle irregularities, anovulation and early menopause (Hugues *et al.*, 1980). However, for moderate alcohol consumption, there is growing evidence of a positive association with the sex hormones that are linked to breast cancer (i.e. estradiol, dehydroepiandrosterone, androstenedione and testosterone).

Many observational studies on ethanol consumption and serum hormone levels were limited by small sample sizes and/or limited ranges of alcoholic beverage intake. In the largest cross-sectional study reported to date, serum samples collected from 790 pre- and 1291 postmenopausal women in eight European countries who were not taking exogenous hormones were assessed for endogenous sex steroids and sex hormone-binding globulin (SHBG) concentrations (Rinaldi *et al.*, 2006). Premenopausal women who consumed more than 25 g alcohol per day had nearly 40% higher estrone, 20% higher androstenedione and 30% higher dehydroepiandrosterone sulfate, testosterone and free testosterone concentrations compared with women who were non-drinkers, while SHBG concentrations showed no association with alcoholic beverage intake. In postmenopausal women, the serum concentrations of all steroids mentioned above were 10–20% higher in women who consumed more than 25 g alcohol per day compared with non-drinkers, while SHBG levels were about 15% lower. Estradiol or free estradiol did not show any association with alcoholic beverage intake in either pre- or postmenopausal women.

In controlled feeding studies with human volunteers, a direct relationship was found between alcoholic beverage intake and circulating androgen and estrogen levels (Reichman *et al.*, 1993; Ginsburg *et al.*, 1996; Sarkola *et al.*, 1999, 2000, 2001; Mahabir *et al.*, 2004; Sierksma *et al.*, 2004). In a study of postmenopausal women who were not taking hormone replacement therapy, and who consumed either 15 or 30 g alcohol per day in a controlled diet for 8 weeks, serum concentrations of estrone

sulfate significantly increased by 7.5% and 10.7%, and dehydroepiandrosterone sulfate increased by 5.1% and 7.5%, respectively, relative to the concentrations measured in women who consumed placebo. In this study, there was no change in estradiol, testosterone or progesterone levels (Dorgan *et al.*, 2001). In a cross-sectional study of premenopausal women who were not taking oral contraceptives, alcohol ingestion was not associated with plasma estrogen concentrations at any of three time intervals during the menstrual cycle. Alcohol consumption was positively associated with average plasma concentrations of androstenedione (Dorgan *et al.*, 1994).

A study in premenopausal women (mean age, 23–32 years) showed that acute intake of alcohol (0.7 g/kg) induced a significant increase in plasma estradiol levels, which reached a peak value at 25 min after initiation of drinking when blood alcohol levels averaged 34 mg/mL (Mendelson *et al.*, 1988). In premenopausal women (aged ~25–35 years), ethanol was found to elevate testosterone levels in blood plasma regardless of the dose of alcohol (0.3–1.0 g/kg). This effect was most pronounced during the ovulatory phase of the normal menstrual cycle and in women who were currently using oral contraceptives (Eriksson *et al.*, 1994), and has been attributed to inhibited catabolism of testosterone in the liver (Sarkola *et al.*, 2001).

Observational and intervention studies generally suggest that alcoholic beverage intake is associated with increased levels of estradiol in plasma. These findings led to the hypothesis that the elevation of estradiol plays a role in the mechanism that underlies the association between alcoholic beverage consumption and the development of breast cancer (Pöschl & Seitz, 2004).

The mechanism by which ethanol affects the levels of sex hormones in women has been suggested to be an ethanol-mediated increase in the liver redox state, which is represented by an increase in the hepatic NADH-to-NAD ratio that decreases steroid catabolism (Sarkola *et al.*, 1999, 2001). Alternatively, it has been hypothesized that the effect of alcoholic beverage intake, even of moderate amounts, on circulating sex hormone concentrations may be mediated by melatonin, which inhibits estrogen production (Stevens *et al.*, 2000). In addition, some alcoholic beverages contain phytoestrogens that may contribute to total estrogen in plasma (Gavaler, 1998).

Effect on sex hormones in men

Studies in alcoholic men showed that ethanol and its metabolites have direct toxic effects on the testes, which results in decreased testosterone levels and reduced sexual function (IARC, 1988). Among non-alcoholic men, a high dose of alcohol (>1 g/kg) has been found to decrease the concentration of circulating testosterone (Välimäki *et al.*, 1984, 1990). The effect is more pronounced at the later stage of intoxication and during the hangover phase, which has been attributed to a physiological stress condition associated with elevated cortisol levels (Välimäki *et al.*, 1984). The reduction in testosterone has generally been explained, on the basis of research in experimental animals, by direct inhibition of testosterone biosynthesis in the testis (Eriksson *et al.*, 1983). In contrast to high doses of alcohol, lower doses seem to elevate testosterone levels in men (Sarkola & Eriksson, 2003). It is not clear under what conditions this effect occurs.

(v) *Cardiovascular system*

Alcoholic beverage consumption poses a substantial risk for cardiovascular diseases overall, but a J-shaped curve has been noted for light-to-moderate drinking, which is associated with a protective effect on the cardiovascular system.

The mechanism of the protective effect of moderate alcohol intake was explained by the dose-dependent ability of ethanol to increase high-density lipoprotein cholesterol, decrease low-density lipoprotein cholesterol, reduce plasma fibrinogen, inhibit platelet aggregation and reduce plasma apolipoprotein (A) concentration. Thus, ethanol at moderate doses reduces the risk for cardiovascular diseases by inhibiting the formation of atheroma and by decreasing the rate of blood coagulation (Agarwal, 2002; Klatsky, 2002).

Various mechanisms have been suggested for ethanol-mediated cardiovascular pathologies. FAEEs, esterification products of fatty acids and ethanol are mediators of ethanol-induced cell injury (Laposata *et al.*, 2002). Chronic ethanol-induced damage to the vascular endothelium has been linked to the increased release of tumour necrosis factor α (Luedemann *et al.*, 2005). Apoptosis is implicated in the pathogenesis of ethanol-induced tissue damage including that of the cardiac muscle (Fernández-Solà *et al.*, 2006).

The role of heavy drinking in the development of cardiac disease has been observed in humans as well as in various animals species. Abnormalities include reduction of ventricular function, and metabolic and morphological changes. Increased cardiovascular risks of heavy drinking include various effects, such as alcoholic cardiomyopathy, hypertension, arrhythmia and a haemorrhagic stroke (Regan *et al.*, 1977).

A recent meta-analysis summarized the findings on the association between alcoholic beverage consumption and the risk for stroke (Reynolds *et al.*, 2003). From 122 studies, a random-effects model and meta-regression analysis were used to obtain the overall results. Compared with abstaining, heavy drinking of more than 60 g alcohol per day was associated with an increased relative risk for total stroke, ischaemic stroke and haemorrhagic stroke (relative risk range, 1.64–2.18), while drinking of less than 12 g alcohol per day was associated with a reduced risk for total stroke and ischaemic stroke (relative risk, 0.83 and 0.80, respectively) and drinking of 12–24 g per day with a reduced relative risk for ischaemic stroke (relative risk, 0.72). The analysis supported a significant non-linear relationship of alcoholic beverage consumption with total and ischaemic stroke, and a linear relationship with haemorrhagic stroke.

The association between alcoholic beverage consumption and the risk for coronary heart disease has been reviewed (Marmot, 1984, 2001). Based on seven longitudinal studies and six case–control studies, an increased risk among heavy drinkers and a reduced risk among moderate drinkers were found. Other reviews or meta-analyses generally corroborated these findings (Rimm *et al.*, 1996; Corrao *et al.*, 2000). Evidence from eastern Europe showed that irregular (binge) drinking caused cardiovascular disease even at the level of moderate alcohol intake (Britton & McKee, 2000).

Therefore, not only the amount but also the pattern of drinking is important in assessing the effects of alcoholic beverage consumption. Binge drinking may increase silent myocardial ischaemia in those with pre-existing coronary artery disease, marked fluctuation in blood pressure, adverse changes in the balance of fibrinolytic factors and ethanol-induced arrhythmia (Puddey *et al.*, 1999).

A recent position paper was published by the National Institute on Alcohol Abuse and Alcoholism on the health risks and potential benefits of moderate alcoholic beverage use (Gunzerath *et al.*, 2004). This paper concluded that consumption of two drinks per day for men and one for women is unlikely to increase health risks, and cautioned that men should not exceed four drinks on any day and women not exceed three on any day, with emphasis on the importance of drinking patterns as well as the amount consumed.

In contrast to numerous original studies and meta-analyses that support the J-shaped association between alcoholic beverage consumption and cardiovascular risk, a recent meta-analysis argued that the apparent cardioprotective effect of moderate drinking arose from a misclassification bias by including in the category 'abstainers' those who had reduced or stopped drinking in view of their age or ill health (Fillmore *et al.*, 2006).

(vi) *Immune system*

The adverse effects of ethanol on the host defence system have been known for a long time, based on the observations that alcoholics are vulnerable to various infectious agents. In addition, once certain types of infection occur, the course tends to be more severe, with higher rates of complications and mortality (Brayton *et al.*, 1970). Carefully controlled studies have been conducted to avoid confounding by nutritional deficiency and complications from alcoholic liver diseases. Findings from clinical and experimental studies have been summarized in several recent reviews (Szabo, 1999; Díaz *et al.*, 2002; Pavia *et al.*, 2004). The effects of ethanol on immunity are widespread over many aspects of the immune system. The immune system functions in two main components: innate, or non-specific, immunity and adaptive, or specific, immunity. The innate immune system involves mainly macrophages and neutrophils that provide a first line of defence. The adaptive immune system involves lymphocytes such as T cells and B cells, and responds to the specific antigens that escape the defence by innate immunity. Numerous studies have shown that ethanol affects both innate and adaptive immune systems.

Inflammation is a key aspect of innate immunity in response to bacterial pathogens. Macrophages and neutrophils play major roles in the inflammatory process to destroy pathogens, and various cytokines are secreted to maintain communication among cells. Exposure to ethanol impairs phagocytic function of macrophages and neutrophils, as observed in human and animal studies. In chronic alcoholic beverage abusers, inflammatory cytokine levels were significantly increased, leading to the pathological changes observed in alcoholic hepatitis (Szabo, 1997, 1999).

The most important cells involved in the adaptive immune system are T and B lymphocytes. Both groups of cell are affected by chronic exposure to ethanol. The numbers of all subpopulations of T cells are decreased in humans and animals during chronic ingestion of ethanol. Ethanol reduces the ability of T cells to proliferate appropriately in response to an antigen. Acute exposure to ethanol induced programmed cell death or apoptosis of T cells. Overall, exposure to ethanol resulted in a reduced cell-mediated immune response that depended on T cells (Szabo, 1999). The effects of ethanol on B cells mainly appeared to be the elevated levels of serum antibodies (Cook, 1998). Total serum immunoglobulin E (IgE) is increased by alcoholic beverage intake, and the causal role of ethanol seems well supported. The mechanism of this effect is not clear, and several possibilities have been suggested: a direct effect on B cells that increases IgE production, or an ethanol-induced increase in intestinal wall permeability which may result in increased exposure to antigens. Alterations in the cytokine balance that favour Th2 cytokine predominance may also promote IgE synthesis (Gonzalez-Quintela *et al.*, 2004).

The effects of ethanol on the immune response, particularly the stimulation of cytokine secretion, are known to result in tissue damage in alcoholic hepatitis patients (Martinez *et al.*, 1992). Associated with induction of CYP2E1, an altered immune response increases susceptibility to viral infection from HBV and HCV (Djordjević *et al.*, 1998; Albano, 2006). Furthermore, ethanol-induced immunosuppression was hypothesized to be a cofactor in the promotion of cancer in general (Mufti *et al.*, 1989).

Emerging evidence suggests that ethanol acts as a neurochemical messenger that affects the network of the nervous, endocrine and immune systems (Haddad, 2004). In particular, ethanol regulates the hypothalamus–pituitary–adrenal axis that modulates the release of hormones, especially adrenocorticotropic hormone and corticosterone, which in turn influences the immune status.

(b) Acetaldehyde

(i) *Irritation of the eyes and the respiratory tract*

Upon acute exposure to moderate concentrations of acetaldehyde, humans experience irritation of the eyes and respiratory tract. In a study with 24 volunteers, eye irritation occurred in sensitive persons after a 15-min exposure to a concentration of 25 ppm and, in the majority, after exposure to 50 ppm. Irritation of the respiratory tract was noted at around 130 ppm during 30 min, and irritation of nose and throat at 200 ppm during 15 min (Verschueren 1983). Intravenous infusion of young male volunteers with 5% (v/v) acetaldehyde at a rate of approximately 20–80 mg/min for up to 36 min resulted in an increased heart rate, increased ventilation rates and respiratory dead space, and a decreased alveolar carbon dioxide level (Asmussen *et al.* 1948). The irritant effects of acetaldehyde vapour, such as coughing and and a burning sensation in the nose, throat and eyes, usually prevents exposure to concentrations that are sufficient to cause depression of the central nervous system (IARC, 1985). The results

of one study in human volunteers indicated that acetaldehyde penetrates the human blood-cerebrospinal fluid barrier (Hillbom *et al.* 1981).

(ii) *Dermal effects*

Prolonged dermal exposure to acetaldehyde can cause erythema and burns in humans; repeated contact may result in dermatitis, due to irritation or sensitization (IARC, 1985). In patch tests on dry skin, acetaldehyde (10%) caused local cutaneous erythema in 12 volunteers (Haddock & Wilkin 1982). The ethnic predisposition to ethanol-provoked flushing among diverse East Asian populations is probably the consequence of accumulation of acetaldehyde. Topical application of acetaldehyde (75% in water) caused acute cutaneous erythema in 12 volunteers of Oriental ancestry. In persons with this genetic predisposition, cutaneous erythema was also observed after topical application of ethanol or propanol, and the cutaneous vascular reaction to these primary alcohols is probably provoked by the corresponding aldehyde (Wilkin & Fortner 1985a,b).

4.5.2 *Experimental systems*

(a) Ethanol

(i) *Liver*

A variety of mechanisms have been proposed to explain the pathogenesis of ethanol-induced liver injury (reviewed in Wheeler *et al.*, 2001a,b; Lieber, 2004b; Siegmund & Brenner, 2005; Albano, 2006; Dey & Cederbaum, 2006).

The pathological changes caused by alcohol in rodent liver are very similar to those observed in humans. Subchronic administration of alcohol to rats and mice leads to steatosis, steatohepatitis and initial stages of fibrosis. Cirrhosis has not been observed in rodent studies with alcohol alone. ADH-mediated ethanol metabolism modifies the cellular redox state (decreases the NAD^+/NADH redox ratio), which promotes steatosis by stimulating fatty acid synthesis and inhibiting fatty acid oxidation (reviewed in Lieber, 2004b). Administration of a bolus dose of ethanol to rats rapidly accelerated metabolism of ethanol in the liver of animals and resulted in downstream hypoxia in the pericentral region of the liver lobule (reviewed in Bradford & Rusyn, 2005). High doses of ethanol caused vasoconstriction and impaired microcirculation in isolated perfused rat liver (Oshita *et al.*, 1992). The development of hypoxia after acute administration of ethanol to rats could be confirmed by means of the hypoxia marker, pimonidazole (Arteel *et al.*, 1996).

An important enzyme in the microsomal ethanol-oxidizing system is the ethanol-inducible CYP2E1, which produces various reactive oxygen species, including the superoxide anion and hydrogen peroxide; more powerful oxidants, including the hydroxyl radical, ferryl oxidants and the 1-hydroxyethyl radical, are produced in the presence of iron (reviewed in Cederbaum, 2003). CYP2E1-derived oxidants stimulated type I collagen synthesis in hepatic stellate cells (the key cell type of liver fibrogenesis)

and caused mitochondrial injury and induction of oxidant damage to DNA in rodents (Bradford *et al.*, 2005; Albano, 2006). Polyenylphosphatidylcholine, a mixture of polyunsaturated phosphatidylcholines extracted from soya beans, decreased CYP2E1 activity in rats and inhibited hepatic oxidative stress and fibrosis in baboons fed ethanol (Lieber *et al.*, 1994). While ethanol-induced liver pathology correlated with CYP2E1 levels and increased lipid peroxidation in rats that had been intragastrically infused with ethanol (French *et al.*, 1993; Tsukamoto *et al.*, 1995), *CYP2E1*-knockout mice were not protected from ethanol-induced liver injury (Kono *et al.*, 1999).

Chronic feeding of ethanol decreased the number of microtubules (Matsuda *et al.*, 1979) and reduced the amount of tubulin in rat liver, which resulted in impaired microtubule-dependent protein trafficking and hepatocyte ballooning (Tuma *et al.*, 1991). Similar effects were seen with the oxidation products of ethanol, i.e. acetaldehyde and acetate. Decreased hepatic microtubules and increased hepatic export-protein content were observed in ballooned hepatocytes in patients with alcoholic liver disease (Matsuda *et al.*, 1985). The reactive compounds acetaldehyde, malondialdehyde, 4-hydroxy-2-nonenal and the 1-hydroxyethyl radical react with proteins to form protein adducts, which are immunogenic and may contribute to alcohol-induced liver tissue damage (reviewed in Albano, 2006).

Ethanol-induced oxidative stress causes dysfunction and depolarization of mitochondria and changes their permeability. These mitochondrial alterations are now recognized as a key step in apoptosis; they enhance the sensitivity of cells to other pro-apoptotic or damage signals (reviewed in Adachi & Ishii, 2002). The imbalance between oxidant production and hepatic antioxidant defence, especially by GSH, plays an important role in the pathogenesis of ethanol-induced liver injury. Reduction of mitochondrial GSH content by chronic administration of ethanol preferentially occured in pericentral hepatocytes (Hirano *et al.*, 1992). Introduction of the superoxide dismutase gene via adenovirus-mediated gene transfer (Wheeler *et al.*, 2001b) and the use of drugs or nutritional antioxidants, such as the GSH precursor *S*-adenosylmethionine, have been found to protect hepatocytes against ethanol-induced toxicity (reviewed in Lieber, 2002).

Ethanol-induced oxidative stress and induction of damage in mitochondrial DNA have been studied intensively in the liver of rodents, and these pathological processes are also conceivable in tissues other than the liver (Hoek *et al.*, 2002). Ethanol increases the generation of reactive oxygen species by enhanced redox pressure through NADH, which is produced during oxidation of ethanol by ADH (cytosolic NADH) and also upon oxidation of acetaldehyde by mitochondrial ALDH2. The induction of CYP2E1 by chronic heavy ethanol intake is a mechanism that explains the ethanol-induced increase in reactive oxygen species. Mitochondrial proteins and lipids as well as mitochondrial DNA are targets for oxidative damage. Damaged mitochondrial DNA results in mitochondrial dysfunction, and further increases the oxidative stress in the cell. Oxidative damage to mitochondrial DNA is inversely related to the lifespan of mammals (Barja & Herrero, 2000), and is purportedly linked to ageing (Raha & Robinson,

2000). Chronic administration of ethanol caused accumulation of damaged mitochondrial DNA and increased the amount of mitochondrial DNA strand breaks in the liver of rodents (Cahill *et al.*, 2002).

(ii) *Pancreas*

Both acute and chronic administration of high doses of ethanol resulted in a decrease in GSH, a reactive oxygen species scavenger, and an increase in oxidized GSH, proteins and lipids in the pancreatic tissue of rats (Altomare *et al.*, 1996; Grattagliano *et al.*, 1999). Other experiments in rats have shown a fivefold increase in CYP2E1 enzyme concentration in the pancreas and the induction of pancreatic hypoxia after chronic administration of ethanol (Norton *et al.*, 1998; McKim *et al.*, 2003). Chronic ethanol ingestion increased protein synthesis in the pancreas two- to threefold, as measured by the incorporation of ^{3}H-labelled leucine in rats *in vivo* after overnight fasting and *in vitro* in isolated pancreatic acini of these rats (Ponnappa *et al.*, 1988). In an animal model of alcohol-induced pancreatitis (Kono *et al.*, 2001), rats were kept on diets rich in unsaturated fat and given a high dose of ethanol enterally. Within 4 weeks, the animals showed acinar cell atrophy, fat intiltration in acinar and islet cells, inflammatory cell infiltration and focal necrosis, as well as fibrotic changes, together with a substantial increase in collagen α1(I) mRNA expression. Chronic administration of ethanol resulted in macroscopic and structural abnormalities of B-cells in rats (Koko *et al.*, 1995).

In summary, high doses of ethanol cause pancreatitis in animals, which serves as a model for human pancreatitis.

(iii) *Gastrointestinal tract*

High concentrations of acetaldehyde were found in the colorectal content in piglets after administration of ethanol. Ethanol was oxidized by microbial ADH and acetaldehyde accumulated in high concentrations because ALDH activity was low in the colorectal mucosa of these animals (Jokelainen *et al.*, 1996). The mucosal concentration of acetaldehyde was inversely related to folate levels in the colorectal mucosa of rats that received 3 g/kg bw of ethanol, twice a day for two weeks (Homann *et al.*, 2000b).

In animals that received ethanol in long-term studies, structural alterations indicative of cellular proliferation were observed in the oropharynx and oesophagus, and mucosal atrophy was seen in the oral floor. Pro-inflammatory features such as infiltration of neutrophils and release of reactive oxygen species were noted in the gastric and small intestinal mucosa in rodents shortly after oral or intragastric administration of ethanol (reviewed in Bode & Bode, 2003; Siegmund *et al.*, 2003). Perfusion of jejunal segments of rabbits with 6% (w/v) ethanol caused mucosal injury and enhanced epithelial permeability, which were mediated by the release of radical oxygen species associated with leukocyte infiltration (Dinda *et al.*, 1996). In this study, the ethanol concentration corresponded to the intraluminal concentrations reached in humans

during moderate alcohol consumption (0.8 g/kg bw) (Beck & Dinda, 1981). Gastric mucosal changes associated with chronic ad-libitum ingestion of ethanol comprised epithelial regeneration with enhanced DNA synthesis as a consequence of mucosal injury (Siegmund *et al.*, 2003).

Increased cell proliferation was consistently observed in the large intestine of rodents fed ethanol chronically (Simanowski *et al.*, 1986; 1995). Chronic administration of ethanol via liquid diets led to increased activity of ornithine decarboxylase, a marker enzyme of cell growth and proliferation, in the rectal mucosa of rats (Seitz *et al.*, 1990).

(b) Acetaldehyde

The acute toxicity of acetaldehyde is relatively low: the oral LD_{50} (dose that was lethal to 50% of animals) in rats and mice ranged from 660 to 1930 mg/kg bw and the inhalation LC_{50} (concentration in air that was lethal to 50% of animals) in rats and Syrian hamsters varied from 24 to 37 g/m^3 (IPCS, 1995). Upon repeated dosing by the oral route and inhalation, toxic effects at relatively low concentrations were limited principally to the sites of initial contact. In a 28-day drinking-water study in which acetaldehyde was given to rats at up to 675 mg/kg bw daily for 4 weeks, focal hyperkeratosis of the forestomach was observed at the highest dose (Til *et al.*, 1988). Following inhalation, the respiratory effects seen in rats exposed for 5 weeks and in hamsters exposed for 13 weeks were degenerative changes in the olfactory epithelium (rats, 437 mg/m^3 [243 ppm]; Saldiva *et al.*, 1985) and the trachea (hamsters, 2400 mg/m^3 [1340 ppm]; Kruysse *et al.*, 1975). At higher concentrations, degenerative changes in the respiratory epithelium and larynx were observed.

Effects of acetaldehyde in the liver have been reported at high doses. Intraperitoneal injection of male albino rats with 200 mg/kg bw daily for 10 days caused accumulation in the liver of total lipids, triacyl glycerols and total cholesterol. Other effects were increased glycogenolysis, a shift in metabolism from the citric acid cycle towards the pentose phosphate pathway and an increase in levels of serum triacyl glycerol, total cholesterol and free fatty acids (Prasanna & Ramakrishnan, 1984, 1987). This treatment also altered thyroid function, as indicated by lower serum thyroxine and decreased iodine uptake, but these these effects may have been secondary to the observed hepatic changes (Prasanna *et al.*, 1986). In a similar study with female Sprague-Dawley rats, histopathological changes in the pancreas were noted, with decreased trypsinogen levels and amylase activity (Majumdar *et al.*, 1986).

In a 28-month carcinogenicity study, Wistar rats were exposed by inhalation for 6 h per day on 5 days per week to 1350, 2700 or 5400 mg/m^3 [750, 1500 or 3000 ppm] acetaldehyde. Growth retardation and increased mortality were seen at all dose levels. After one year of treatment, degenerative changes in the olfactory nasal epithelium were observed at each dose level, including slight to severe hyperplasia and keratinized stratified metaplasia of the larynx (high dose only) and degenerative changes of the

upper respiratory epithelium. At the high dose, focal flattening and irregular arrangement of the tracheal epithelium was found. When a subgroup of rats was allowed a 26-week recovery period after 52 weeks of exposure, partial regeneration of the olfactory epithelium was observed in the low- and mid-dose groups (Woutersen *et al.*, 1984, 1986; Woutersen & Feron, 1987).

Tissues that are characterized by rapid cell turnover have an increased susceptibility towards chemical carcinogens; various studies have therefore been performed to evaluate the effect of chronic ethanol consumption on mucosal cell turnover. In rats fed ethanol chronically, the size of the basal-cell nuclei of the oral mucosa from the floor of the mouth, the edge of the tongue and the base of the tongue was significantly enlarged. Chronic ingestion of ethanol also significantly stimulated the production of crypt cells in the rectum. This was associated with an expansion of the proliferative compartment of the crypt, which correlates with an increased risk for rectal cancer. Proliferation rates of crypt cells in the rectum could be correlated with mucosal acetaldehyde concentrations, which would underline a toxic effect of acetaldehyde on the rectal mucosa that induces compensatory hyper-regeneration. These data show that chronic ethanol consumption leads to mucosal hyper-regeneration in the gastrointestinal mucosa associated with an increased risk for cancer. This may therefore represent at least one mechanism by which ethanol exerts its co-carcinogenic effect (Simanowski *et al.*, 1995, 2001).

4.6 Reproductive and perinatal toxicity

4.6.1 *Humans*

(a) Effects on reproduction

The effects of alcoholic beverages on reproduction in both men and women have been reviewed previously (IARC, 1988) and more recently (Emanuele & Emanuele, 1998; Dees *et al.*, 2001; Emanuele *et al.*, 2002).

Alcohol can interfere with the function of each of the components of the male reproductive system, and thereby cause impotence, infertility and reduced male secondary sexual characteristics. In the testes, ethanol can adversely affect the Leydig cells, which produce and secrete testosterone. Heavy alcoholic beverage consumption results in reduced testosterone levels in the blood. Ethanol also impairs the function of the testicular Sertoli cells that play an important role in sperm maturation. In the pituitary gland, ethanol can decrease the production, release and/or activity of two hormones with critical reproductive functions: luteinizing hormone and follicle-stimulating hormone. Finally, ethanol can interfere with hormone production in the hypothalamus (Emanuele & Emanuele, 1998).

It is widely accepted that ethanol also has profound effects on the female reproductive system. Alcohol abuse and alcoholism are associated with a broad spectrum of reproductive system disorders (Mello *et al.*, 1989). Amenorrhoea, anovulation, luteal

phase dysfunction and ovarian pathology may occur in alcohol-dependent women and alcoholic beverage abusers. Luteal phase dysfunction, anovulation and persistent hyperprolactinaemia have also been observed in social drinkers who were studied under clinical research ward conditions. The reproductive consequences of alcohol abuse and alcoholism range from infertility and increased risk for spontaneous abortion to impaired fetal growth and development. It has been suggested that the effects of ethanol on pituitary gonadotropins and on gonadal, steroid and adrenal hormones in women are responsible for these effects (Emanuele *et al.*, 2002). Beyond puberty, ethanol has been found to disrupt normal menstrual cycling in women and to affect hormonal levels in postmenopausal women.

(b) Teratogenic effects

(i) *Transplacental (gestational) exposures*

Ethanol is a well documented human developmental teratogen that can cause a spectrum of physical and mental dysfunctions following prenatal exposure. Multiple terms are used to describe the continuum of effects that result from prenatal exposure to ethanol, the most commonly known of which is fetal alcohol syndrome (FAS).

FAS is a collection of the most severe abnormalities caused by maternal alcohol abuse, and includes pre- and/or postnatal growth retardation, characteristic craniofacial dysmorphology, mental retardation, cardiac septal defects and minor joint abnormalities. Less common features of FAS include abnormalities of multiple organs and systems that encompass vision, hearing and vestibular apparatus, urinary, hepatic, immune and skin defects (Chaudhuri, 2000a,b). Many symptoms of FAS persist well into adulthood (see e.g. Streissguth *et al.*, 1991a).

Abel and Sokol (1987) reported a worldwide incidence of FAS of 1.9 per 1000 live births, and estimated that approximately 6% of the offspring of alcoholic women have FAS. For offspring born after a sibling who had FAS, the risk is much higher (up to 70%; Abel, 1988). The prevalence of FAS is probably considerably underestimated, because of the difficulty in making the diagnosis and the reluctance of clinicians to stigmatize children and mothers (Little & Wendt, 1991; Ceccanti *et al.*, 2004).

A large number of qualitative studies on the prenatal effects of ethanol with resepect to physical and mental development (see, e.g., Coles *et al.*, 1987, Coles, 1993; Larkby & Day, 1997), as well as meta-analytical reviews (Polygenis *et al.*, 1998; Testa *et al.*, 2003), have been undertaken.

Major morphological abnormalities associated with FAS result from exposure early in pregnancy, while growth is most seriously affected by late exposure. Central nervous system deficits occur throughout gestation. Thus, offspring who are exposed to ethanol throughout pregnancy will not have the same outcome as offspring who are exposed only during early pregnancy or only at specific times during pregnancy.

Growth deficits

Children with FAS were reported to have lower body weights than age-matched controls (Streissguth *et al.*, 1991b). FAS-related growth retardation is somewhat ameliorated at puberty. The growth deficits are symmetrical and affect height, weight and head circumference to the same degree, and remain significant until the age of 10 years. The relationship between the intensity of prenatal exposure to alcohol and growth deficits is linear. Smith *et al.* (1986) found that the duration of exposure to alcohol, in addition to the amount consumed, affected birth weight.

Morphological abnormalities

These include facial anomalies, i.e. short palpebral fissures, a flattened nasal bridge, an absent or elongated philtrum and a thin upper lip, which are established when the midline of the face is formed during the first trimester of pregnancy (Day *et al.*, 1990).

Central nervous system deficits

Post-mortem examinations conducted in the late 1970s provided the first evidence of structural brain abnormalities in infants and fetuses of mothers who ingested alcoholic beverages during pregnancy. In addition to microcephaly, the observed malformations included cerebral dysgenesis, *hydrocephalus internus* and hypoplasia or complete agenesis of the olfactory bulbs (Clarren, 1981). In-vivo imaging techniques have been used to examine the brains of children with FAS (Ronen & Andrews, 1991; Mattson *et al.*, 2001; O'Hare *et al.*, 2005). These studies demonstrated ethanol-induced central nervous system dysmorphology that ranged from holoprosencephaly to hypoplasia of specific brain regions. Thus, deficiencies in specific brain structures due to prenatal exposure to ethanol may underlie behavioural and cognitive deficits that are characteristic of FAS (Sowell *et al.*, 2002).

Coles *et al.* (1991) compared the cognitive performance of children whose mothers drank an average of 11.8 oz absolute alcohol (i.e. approximately 24 drinks) per week throughout pregnancy with that in children whose mothers stopped drinking in the second trimester or did not drink at all during pregnancy. At an average age of 5 years and 10 months, children who had been exposed throughout gestation performed more poorly than children in the other two groups, and showed deficits in short-term memory and encoding (i.e. sequential processing) and overall mental processing.

A recent examination of the effects of prenatal exposure to ethanol on the mental development of the infant, as assessed by the mental development index, was conducted in a meta-analysis by Testa *et al.* (2003). This study examined the effects of three levels of average daily exposure during pregnancy: <1 drink per day, 1–1.99 drinks per day and ≥2 drinks per day. Analyses were conducted separately for effects derived from observations of 6–8-, 12–13- and 18–26-month-old children. Fetal exposure to ethanol at all three dosage levels was associated with significantly lower mental development index scores among 12–13-month-olds. For younger and older children, the effect of fetal exposure to ethanol did not attain statistical significance at any dose level.

(ii) *Paternal exposures*

Paternal alcoholic beverage consumption and its effects on the offspring have been reviewed (Abel, 2004).

Tarter *et al.* (1984) compared adolescent sons of alcoholics with sons of non-alcoholics. Using a standardized test of educational achievement, adolescent sons of alcoholics performed significantly worse. Furthermore, it was demonstrated that sons of alcoholics have certain neuropsychological deficits in perceptual-motor ability, memory and language processing. They also had auditory and visual attentional impairments and a lower level of achievement in reading comprehension. In addition, the sons of alcoholics presented a more neurotic personality profile than sons of non-alcoholics.

Savitz *et al.* (1991) analysed data on single live births from 1959 to 1966 among 14 685 Kaiser Foundation Health Plan members to assess the impact of paternal age, cigarette smoking and alcoholic beverage consumption on the occurrence of birth defects in the offspring. Prevalence odds ratios for anomalies identified by age 5 years were analysed, contrasting exposed to unexposed fathers with adjustment for maternal age, race, education, smoking and alcoholic beverage use. Alcoholic beverage use by the father was most positively related to the risk for ventricular septal defects in the offspring but the increase in risk was not significant. These data generally do not indicate strong or widespread associations between paternal attributes and birth defects.

4.6.2 *Experimental systems*

Animal studies dealing with the effects of ethanol on reproduction and fetal development have been reviewed (IARC, 1988; Abel, 2004).

(a) Ethanol

(i) *Effects on reproduction*

In general, animal data have demonstrated decreased litter size, increased prevalence of low-birth-weight fetuses and mixed data on the risk for malformations. Cognitive and behavioural changes that include learning and memory deficits, hyperactivity and poor stress tolerance were found to be the most prominent effects.

(ii) *Teratogenic effects*

Data from the experiments on the transplacental effects of ethanol in animal models, including rodents and non-human primates, largely support the findings in humans. These results have been reviewed extensively (IARC, 1988; Becker *et al.*, 1996b; Goodlett *et al.*, 2005).

(b) Acetaldehyde

Several studies on the developmental effects of acetaldehyde have been conducted, primarily to investigate its role in ethanol-induced teratogenicity (O'Shea & Kaufman,

1979, 1981; Bariliak & Kozachuk, 1983; Webster *et al.*, 1983; Ali & Persaud, 1988). In these studies, acetaldehyde was given by amniotic or intraperitoneal injection, not by ingestion or inhalation. Dose-related embryotoxic, fetotoxic and teratogenic effects were seen in most of these studies, particularly in rats, but maternal toxicity was often not assessed adequately or reported in any of these investigations. Dose-related embryotoxic effects were observed in in-vitro studies on rat embryos exposed to acetaldehyde (Popov *et al.*, 1981; Campbell & Fantel, 1983). Effects on the placenta have been observed following intraperitoneal injection of acetaldehyde into pregnant rats (Sreenathan *et al.*, 1984).

Rat postimplantation embryos at gestation day 9.5 were cultured for 48 h and observed for morphological changes following treatment with acetaldehyde. There was significant cytotoxicity in embryonic midbrain cells. In this tissue, the levels of p53, bcl-2, 8-hydroxydeoxyguanine and the number of cells damaged by reactive oxygen species were increased by the treatment. Co-treatment with acetaldehyde and catalase decreased the cytotoxicity. In postimplantation culture, acetaldehyde-treated embryos showed retardation of embryonic growth and development in a concentration-dependent manner. These results show that acetaldehyde induces fetal developmental abnormalities by disrupting cellular differentiation and growth. Some antioxidants can partially protect against the embryonic developmental toxicity (Lee *et al.*, 2006).

4.7 Genetic and related effects

4.7.1 *Humans*

(a) Ethanol

The genetic and related effects of ethanol in humans published before 1987 have been reviewed previously (IARC, 1988).

More recently, Rajah and Ahuja (1996) evaluated the genotoxicity of a dual exposure to ethanol and lead in workers in the printing industry, and the possible interaction between the two agents. Individuals were classified into four groups: controls, lead-exposed individuals, alcoholic beverage consumers and lead-exposed alcoholic beverage consumers. Alcoholic beverage consumers had a significant increase in the frequency of sister chromatid exchange compared with the controls. Although an increase in the frequency of chromosomal aberrations and sister chromatid exchange was observed in individuals exposed to lead, this increase was not significant. Lead-exposed alcohol consumers had a significant increase in the frequency of chromosomal aberrations and sister chromatid exchange. Statistical analysis did not reveal an interaction between ethanol and lead in either assay.

Maffei *et al.* (2000, 2002) found that the frequency of chromosomal aberrations and micronucleated lymphocytes was significantly higher in 20 alcoholics than in 20 controls. In the alcoholics, no association was found between duration of alcoholic beverage abuse and frequency of genetic damage. In a cytogenetic study with peripheral

blood lymphocytes of 29 chronic alcoholics, 11 alcoholics in abstinence and 10 controls (Burim *et al.*, 2004), the frequencies of chromosomal aberrations for chronic alcoholics and alcoholics in abstinence were higher than those observed in control individuals. The frequencies of chromosomal aberrations seen in alcoholics in abstinence were similar to those obtained for chronic alcoholics. Interestingly, this study found that chromosomal aberrations were not statistically different when smoking and nonsmoking alcoholics were compared, which indicated a lack of interaction. In contrast, several other studies (Castelli *et al.*, 1999; Karaoğuz *et al.*, 2005) reported that the frequency of ethanol-induced sister chromatid exchange, micronucleus formation and chromosomal aberrations was higher in alcoholic beverage abusers who also smoked than in those who did not.

While the majority of the literature shows no increase in the genetic effects of ethanol following abstinence from alcohol drinking, some studies reported conflicting results (De Torok, 1972; Matsushima, 1987). Gattás and Saldanha (1997) compared the frequency of structural and/or numerical chromosomal aberrations in cultures of lymphocytes obtained from alcoholics who were abstinent for between 1 month and 32 years with those from controls who were selected because they did not consume alcoholic beverages. Cytogenetic analyses showed a significant increase of the frequencies of cells with structural aberrations in the abstinent alcoholics (7.1%) compared with controls (2.4%). The frequency of numerical aberrations showed a significant regression with age in both groups.

There is some indication that ethanol may lead to genetic damage in sperm; however, ethanol is not a unique germ-cell mutagen. Adler and Ashby (1989) re-analysed data from the GeneTox Workgroups of the US Environmental Protection Agency and concluded that while ethanol did show clastogenic and aneuploidy-inducing activity, it was not restricted to germ cells. Robbins *et al.* (1997) investigated the potential contribution of common lifestyle exposures (smoking, coffee and alcoholic beverages) to the aneuploidy load in sperm from 45 healthy male volunteers aged 19–35 years. Alcohol consumption was significantly associated with increased frequencies of aneuploidy XX18, diploidy XY18–18 and the duplication phenotype XX18–18, after controlling for caffeine, smoking and donor age.

An increased level of 8-oxo-deoxyguanine in leukocyte DNA was observed in ALDH2-deficient subjects who consumed alcoholic beverages (Nakajima *et al.*, 1996). However, two other studies (van Zeeland *et al.*, 1999; Lodovici *et al.*, 2000) did not detect any increase in 8-oxo-deoxyguanine levels in relation to alcoholic beverage consumption. A multicentre study in Europe (Bianchini *et al.*, 2001) observed an inverse relationship between alcoholic beverage consumption and levels of 8-oxo-deoxyguanine in DNA from leukocytes.

Frank *et al.* (2004) reported a significant increase in 1,N^6-ethenodeoxyadenosine in seven subjects diagnosed with alcoholic fatty liver and three diagnosed with alcoholic fibrosis. Patients with alcoholic fibrosis had a much higher level of these adducts

than patients with alcoholic fatty liver. [The Working Group noted that no diagnostic criteria were provided for patients identified as 'alcoholic'.]

(b) Acetaldehyde

(i) *DNA adduct formation*

Structures of the DNA adducts that result from acetaldehyde (referred to below) are given in Fig. 4.4.

Fang and Vaca (1997) examined the levels of N^2-ethyldeoxyguanosine (N^2-EtdG) adducts in a group of Swedish alcohol abusers compared with controls. The characteristics of the two groups are given in the Table 4.10. Compared with controls, chronic alcoholics had higher levels of the N^2-EtdG adduct in both lymphocytes and granulocytes. The levels of adduct found in both cell types were in the order of 1 lesion/10^7 nucleotides. [The Working Group noted that the alcoholic subjects were also heavy smokers, whereas the control subjects were not. However, the authors reported that N^2-EtdG levels were undetectable in the DNA sample from the one moderate smoker in the control group, and also stated that no adducts were detectable in samples obtained from five additional heavy smokers (>20 cigarettes/week)]. Similar results were found in mice (see Section 4.7.2(*b*)).

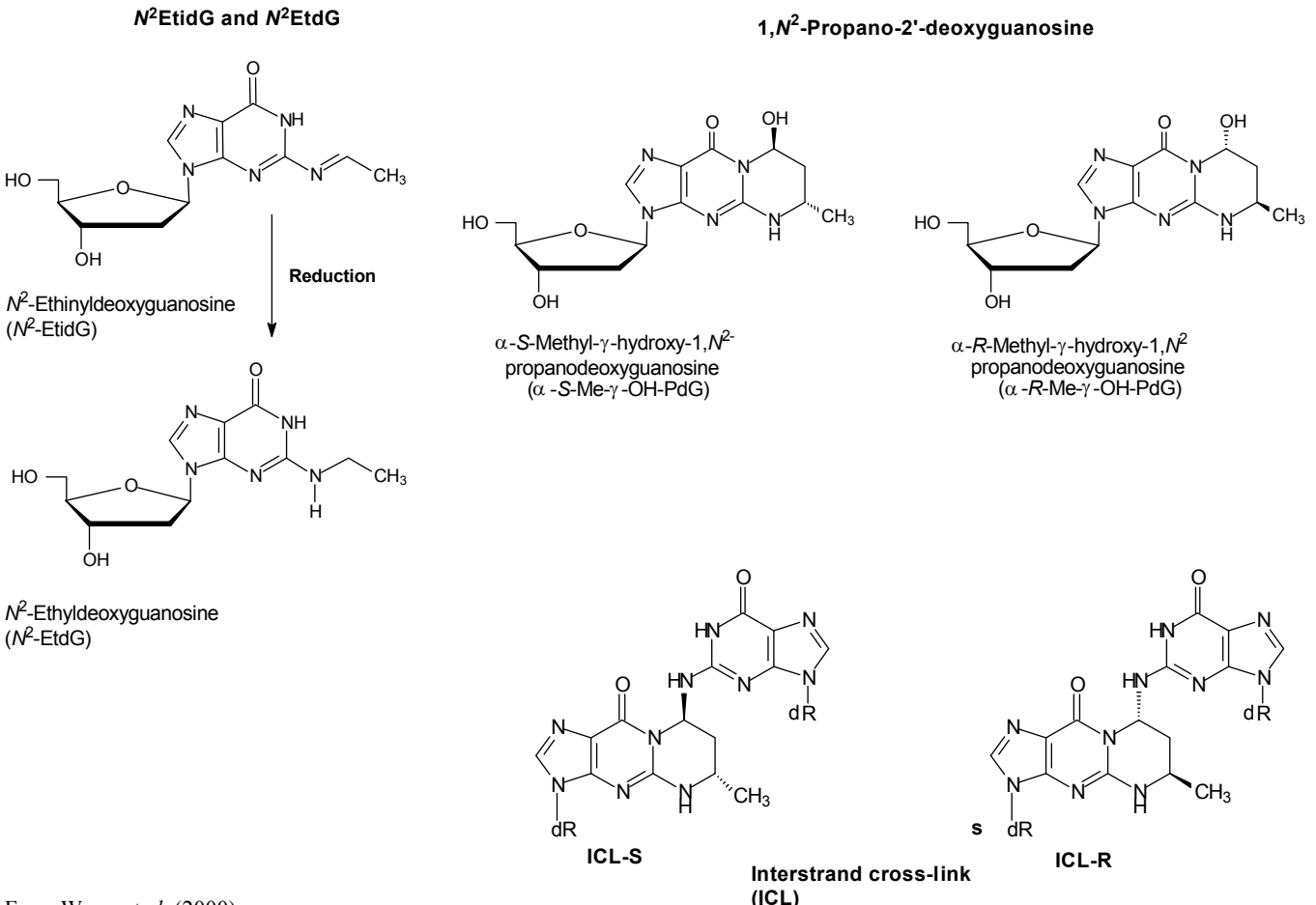
Matsuda *et al.* (2006) analysed the levels of acetaldehyde-derived adducts in DNA samples from the peripheral white blood cells of Japanese alcoholic beverage abusers with two different *ALDH2* genotypes: *2*1/2*1 vs 2*1/2*2* (see Table 4.11). The groups were matched by age, smoking and alcoholic beverage consumption. These authors developed very sensitive and specific liquid chromatography–mass spectrometry assays for three different DNA adducts: N^2-Et-dG, α-methyl-γ-hydroxy-1,N^2-propano-2'-deoxyguanosine (Me-γ-OH-PdG) (both *R* and *S* isomers) and N^2-(2,6-dimethyl-1,3-dioxan-4-yl)-2'-deoxyguanosine (N^2-Dio-dG). The N^2-Dio-dG adduct was not detected in any of the samples studied. However, levels of the other three adducts were significantly higher in *2*1/2*2* carriers than in those with the *2*1/2*1* genotype.

Inclusion of a reducing agent (cyanoborohydride) in the DNA isolation and digestion solutions led to the quantitative conversion of N^2-ethylidene-2'-deoxyguanosine (N^2-EtidG), the major adduct formed by acetaldehyde, to N^2-EtdG. Wang *et al.* (2006) concluded that N^2-EtidG is in fact an endogenous adduct that is present in normal animal and human liver DNA at levels in the range of 0.1 lesion/10^6 normal nucleotides.

Using this methodology, Chen *et al.* (2007) found that the amount of N^2-EtdG in white blood cells showed a small but statistically significant decrease after cessation of smoking, which could be related to a reduction of exposure to acetaldehyde derived from cigarette smoke.

In this study, subjects were eligible to participate only if they normally drank less than six alcoholic beverages per month and abstained from drinking throughout the study. The authors noted that it is difficult to rule out occasional drinking, and therefore

Figure 4.4 DNA adducts that result from acetaldehyde



From Wang *et al.* (2000)

Table 4.10 DNA adducts in alcoholics and controls (characteristics of subjects)

	Controls/moderate drinkers	Alcohol abusers
No. of subjects	12 (8 men, 4 women)	24 (19 men, 5 women)
Median age (range)	32 (25–46) years	46 (31–64) years
Alcohol consumption	None (6 subjects) <50 g/week (6 subjects)	>500 g/week
Smoking	11 nonsmokers 1 moderate smoker (<10 cigarettes/week)	>20 cigarettes/day
DNA-adduct measurements		
Cell type	N^2-*EtdG/10^7 nucleotides*	N^2-*EtdG/10^7 nucleotides*
Granulocytes	Undetectable	3.4±3.8 $p<0.001$
Lymphocytes	0.35 (from 2 subjects; adducts were undetectable in 10 others)	2.1±0.8 $p<0.001$

From Fang & Vaca (1997) EtdG, ethyldeoxyguanosine

no firm conclusions can be drawn from this study about acetaldehyde derived from ethanol metabolism and its role in the formation of this adduct.

Matsuda *et al.* (1999) reported that detectable levels of N^2-EtdG were found in the urine of healthy Japanese individuals who had abstained from ethanol for at least 1 week. These authors proposed that the lesion resulted from endogenously formed acetaldehyde.

Table 4.11 DNA-adduct formation in subjects with different *ALDH2* genotypes

ALDH2 **genotype**	*2*1/2*1*	*2*1/2*2*
No. of subjects	19 men	25 men
Median age (range)	52±11 years	51±11 years
Alcohol consumption	130±54 g/day (910 g/week)	105±59 g/day (735 g/week)
Smoking (cigarettes/day)	22±13	24±15
DNA adducts (fmol/μmol dG)		
N^2-EtdG	17.8±15.9 (adduct detectable in 2/19 samples) 3.9 adducts/10^9 nucleotides[a]	130±52 (p=0.003)* (adduct detectable in 14/25 samples) 28.3 adducts/10^9 nucleotides[a]
α-*S*-Me-γ-OH-PdG	42.9±6.0	92.4±12.9 (p=0.001)*
α-*R*-Me-γ-OH-PdG	61.3±6.4	114±15 (p=0.002)*

From Matsuda *et al*. (2006) ALDH, aldehyde dehydrogenase; dG, deoxyguanosine; EtdG, ethyldeoxyguanosine; Me-γ-OH-PdG, α-methyl-γ-hydroxy-1,N^2-propano-deoxyguanosine * Significantly higher than in *2*1/2*1*; Mann-Whitney U test for N^2-EtdG, t-test for Me-γ-OH-PdG adducts [a] Data converted to adducts/10^9 nucleotides to allow comparison with the study presented in Table 4.10. [The differences probably reflect the greater accuracy from the use of liquid chromatography–mass spectrometry with internal standards by Matsuda *et al*.]

(ii) *Cytogenetic abnormalities in relation to alcoholic beverage consumption*

While studies of chromosomal aberrations in alcoholic beverage abusers do not directly implicate acetaldehyde, these investigations are considered here since numerous other in-vitro studies (see Section 4.7.2(*b*)) have shown that acetaldehyde causes cytogenetic abnormalities in eukaryotic cells *in vitro*. Earlier studies of chromosomal aberrations in the peripheral blood lymphocytes of alcoholics have been reviewed (Obe & Anderson, 1987). The overall results show higher frequencies of chromosomal aberrations (five studies) and sister chromatid exchange (four studies) in alcoholics compared with non-alcoholics. The results of three more recent studies are discussed below, and details are given in Table 4.12. Additional cytogenetic studies in alcoholics are mentioned in Table 4.13.

Gattás and Saldanha (1997) studied chromosomal aberrations in abstinent Brazilian alcoholics *vs* controls (not screened for alcoholic beverage consumption) and observed a significant difference in the percentage of cells with chromosomal aberrations (7.1% for abstinent alcoholics, 2.4% for controls).

Maffei *et al*. (2002) found that alcoholics who consumed >120 g alcohol per day had significantly more chromatid breaks, chromosome breaks, total chromosomal aberrations and cells with micronuclei than either non-drinking controls or abstinent alcoholics. The three groups were matched for age, sex and smoking. These results confirmed those of an earlier study by the same laboratory (Castelli *et al*., 1999). Another study by the same group combined fluorescence *in-situ* hybridization with the analysis of micronucleus formation and showed an increase in the number of cells with micronuclei (Maffei *et al*., 2000).

In a combined analysis of three different studies, Iarmarcovai *et al*. (2007) observed a small but significant increase in micronucleus formation in alcoholic beverage users compared with controls (odds ratio, 1.24; 95% CI, 1.01–1.53).

(iii) *Other data on genetic toxicology in alcoholic beverage abusers*

Pool-Zobel *et al*. (2004) used the comet assay to assess DNA damage and repair in human rectal cells obtained from biopsies. Unexpectedly, they observed that male alcoholic beverage abusers had significantly less genetic damage than male controls. [The authors suggested that this may be the result of an enhancing effect on endogenous defence, e.g. through upregulation of DNA repair in response to damage. Alternatively, a reduced amount of DNA in the comet tails could reflect DNA–protein cross-links resulting from exposure to endogenous acetaldehyde.]

4.7.2 *Experimental systems*

(a) Ethanol

The genotoxic potential of ethanol has been evaluated extensively in lower organisms, plants, mammalian systems and in human cells. Ethanol is generally considered

Table 4.12 Recent studies of chromosomal aberrations/micronuclei in human alcoholics

Reference, study location	Characteristics of subjects	Characteristics of controls	Matching factors	Alcohol consumption	Tissue and genetic biomarker	Results	Comments
Gattás & Saldanha (1997), Brazil	45 men (41.8± 9.2 years old), 10 women (37.9±10 years old) from an Alcoholics Anonymous group	31 men (36.5±9.2 years old), 24 women (31.5±7.5 years old) not screened for alcohol	Age	19.1 years of drinking (range 6–35 years); 46 months of abstinence (range, 1–384 months)	Peripheral blood lymphocytes; chromosomal aberrations	7.1% of cells with aberrations in abstinent alcoholics versus 2.4% in controls $p<0.0001$	Significantly greater numbers of aberrations in >5 years versus <5 years of abstinence, but effect confounded by age difference
Maffei *et al*. (2002), Italy	20 alcoholics, 20 abstinent alcoholics; several clinical tests administered to rule out a general state of malnutrition in alcoholics	20 controls	Age, sex, smoking	Controls: none; alcoholics: alcohol abuse for 19.5±8.8 years (range, 4–40 years) >120 g/day; abstinent alcoholics: >120g/day for at least 5 years before quitting, abstinent for 32.5±15.5 months	Peripheral blood lymphocytes; chromosomal aberrations, binucleated cells with MN	Alcoholics had significantly more chromitid breaks, chromosome breaks, total chromosome aberrations and binucleated cells with MN than either controls or abstinent alcoholics.	Consistent with results from earlier study by same group showing increased chromosomal aberrations and MN in alcoholics, and reversibility in abstinence. Earlier study (Castelli *et al*., 1999) did not match for age or smoking

Table 4.12 (continued)

Reference, study location	Characteristics of subjects	Characteristics of controls	Matching factors	Alcohol consumption	Tissue and genetic biomarker	Results	Comments
Iarmarcovai *et al*. (2007), France, Italy	Pooled analysis from three independent studies; 10 cancer patients; 27 welders; 18 pathologists/ anatomists; 50 alcohol drinkers obtained from within these groups	10 controls; 30 unexposed controls; 18 controls; 54 non-drinking controls	Age, sex		Peripheral blood lymphocytes; micronuclei	For alcohol drinkers versus non-drinkers; frequency ratios (95% CI) from multiple regression analysis; total MN, 1.24 (1.01–1.53); one centromere-+ MN, 1.29 (1.01–1.65); one centromere-+ MN, 1.42 (1.07–1.89)	

CI, confidence interval; MN, micronuclei

Table 4.13 Genetic and related effects of alcohol/ethanol

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Escherichia coli K-12 *uvrB/recA*, differential toxicity	–	–	78200	Hellmér & Bolcsfoldi (1992)
Salmonella typhimurium TA100, TA104, TA1535, TA98, TA97, reverse mutation	–	–	10 mg/plate	Zeiger *et al.* (1992)
Salmonella typhimurium TA100, TA1535, TA1537, TA97, TA98, reverse mutation	–	–	5–10 mg/plate	Phillips & Jenkinson (2001)
Saccaromyces cerevisiae, (repair-deficient) strand breaks	+	NT	39100	Ristow *et al*. (1995)
Aspergillus nidulans, chromosome malsegregation	+	NT	35500	Crebelli *et al*. (1989)
Vicia faba, sister chromatid exchange	+	NT	16000	Zhang *et al*. (1991)
Hordeum species, sister chromatid exchange	+	NT	16000	Zhang *et al*. (1991)
Plant (other), sister chromatid exchange	+	NT	16000	Zhang *et al*. (1991)
Drosophila melanogaster, somatic mutation (and recombination)	–	NT	120000	Graf *et al*. (1994)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	(+)	(+)	4200	Wangenheim & Bolcsfoldi (1988)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	–	–	35900	Phillips & Jenkinson (2001)
Sister chromatid exchange, mouse embryos *in vitro*	+	NT	300	Lau *et al.* (1991)
Chromosomal aberrations, Chinese hamster lung cells *in vitro*	–	–	8000	Phillips & Jenkinson (2001)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	–	NT	32000	Lin *et al.* (1989)
Chromosomal aberrations, mouse embryos *in vitro*	+	NT	800	Lau *et al.* (1991)
DNA strand breaks, human lymphocytes *in vitro*	+	NT	1380	Blasiak *et al*. (2000)
DNA strand breaks, human colonic mucosa *in vitro*	+	NT	460	Blasiak *et al*. (2000)
DNA strand breaks, human gastric mucosa *in vitro*	+	NT	46000	Blasiak *et al*. (2000)
Sister chromatid exchange, human lymphocytes *in vitro*	–	NT	40000	Zhang *et al*. (1991)

Table 4.13 (continued)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Chromosomal aberrations, human lymphocytes *in vitro*	–	–	8000	Phillips & Jenkinson (2001)
Chromosomal aberrations, human lymphoid cell lines *in vitro*	–	NT	32000	Hsu *et al.* (1991)
Chromosomal aberrations, human lymphoblast cell lines *in vitro*	–	NT	8000	Brown *et al.* (1991)
DNA adducts, BD_6 rat tissues *in vivo*	–		4300	Izzotti *et al.* (1998)
DNA strand breaks, rat brain cells *in vivo*	+		4000	Singh *et al.* (1995)
DNA strand breaks, Wistar rat liver cells *in vivo*	+		5000	Navasumrit *et al.* (2000)
Sister chromatid exchange, mouse cells *in vivo*	+		1600	Zhang *et al.* (1991)
Sister chromatid exchange, mouse bone marrow *in vivo*	+		600	Piña Calva & Madrigal-Bujaidar (1993)
Micronucleus formation, B6C3F1 mouse spermatids *in vivo*	–		28500	Pylkkänen & Salonen (1987)
Micronucleus formation, BD_6 rat bone-marrow cells and pulmonary alveolar macrophages *in vivo*	–		50 g/L in drinking-water	Balansky *et al.* (1993)
Micronucleus formation, CD-1 mouse polychromatic erythrocytes *in vivo*	–		3500	Choy *et al.* (1995)
Micronucleus formation, CD-1 mouse polychromatic erythrocytes *in vivo*	–		2500	Choy *et al.* (1996)
Micronucleus formation, mouse *in vivo*	–		2000	Phillips & Jenkinson (2001)
Chromosomal aberrations, Wistar rat bone marrow *in vivo*	–		200 g/L in drinking-water	Tavares *et al.* (2001)
Aneuploidy, Chinese hamster spermatogonia *in vivo*	–		6250	Daniel & Roane (1987)
Aneuploidy, (C57BL x CBA) F_1 Mouse oocytes *in vivo*	+		4800	O'Neill & Kaufman (1987)

Table 4.13 (continued)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Dominant lethal test, mice	(+)		1260 × 3	Rao *et al.* (1994)
Dominant lethal test, mice	+		25000	Berryman *et al.* (1992)
Studies on alcoholics				
Gene mutation, human lymphocytes, *HPRT* locus *in vivo*	–			Cole & Green (1995)
Sister chromatid exchange, human lymphocytes *in vivo*	+			Butler *et al.* (1981)
Sister chromatid exchange, human lymphocytes *in vivo*	(+)			Seshadri *et al.* (1982)
Sister chromatid exchange, human lymphocytes *in vivo*	+			Kucheria *et al.* (1986)
Sister chromatid exchange, human lymphocytes *in vivo*	+			Rajah & Ahuja (1996)
Sister chromatid exchange, human lymphocytes *in vivo*	+[c]			Karaoğuz *et al.* (2005)
Micronucleus formation, human buccal mucosa cells *in vivo*	–			Stich & Rosin (1983)
Micronucleus formation, human buccal epithelium *in vivo*	+			Ramirez & Saldanha (2002)
Micronucleus formation, human lymphocytes *in vivo*	+ [c]			Castelli *et al.* (1999)
Micronucleus formation, human lymphocytes *in vivo*	+			Maffei *et al.* (2000)
Micronucleus formation, human lymphocytes *in vivo*	+			Maffei *et al.* (2002)
Micronucleus formation, human lymphocytes *in vivo*	(+)			Ishikawa *et al.* (2006)
Chromosomal aberrations, human lymphocytes *in vivo*	+			De Torok (1972)
Chromosomal aberrations, human lymphocytes *in vivo*	+			Lilly (1975)
Chromosomal aberrations, human lymphocytes *in vivo*	+			Mitelman & Wadstein (1978)
Chromosomal aberrations, human lymphocytes *in vivo*	+			Obe *et al.* (1980)
Chromosomal aberrations, human lymphocytes *in vivo*	+			Badr & Hussain (1982)
Chromosomal aberrations, human lymphocytes *in vivo*	+			Kucheria *et al.* (1986)
Chromosomal aberrations, human lymphocytes *in vivo*	–			Rajah & Ahuja (1996)

Table 4.13 (continued)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Chromosomal aberrations, human lymphocytes *in vivo*	+			Gattás & Saldanha (1997)
Chromosomal aberrations, human lymphocytes *in vivo*	+[c]			Castelli *et al*. (1999)
Chromosomal aberrations, human lymphocytes *in vivo*	+			Hüttner *et al*. (1999)
Chromosomal aberrations, human lymphocytes *in vivo*	+			Maffei *et al*. (2002)
Chromosomal aberrations, human lymphocytes *in vivo*	+			Burim *et al*. (2004)
Aneuploidy, human sperm *in vivo*	+			Robbins *et al*. (1997)

[a] +, positive; (+), weak positive; –, negative; NT, not tested [b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day [c] In these studies, people who consumed alcohol were also heavy smokers.

to be non-mutagenic. The genotoxicity data for ethanol have been reviewed (IARC, 1988; Phillips & Jenkinson, 2001). The activity profile of alcohol in short-term genotoxicity tests published since the previous monograph is shown in Table 4.13 (with references) and summarized below.

The available published data from genotoxicity tests of ethanol in bacteria and *Drosophila* largely show that it is not a mutagen, even in the presence of exogenous metabolic activation systems. This was also confirmed in studies that used ethanol as a vehicle control in assays that involved these organisms, which suggests that it is not mutagenic or clastogenic *in vitro*. Ethanol caused anomalous chromosome segregation in *Aspergillus*, DNA strand-breaks in yeast, and chromosomal aberrations and sister chromatid exchange in plants.

In human and mammalian cells *in vitro*, ethanol generally did not induce genetic damage; however, it induced sister chromatid exchange and chromosomal aberrations in preimplantation mouse embryos cultured *in vitro*. In human lymphocytes and lymphoblastoid cells *in vitro*, most of the evidence showed no effect of ethanol in these assays. In animals *in vivo*, ethanol induced a variety of genetic effects, including DNA strand breaks, induction of sister chromatid exchange and dominant lethal mutations. Several studies showed no effect of ethanol in the micronucleus assay. Strain-dependent differences in the activity of ethanol in the dominant lethal assay in rodents have been reported.

In studies in rats, exposure to ethanol leads to alterations in the structural and functional integrity of hepatic mitochondria, to increased mitochondrial DNA oxidation and to a decrease in the amount of mitochondrial DNA (Cahill *et al*., 1997, 2005). Several studies showed that administration of ethanol to rats and mice leads to changes in activity and amount of DNA-repair proteins in the liver (Navasumrit *et al*., 2001a; Bradford *et al*., 2005).

Several types of DNA damage have been associated with administration of ethanol to rats, which leads to the accumulation of DNA single-strand breaks in liver parenchymal cells, an effect that closely matched the timing of CYP2E1 induction and was inhibited by dietary antioxidants (Navasumrit *et al*., 2000). An increase in the lipid peroxidation-derived DNA adduct, ethenodeoxycytidine, was seen in rats given a single dose of ethanol (5 g/kg bw) or a 1-week treatment with ethanol (5% w/v) in a liquid diet (Navasumrit *et al*., 2001b). Fang and Vaca (1995) found that exposure of mice to 10% (v/v) ethanol in the drinking-water for five weeks resulted in levels of 1.5±0.8 (n=7) N^2-EtdG/10^8 nucleotides in liver DNA. Adducts were undetectable in control mice. Bradford *et al*. (2005) found that rats and mice exposed to ethanol by intragastric feeding (14–28 g/kg bw per day for 28 days) showed increased levels of oxidative DNA damage (abasic sites and 8-hydroxydeoxyguanine) in the liver. In the same study and under the same conditions of ethanol administration, these effects were observed in transgenic mice that expressed human CYP2E1, but not in *CYP2E1*-knockout mice or in the presence of a CYP2E1 inhibitor.

(b) Acetaldehyde (see Table 4.14)

(i) *DNA adduct formation*

N^2-Ethyl-2′-deoxyguanosine (N^2-EtdG)

The most abundant adduct that results from the reaction of acetaldehyde with DNA is N^2-EtidG (see Fig. 4.4). This adduct is too unstable for purification, but can be converted to a stable adduct, N^2-EtdG, by treatment with a reducing agent (sodium cyanoborohydride). *In vitro*, the reduction step can also be carried out by a mixture of GSH and ascorbic acid, which may reflect *in vivo* conditions (Wang *et al.*, 2006; see also Fang & Vaca, 1995).

Other acetaldehyde-derived DNA adducts

In addition to the major adduct, N^2-EtidG (and N^2-EtdG after reduction with borohydride), three additional acetaldehyde-derived DNA adducts have been identified. These are: N^2-Dio-dG, an interstrand cross-link, and two diasteresmers (*R* and *S*) of Me-α-OH-PdG (see Fig. 4.4). (Wang *et al.*, 2000).

The formation of the Me-α-OH-PdG adducts can be facilitated by including either basic amino acids, histones (which are rich in basic amino acids), or polyamines in the reaction mixture. In the presence of physiologically relevant polyamine concentrations, detectable amounts of these adducts were formed at concentrations as low as 100 μM acetaldehyde (Theruvathu *et al.*, 2005). Such concentrations are within the range of those formed in the saliva of human volunteers who drank alcoholic beverage in a laboratory setting (Homann *et al.*, 1997). Finally, acetaldehyde can react with malondialdehyde, and the resulting conjugate can form DNA adducts *in vitro* (Pluskota-Karwatka *et al.*, 2006).

(ii) *Mutagenic activity of acetaldehyde-derived DNA adducts*

The mutagenic potential of specific DNA adducts can be tested with single-stranded DNA vectors that contain a single adduct located within a reporter gene. These constructs can then be transfected into cells, allowed to replicate and the resulting replication products analysed for mutations by various methods, depending on the specific nature of the reporter gene. Using such an approach, the N^2-EtdG adduct was only minimally mutagenic to the *supF* gene in the reporter plasmid pLSX (mean mutant fraction, 0.9±0.2% for the adduct-containing construct vs 0.4±0.2% for the lesion-free control) when replicated in *E. coli* (P=0.09). When deoxyuridines were placed on the complementary strand at 5′ and 3′ positions flanking the adduct, the mutant fractions increased to 1.4±0.5% for the lesion vs 0.6±4% for the control (P=0.04) (Upton *et al.*, 2006). [It should be pointed out that this study was carried out with N^2-EtdG, whereas, *in vivo*, most probably the N^2-EtidG adduct is formed predominantly.]

Two separate studies have shown that Me-α-OH-PdG adducts result in mutant fractions of 5–11% when inserted in a shuttle vector and replicated in either monkey kidney cells (Fernandes *et al.*, 2005) or SV40-transformed human fibroblasts (Stein *et al.*, 2006). In both cases, the predominant mutagenic event observed was a G→T

Table 4.14 Genetic and related effects of acetaldehyde

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
*Escherichia coli pol*A, differential toxicity (spot test)	(+)	NT	10 µL/plate	Rosenkranz (1977)
Escherichia coli K-12 *uvrB/recA*, differential toxicity	–	NT	16300	Hellmér & Bolcsfoldi (1992)
Salmonella typhimurium TA100, TA1535, TA1537, TA98 reverse mutation	–	–	3333 µg/plate	Mortelmans *et al*. (1986)
Salmonella typhimurium TA100, TA1535, TA1537, TA98, reverse mutation	–	–	0.5% in air	JETOC (1997)
Salmonella typhimurium TA102, TA104, reverse mutation	–	NT	1 mg/plate	Marnett *et al*. (1985)
Salmonella typhimurium TA1535, reverse mutation	–	NT	10 µL/plate	Rosenkranz (1977)
Salmonella typhimurium TA1538, reverse mutation	–	NT	10 µL/plate	Rosenkranz (1977)
Escherichia coli WP2 *uvrA*, reverse mutation	–	–	0.5% in air	JETOC (1997)
Aspergillus nidulans, aneuploidy (chromosome malsegregation)	+	NT	200	Crebelli *et al*. (1989)
Drosophila melanogaster, sex-linked recessive lethal mutations	+		22500 ppm inj × 1	Woodruff *et al*. (1985)
Drosophila melanogaster, sex-linked recessive lethal mutations	–		25000 ppm feed, 3 d	Woodruff *et al*. (1985)
DNA–protein cross-links, Fischer 344 rat nasal mucosa cells *in vitro*	+	NT	4400	Lam *et al*. (1986)
DNA–protein cross-links, plasmid DNA and histones, *in vitro*	+	NT	440	Kuykendall & Bogdanffy (1992)
Comet assay, cultured rat neurons *in vitro*	+		11	Lamarche *et al.* (2004)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	+	NT	176	Wangenheim & Bolcsfoldi (1988)
Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	3.9	Obe & Ristow (1977)

Table 4.14 (continued)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	1.9	Obe & Beek (1979)
Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	+	7.8	de Raat *et al*. (1983)
Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	1.3	Brambilla *et al*. (1986)
Micronucleus formation, Sprague-Dawley rat primary skin fibroblasts *in vitro*	+	NT	22	Bird *et al*. (1982)
Chromosomal aberrations, Sprague-Dawley rat primary skin fibroblasts *in vitro*	+	NT	4.4	Bird *et al*. (1982)
Chromosomal aberrations, Chinese hamster embryonic diploid fibroblasts *in vitro*	+	NT	31	Dulout & Furnus (1988)
Cell transformation, C3H 10T½ mouse cells	–[c]	NT	100	Abernethy *et al*. (1982)
Cell transformation, rat kidney cells	–[c]	NT	132	Eker & Sanner (1986)
DNA strand breaks, human lymphocytes *in vitro*, alkaline elution	–	NT	440	Lambert *et al*. (1985)
DNA cross-links, human lymphocytes *in vitro*, alkaline elution	+	NT	440	Lambert *et al*. (1985)
DNA strand breaks and DNA–protein cross-links, human bronchial epithelial cells *in vitro*	–	NT	44	Saladino *et al*. (1985)
DNA strand breaks, human lymphocytes *in vitro*	+	NT	68.8	Singh & Khan (1995)
Comet assay, cultured human lymphocytes *in vitro*	+		132	Blasiak *et al.* (2000)
Comet assay, cultured colonic and gastric mucosa *in vitro*	+		4400	Blasiak *et al.* (2000)
Gene mutation, human lymphocytes, *HPRT* locus *in vitro*	+	NT	11	He & Lambert (1990)

Table 4.14 (continued)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	7.9	Obe *et al*. (1978); Ristow & Obe (1978)
Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	4	Jansson (1982)
Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	15.9	Böhlke *et al*. (1983)
Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	4.4	He & Lambert (1985)
Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	4.4	Knadle (1985); Helander & Lindahl-Kiessling (1991)
Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	11	Norppa *et al*. (1985); Sipi *et al*. (1992)
Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	15.9	Obe *et al*. (1986)
Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	20	Badr & Hussain (1977)
Chromosomal aberrations, human lymphocytes *in vitro*	–	NT	15.9	Obe *et al*. (1979)
Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	31.7	Böhlke *et al*. (1983)
Chromosomal aberrations, human Fanconi's anaemia lymphocytes *in vitro*	+	NT	7.9	Obe *et al*. (1979)
Micronucleus formation, human lymphocytes *in vitro*	+[d]		26.4	Migliore *et al*. (1996)
Micronucleus formation, human HepG2 and Hep3B cells *in vitro*	+	NT	39.6	Majer *et al.* (2004)
DNA–protein cross-links, Fischer 344 rat nasal mucosa *in vivo*	+	–	1000 ppm inh 6 h/d × 5 d	Lam *et al*. (1986)
Sister chromatid exchange, male C3A mouse bone-marrow cells *in vivo*	+		0.4 µg/mouse ip × 1	Obe *et al*. (1979)
Sister chromatid exchange, Chinese hamster bone-marrow cells *in vivo*	+		0.5 mg/kg ip × 1	Korte *et al*. (1981)

Table 4.14 (continued)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Sister chromatid exchange, male C3A mouse bone-marrow cells *in vivo*	+		40 mg/kg ip × 1	Torres-Bezauri *et al.* (2002)
Micronucleus formation, C57BL/6J × C3H/He mouse spermatocytes *in vivo*	–		375 mg/kg ip × 1	Lähdetie (1988)
Chromosomal aberrations, rat embryos *in vivo*	+		158 µg iam × 1	Bariliak & Kozachuk (1983)
N^2-EtdG adduct formation, human buccal cells, *in vitro*	+		440	Vaca et al. (1995)
N^2-EtdG adduct formation, calf thymus DNA *in vitro*	+		72100	Fang & Vaca (1995)
N^2-EtdG adduct formation, deoxynucleosides *in vitro*	+		158580	Vaca *et al.* (1995)
PdG adduct formation, pig liver DNA *in vitro* (in presence of polyamines)	+		4.4	Theruvathu *et al.* (2005)
PdG adduct formation, calf thymus DNA *in vitro* (in presence of histones)	+		26430	Sako *et al.* (2003)
Binding (covalent) to calf thymus DNA *in vitro*	+	NT	44050	Ristow & Obe (1978)
Binding (covalent) to deoxynucleosides *in vitro*	+	NT	158580	Vaca *et al.* (1995)
Sperm morphology, C57BL/6J × C3H/He mouse early spermatids *in vivo*	–		250 ip × 5	Lähdetie (1988)

EtdG, ethyldeoxyguanosine; PdG, 1,N^2-propanodeoxyguanosine

[a] +, positive; (+), weak positive; –, negative; NT, not tested [b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; d, day; iam, intra-amniotic; inh, inhalation; inj, injection; ip, intraperitoneal [c] Positive results when acetaldehyde treatment was followed by exposure of the cells to 12-*O*-tetradecanoylphorbol 13-acetate: 10 µg/mL (Abernethy *et al.*, 1982), 10^{-5}M (Eker & Sanner, 1986) [d] A dose-related increase in centromere-positive micronuclei was observed with fluorescence in-situ hybridization but it was not significantly different from the negative control.

transversion, but G→A and G→C mutations were also found. In comparison, the ethenodeoxyadenosine adduct resulted in mutant fractions as a high as 70% in COS7 monkey kidney cells (Pandya & Moriya, 1996), but the mutant fraction was only 7–14% in human cells (Levine *et al.*, 2000). Methodological differences, differences in the host cells used or in the local sequence in the shuttle vectors may be responsible for the different results.

An important feature of the deoxyguanosine adducts, which is not shared by N^2-EtidG or N^2-EtdG, is that they can undergo ring-opening when located in double-stranded DNA (Mao *et al.*, 1999). The ring-opened forms of the Me-α-OH-PdG adducts can react with proteins to generate DNA–protein cross-links (Kurtz & Lloyd, 2003). With a deoxyguanosine residue in the opposite strand of the helix, a DNA–intrastrand cross-link can be formed (Wang *et al.*, 2000). Intrastrand cross-links generated in this manner are also mutagenic (mutant fraction, 3–6%) in mammalian cells, and generate primarily G→T transversions, as well as deletion and insertion mutations (Liu *et al.*, 2006). Matsuda *et al.* (1998) exposed plasmid DNA that contains a *supF* mutation reporter gene to concentrations of acetaldehyde up to 1M, and allowed the plasmid to replicate in human XP-A cells, which are deficient in nucleotide excision repair. In contrast to the results for Me-α-OH-PdG adducts, these authors observed GG→TT mutations. The DNA lesions responsible for these mutations are most probably not propano-deoxyguanosine adducts, but the intrastrand cross-links.

4.8 Mechanistic considerations

4.8.1 *Ethanol*

The mechanisms of the induction of cancer by consumption of alcoholic beverages and more specifically ethanol are not entirely clear, and are certainly complex. In this section some of the diverse effects that could contribute to ethanol-induced carcinogenesis are discussed.

(a) Tumour initiation

(i) *Molecular genetic epidemiology of ethanol-metabolizing systems (see Section 4.3)*

The role of the metabolism of ethanol in carcinogenesis associated with alcoholic beverage consumption is suggested by several positive associations between different forms of cancer and certain polymorphisms in genes that are involved in the activation of ethanol. The degree to which these associations are explained by acetaldehyde production, redox changes, formation of radicals, effects on intermediary metabolism and/or effects on other pro-carcinogens can not be established from current findings. However, the results of these studies strongly indicate a prominent role for acetaldehyde, the primary metabolite of ethanol.

(ii) *Oxidative stress*

Ethanol promotes the production of reactive oxygen species both directly, through the formation of the α-hydroxyethyl radical, and indirectly, via induction of oxidative stress. Oxidative stress results from ethanol metabolism, tissue inflammation and increased iron storage. Ethanol-induced CYP2E1 produces various reactive oxygen species, which lead to the formation of lipid peroxides such as 4-hydroxy-nonenal. Furthermore, ethanol impairs the antioxidant defence system, which results in enhanced mitochondrial damage and apoptosis. Alcoholic beverage consumption leads to the activation of resident macrophages in the liver (Kupffer cells) and to the recruitment of other immune cells that are capable of producing reactive oxygen and nitrogen species. Increased iron overload of certain tissues has also been reported following alcoholic beverage intake, which may lead to the exacerbation of oxidative stress through iron-mediated production of radicals by the Fenton reaction. DNA damage is the outcome of increased oxidative stress that is associated with ethanol-induced carcinogenesis in many organs. Direct damage results from the metabolism of ethanol to acetaldehyde, which can damage DNA and inhibit DNA-repair systems. Indirect DNA damage is the result of increased production of oxidants and DNA-reactive lipid peroxides that can form carcinogenic DNA adducts (reviewed by Seitz & Stickel, 2006).

(iii) *Toxicokinetics*

Ethanol modifies the toxicokinetics and toxicodynamics of other chemicals (see Section 4.4). It has major effects on the metabolism and clearance of a variety of carcinogens and toxicants, including nitrosamines, urethane, vinyl chloride, benzene and many other solvents. These chemicals are ubiquitous in food, tobacco, air and occupational settings, and at least one nitrosamine, NDMA, is generated endogenously. The effects of ethanol on the metabolism of these substances are therefore of general interest as a potential element in the mechanism of alcohol-induced carcinogenesis. Although ethanol may in theory potentiate the tissue-specific effects of carcinogens by inducing CYP-dependent activation, most findings indicate that a predominant mechanism is competitive inhibition of clearance of the carcinogens, especially in the liver, which results in increased dose delivery to peripheral target organs, with a consequent increase in DNA damage and tumour initiation. Such effects are often quite large: fivefold increases are common, and up to 20-fold enhancements have been observed. Competitive inhibition by ethanol of CYP2E1 is the best understood, but ethanol also inhibits human CYP1A1, -2B6 and -2C19 (reviewed by Lieber *et al.*, 1987; Swann *et al.*, 1987; Anderson *et al.*, 1995).

(b) Tumour promotion

(i) *Ethanol-mediated tumour promotion*

Ethanol has been purported to have tumour-promoting abilities. Several studies in experimental animals have shown that administration of ethanol reduces the latency

of tumour development after treatment with genotoxic carcinogens. Several possible pathways have been suggested to account for this apparent promotional activity. First, the cytotoxicity of ethanol may induce regenerative growth, which increases cell-proliferation rates in affected tissues. Activation of the innate immune response in organs affected by ethanol, such as the liver, has been well documented and this may result in the production of mitogenic cytokines. In addition, treatment with ethanol leads to excess production of oxygen free radicals and lipid peroxidation. An increase in lipid peroxidation was observed in the liver as well as other tissues that were targets for site-specific carcinogens. This process was enhanced by ethanol. An increase in arachidonate and an over-production of polyunsaturated fatty acids involved in eicosanoid synthesis have also been reported as a consequence of treatment with ethanol and may play a key role in excessive cell proliferation and selective outgrowth of initiated cells (reviewed by Mufti, 1998).

(ii) *Induction of mitogen-activated protein kinases (MAPK)*

Ethanol induces expression of inhibitory G-proteins which in turn activate the mitogen-activated protein kinase (MAPK) -signalling cascade that is essential in the initiation of cell proliferation and differentiation, apoptosis, stress and inflammatory responses. Acute exposure to ethanol gives rise to modest activation of p42/44 MAPK in hepatocytes, astrocytes and vascular smooth muscle cells. Acute and chronic exposure to ethanol also results in potentiation or prolonged activation of MAPK in an agonist-selective manner, especially in innate immune cells that promote inflammation and tissue damage. Ethanol-induced activation of MAPK-signalling is also involved in collagen expression in hepatic stellate cells, and thus promotes liver fibrosis and cirrhosis. Some of the effects of ethanol on MAPK-signalling are thought to be mediated by acetaldehyde, rather than by ethanol itself (reviewed by Aroor & Shukla, 2004).

(iii) *Vitamin A (retinol)*

Retinoic acid plays an important role in controlling cell growth, differentiation and apoptosis. Alcoholic beverage consumption is associated with a decrease in hepatic levels of vitamin A, a precursor of retinoic acid. Thus, it has been suggested that ethanol-induced changes in retinoic acid levels in tissues will lead to impairment of retinoic acid-dependent signalling pathways, interference of 'cross-talk' with MAPK cascades and disturbances in cell-cycle regulation that may lead to carcinogenesis. Several possible mechanisms for the interaction between ethanol and retinoic acid have been proposed. Ethanol may act as a competitive inhibitor of the oxidation of vitamin A to retinoic acid that involves ADHs and ALDHs; ethanol-induced CYP enzymes, particularly CYP2E1, may enhance catabolism of vitamin A and retinoic acid; and ethanol may alter retinoid homeostasis by increasing vitamin A mobilization from the liver to extrahepatic tissues (reviewed by Leo & Lieber, 1999; Wang, 2005).

(iv) *Insulin-like growth factors (IGFs)*

The insulin-like growth factors (IGFs) are mitogens that play a pivotal role in the regulation of cell proliferation, differentiation and apoptosis. Their effects are mediated through the IGF-I receptor, which is also involved in cell transformation induced by tumour virus proteins and oncogene products. It has been suggested that ethanol-induced carcinogenesis, e.g., in the breast, is associated with effects on IGFs, but the relationship between alcoholic beverage consumption and IGF levels is unclear. Different patterns of alcoholic beverage consumption may have opposite effects on IGF levels. Long-term and heavy drinking can cause severe damage to the liver, and loss of liver function may result in a decline in the production of IGFs. Alcoholics are reported to have relatively low levels of IGF-I, but, in animal studies, ethanol enhanced the action and expression of IGF-I (reviewed by Yu & Berkel, 1999; Yu & Rohan, 2000) .

(v) *Folate and DNA methylation (reviewed in Section 4.3)*

Folate deficiency is associated with different forms of cancer, of which colon cancer is the most commonly described. Ethanol *per se* and an underlying unhealthy lifestyle associated with high alcoholic beverage consumption are known to cause folate deficiency, which increases the risk for cancer. The degree to which the relation between alcohol drinking, folate deficiency and cancer may be explained by the metabolism of ethanol is not known.

(vi) *Ethanol and sex hormones*

Estrogens and androgens are well known activators of cellular proliferation, which is associated with an increased risk for carcinogenesis. Alcoholic beverage use in women causes an increase in the levels of estrogen and/or androgen, which may promote the development of breast cancer (reviewed by Gavaler, 1995; Singletary & Gapstur, 2001; Dumitrescu & Shields, 2005).

(vii) *Cirrhosis*

Ethanol causes hepatocellular injury that can lead to enhanced fibrogenesis and finally cirrhosis. Liver cirrhosis is strongly associated with an increased risk for hepatocellular carcinoma. Ethanol-related hepatocellular carcinoma without pre-existing cirrhosis is rare, which indicates that the pathogenic events that lead to cirrhosis precede those that cause cancer, or that the structural alterations in the liver during cirrhosis, together with other factors, favour the transformation of hepatocytes (reviewed by Stickel *et al.*, 2002; Seitz & Stickel, 2006)

(c) Tumour progression

(i) *Immunodeficiency and immunosuppression*

Alcoholic beverage drinking increases immunodeficiency and immunosuppression, conditions that may facilitate carcinogenesis by silencing immune-related defence mechanisms in various organs. It is widely recognized that chronic alcoholics are more

susceptible to infections and to certain neoplasms. The following factors related to alcoholism affect the immune system: malnutrition, vitamin deficiencies, established cirrhosis and ethanol itself. The suppression by ethanol of natural killer cells, which are implicated in the control of tumour development and growth, has been shown in cultured cells, animal studies and in human alcoholics. Although there is general agreement on the impact of alcohol consumption on the immune system, the mechanisms by which ethanol compromises anti-tumour immune surveillance are not yet known completely (reviewed by Watson *et al.*, 1992; Cook, 1998; Stickel *et al.*, 2002).

4.8.2 *The role of acetaldehyde in alcohol-induced carcinogenesis*

Over the past 10 years, epidemiological evidence of enhanced cancer risks among heterozygous carriers of the inactive allele of the ALDH2 enzyme has become much stronger, in particular for oesophageal cancer: all nine case–control studies conducted in Japan among independent populations who consumed alcoholic beverages show significantly increased odds ratios (range, 3.7–13.5) for carriers of the inactive *ALDH2* allele. These data suggest that acetaldehyde is the key metabolite in the development of oesophageal cancer associated with alcoholic beverage consumption in these populations. The mechanistic considerations that support this suggestion can be summarized as follows: (*a*) there is a causal relationship between alcoholic beverage consumption and cancer in the oral cavity, pharynx, larynx, oesophagus and liver; (*b*) it is generally accepted that ethanol in alcoholic beverages is the principal ingredient that renders these beverages carcinogenic; (*c*) in the body, ethanol is converted by ADH to acetaldehyde, which is oxidized by ALDH to acetate; (*d*) the formation of acetaldehyde starts in the mouth (mediated by oral bacteria) and continues along the digestive tract; production of acetaldehyde is also found in the liver and in the gut. This largely parallels the target organ sites known to date to be susceptible to ethanol-induced cancer. Given its volatile nature, it is conceivable that ingested acetaldehyde reaches the respiratory tract; (*e*) acetaldehyde is a cytotoxic, genotoxic, mutagenic and clastogenic compound. It is carcinogenic in experimental animals; (*f*) after alcoholic beverage consumption, carriers of an inactive allele of the ALDH2 enzyme show accumulating levels of acetaldehyde in the peripheral blood, which is a direct consequence of their enzyme deficiency, and show increased levels of N^2-EtdG and Me-α-OH-PdG adducts in lymphocyte DNA. The latter adducts have been shown to be formed from acetaldehyde; during DNA replication, these adducts cause mutations; (*g*) consumers of alcoholic beverages have a higher frequency of chromosomal aberrations, sister chromatid exchange and micronucleus formation in the peripheral lymphocytes than control nondrinkers. These effects may be attributable to acetaldehyde, which is a clastogen; (*h*) several of the observations made in ALDH2-deficient individuals have been confirmed in *ALDH2*-knockout mice.

In view of these considerations, the Working Group concluded that acetaldehyde, the primary metabolite of ethanol, is the carcinogen that leads to the formation of oesophageal cancer in carriers of the inactive *ALDH2* allele who consume alcoholic beverages.

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5. Summary of Data Reported

5.1 Exposure data

The consumption of alcoholic beverages has been practiced as a part of human culture for centuries. In addition to ethanol and water, alcoholic beverages may also contain a multitude of other compounds derived from fermentation, contamination and the use of food additives or flavours. The normal by-products of fermentation, other than ethanol, are generally regarded as safe, but alcoholic beverages may contain contaminants that have been evaluated by the IARC as carcinogenic (e.g. nitrosamines and aflatoxins). However, contaminants are usually present at low concentrations and, over the past decades, these have been further reduced, at least in developed countries. For example, the concentration of nitrosamines in beer and that of lead in wine have declined significantly over the past 30 years.

Throughout the world, most alcoholic beverages are produced and consumed within the same country. Consumption has increased in developing regions, and the country that now has the highest total production is China, followed by India and Brazil. The trade in alcoholic beverages has increased over the last four decades, but its proportion has remained at approximately 0.5% of total world trade.

The consumption of alcoholic beverages can be divided into recorded consumption (estimated from sales, production and national taxation records) and unrecorded consumption (e.g. illegal production, smuggling, home production and private importation). Overall, recorded consumption has increased slightly over the past 20 years, but more substantial increases have occurred in China and some other developing countries. In contrast, an overall decline in recorded consumption is evident in several developed countries.

More than 1.9 billion adults (1.2 billion men and 750 million women) around the world were estimated to consume alcoholic beverages in 2002, and 22% of the men and 3% of the women drank 40 g alcohol or more per day. In all regions of the world, men drink more often and in larger quantities than women, but the gender differences

are largely culturally dependent; smaller differences are observed in Europe and larger differences in developing parts of the world. Consumption of alcohol is age-dependent: the frequency of drinking increases until middle age and the prevalence of heavy episodic drinking decreases over the adult life-span. Those of the lowest socioeconomic class tend to drink the cheapest beverage available in their respective countries.

A large variety of substances that are not intended for human consumption are nevertheless being consumed as alcohol (surrogate alcohol such as hair spray, after-shaves, lighter fluid and medicines). They usually contain very high concentrations of ethanol and may also contain higher alcohols and toxic concentrations of methanol.

In addition to international regulations such as the *Codex alimentarius*, countries tend to regulate traditional local alcoholic beverages (e.g. beer, whisky and vodka), but emerging products (e.g. alcopops) are initially subject to few regulations.

5.2 Human carcinogenicity data

The effect of alcoholic beverages on the risk for human cancer was last evaluated in the *IARC Monographs* series in 1988. At that time, it was concluded that there was *sufficient evidence* of carcinogenicity for cancers of the oral cavity, pharynx, larynx, oesophagus and liver. Since that time, several hundred additional epidemiological studies reported on the association between the consumption of alcoholic beverages and the risk for cancer at various sites. For the present Volume, the published evidence for 27 cancer sites was reviewed by the Working Group.

5.2.1 *Cancers of the oral cavity and pharynx*

A large body of evidence from epidemiological studies of different design and conducted in different populations consistently shows that consumption of alcoholic beverages is associated with a higher risk for both oral and pharyngeal cancer, and that the risk increases with increasing amounts of alcohol consumed. Compared with non-drinkers, regular consumption of about 50 g alcohol (ethanol) per day is associated with an approximately threefold increase in risk for these cancers. These associations were consistently found for the types of alcoholic beverage that are commonly drunk in the areas where the studies were conducted.

Tobacco smoking is an important cause of oral and pharyngeal cancer. The association of consumption of alcoholic beverages with these cancers was evident in both smokers and nonsmokers. The effects of smoking and consumption of alcoholic beverages appear to be multiplicative, such that the largest relative risks are seen in people who both smoke tobacco and drink alcoholic beverages.

Some data were available on the cessation of consumption and the risk for oral and pharyngeal cancer. The available evidence suggests that former drinkers have lower risks for oral and pharyngeal cancer than current drinkers of alcoholic beverages.

5.2.2 *Cancer of the larynx*

Studies of different design conducted in Asia, Europe, North America and South America have shown a consistent association between the consumption of alcoholic beverages and the risk for laryngeal cancer. This association increases with increasing amounts of alcoholic beverages consumed and, compared with non-drinkers, regular consumption of about 50 g alcohol per day is associated with an approximately two-fold increase in risk. These associations were observed for various types of alcoholic beverage.

Tobacco smoking is an important cause of laryngeal cancer. The association with the consumption of alcoholic beverages was evident in both smokers and nonsmokers. The effects of smoking and consumption of alcoholic beverages appear to be multiplicative and the largest relative risks are seen in smokers who also consume alcoholic beverages. There is little information on the duration or cessation of consumption of alcoholic beverages on the risk for laryngeal cancer.

5.2.3 *Cancer of the oesophagus*

More than 50 prospective and case–control studies from most regions of the world found a consistent association between the risk for oesophageal cancer (squamous-cell carcinoma) and the consumption of alcoholic beverages. The risk increases with increasing amounts of alcoholic beverage consumed and, compared with non-drinkers, regular consumption of about 50 g alcohol per day is associated with an approximately twofold increase in risk. The increased risk for oesophageal cancer was consistently observed for a range of different types of alcoholic beverage. However, the association, if any, is weak for adenocarcinoma of the oesophagus.

Of 13 cohort studies among the general population, 10 studies reported a statistically significant association between alcoholic beverage consumption and the risk for oesophageal cancer when controlled for tobacco smoking. Four cohort studies were based on special populations: three studies of alcoholics and one of brewery workers reported statistically significant associations.

Among 20 case–control studies published in the English literature, 18 (91%) studies adjusted for tobacco smoking. Sixteen of these 18 (81%) studies on the association between alcoholic beverage drinking and the risk for oesophageal cancer reported statistically significant associations. Among 18 case–control studies identified in the Chinese literature, eight (44%) studies reported a positive association with alcoholic beverage consumption. The evidence on the risk for oesophageal cancer in the Chinese literature is consistent with that in the English literature. In addition, the results from case–control studies are consistent with results from prospective cohort studies.

Data on adenocarcinoma of the oesophagus were available from one prospective study among alcoholics, one nested case–control study and eight case–control studies. Two case–control studies reported that an increased risk for adenocarcinoma of the

oesophagus is associated with a higher level of alcoholic beverage drinking, but the other eight studies did not.

Epidemiological evidence indicates that drinking alcoholic beverages is causally related to cancer of the oesophagus. There is no indication that the effect of alcoholic beverage consumption is dependent on the type of beverage. Tobacco smoking also increases the risk for oesophageal cancer and the effect of consumption of alcoholic beverages on this cancer is evident in both smokers and nonsmokers. The effects of smoking and consumption of alcoholic beverages appear to be multiplicative and the largest relative risks are seen in smokers who also consume alcoholic beverages.

The available data from molecular–genetic epidemiological studies provide ample evidence that the heterozygous aldehyde dehydrogenase 2 genotype — which leads to the accumulation of acetaldehyde, e.g. in the blood, saliva and liver — contributes substantially to the development of oesophageal cancers (squamous-cell carcinomas) that are related to the consumption of alcoholic beverages.

There is uncertainty about the effects of cessation of alcohol beverage intake and the duration of consumption on the risk for oesophageal cancer. The available evidence suggests that former drinkers have lower risks for oesophageal cancer than current drinkers.

5.2.4 *Cancer of the liver*

A large body of data derives from cohort studies, including cohorts of heavy drinkers, and case–control studies from most regions of the world, many of which were carried out in China. These studies provide firm evidence that the consumption of alcoholic beverages is an independent risk factor for primary liver cancer. Various types of alcoholic beverage consumed do not have substantially different effects on liver cancer.

Chronic infections with hepatitis viruses B and C are the major causes of liver cancer and the increased risk associated with alcoholic beverage intake has been found consistently among individuals infected with hepatitis viruses as well as among uninfected individuals. Quantification of the effect of alcohol on the risk for liver cancer cannot be achieved reliably since cirrhosis and other liver disorders that often predate liver cancer tend to lead to a decrease in or the cessation of consumption of alcoholic beverages many years before the occurrence of liver cancer.

5.2.5 *Cancer of the female breast*

More than 100 epidemiological studies conducted in all regions of the world have evaluated the association between the consumption of alcoholic beverages and female breast cancer, and have consistently found an increased risk with increasing intake. A pooled analysis of most of the data available worldwide in 2002, which included more than 58 000 women with breast cancer, found a linear increase in risk with increasing consumption of alcoholic beverages. Compared with non-drinkers, regular

consumption of about 50 g alcohol per day is associated with a relative risk for breast cancer of about 1.5; for regular consumption of 18 g alcohol per day, the relative risk is still significantly increased at 1.13. Broadly similar patterns of association were observed with different types of alcoholic beverage.

The risk for breast cancer is affected by a variety of hormonal and reproductive factors, and the effect of consumption of alcoholic beverages on the risk for breast cancer does not vary significantly by child-bearing patterns, menopausal status, use of oral contraceptives or hormone replacement therapy or having first-degree relatives with a history of breast cancer.

The effects of duration or cessation of consumption of alcoholic beverages on the risk for breast cancer are uncertain.

5.2.6 *Colorectal cancer*

More than 50 prospective and case–control studies reported on the association between consumption of alcoholic beverages and the risk for colon, rectal or colorectal cancer. Results of pooling the data from six cohort studies and those of recent meta-analyses suggest an increased risk for colorectal cancer with the consumption of alcoholic beverages. The association does not appear to be confounded by age, gender, race or ethnicity or body mass index, and some studies showed no confounding by diet or physical activity. Based on results of the pooled data from the six cohort studies and the recent meta-analysis of prospective cohort studies, regular consumption of about 50 g alcohol per day is associated with a relative risk for colorectal cancer of 1.4 compared with non-drinkers. However, there is uncertainty regarding the shape of the dose–response relationship. Based on the available data, the association is similar for colon and for rectal cancer and does not appear to vary by type of alcoholic beverage.

There is no consistent evidence that the association of colorectal cancer with the consumption of alcoholic beverages is modified by gender or by tobacco smoking. It is unclear whether obesity or dietary lifestyle factors, such as folate intake, modify the effect of alcoholic beverage intake on colorectal cancer, as few studies have examined these relationships.

The data on the effects of duration and cessation of consumption of alcoholic beverages on the risk for colorectal cancer are inadequate.

5.2.7 *Cancer of the lung*

Tobacco smoking is by far the most important cause of lung cancer. In most populations, there is a strong correlation between the use of tobacco and the consumption of alcoholic beverages. Therefore, the most important consideration in the interpretation of results from epidemiological studies of the consumption of alcoholic beverages and lung cancer is whether any observed association might be confounded by the effect of smoking.

Several studies have reported an increased risk for lung cancer associated with the consumption of alcoholic beverages, but it is not generally possible to exclude residual confounding by smoking. The findings from some of the studies that presented separate data on the risk for lung cancer in nonsmokers suggest a possible increased risk with consumption of alcoholic beverages, but others do not. No data relating to cessation of consumption of alcoholic beverages were available.

5.2.8 *Cancer of the stomach*

Epidemiological studies conducted in Asia, Europe and Latin America have reported inconsistent results on the risk for stomach cancer associated with the consumption of alcoholic beverages. Significantly increased risks were reported in some studies, including those from China, Japan, Poland and the Russian Federation.

In no study was it possible to stratify or adjust fully for lifetime infection with *Helicobacter pylori*, the most important known cause of non-cardia stomach cancer. Potential confounding by *H. pylori* infection is not, however, a major concern, since most of the population in areas where an association between consumption of alcoholic beverages and stomach cancer emerged had probably been infected by the bacteria. Of concern, however, is the likelihood that dietary deficiencies exist in these populations and that the consumption of alcoholic beverages may be accompanied by other unfavourable lifestyle factors, such low socioeconomic class and low intake of fresh fruit, vegetables and various micronutrients. Since insufficient allowance was made for these important lifestyle factors, the interpretation of the findings is not unequivocal.

5.2.9 *Cancer of the kidney*

Both cohort and case–control studies provide consistent evidence of no increase in the risk for renal-cell cancer with increasing consumption of alcoholic beverages. In several studies, increasing intake of alcoholic beverages was associated with a significantly lower risk for kidney cancer. These inverse trends were observed in both men and women and with multiple types of alcoholic beverage.

5.2.10 *Non-Hodgkin lymphoma*

The results of prospective cohort studies and evidence from some very large case–control studies showed an inverse association or no association between the consumption of alcoholic beverages and the risk for non-Hodgkin lymphoma. Most studies of non-Hodgkin lymphoma showed a lower risk for drinkers compared with non-drinkers. In general, there was no evidence of substantial differences in the effect between specific beverage types or for specific histological subtypes of non-Hodgkin lymphoma.

5.2.11 *Other sites*

For cancers of the pancreas, cervix, endometrium, ovary, vulva, vagina, male breast, urinary bladder, prostate, testis, brain and thyroid, for skin melanoma, Hodgkin disease, leukaemias and multiple myeloma, the evidence for an association between consumption of alcoholic beverages and risk for the site was generally sparse and/or inconsistent.

Although for some sites, e.g. cervix and prostate, some studies of special populations showed positive associations, bias and confounding could not be excluded. Some case–control studies indicated increased risks, but when, as for childhood brain cancer, testicular cancer and leukaemia, these were based on parental consumption of alcoholic beverages, it was not possible to exclude recall bias as an explanation of the association and, for several of the others, adequate adjustment for potential confounders had not been made.

When data were available, analysis by type of alcoholic beverage, dose, duration of consumption or histology or stratification by other risk factors did not reveal any consistent patterns for any of these sites. No reliable data related to the cessation of consumption of alcoholic beverages were available for most of these sites.

5.3 Animal carcinogenicity data

5.3.1 *Ethanol*

The effect of ethanol on the development of cancer depends on a variety of factors, including doses of ethanol and time of exposure, and also on animal species, strain and sex.

Ethanol was evaluated by a Working Group in 1988 and it was concluded that there was *inadequate evidence* for the carcinogenicity of ethanol in experimental animals. Most of the studies were criticized because of the small numbers of animals studied, the inadequate design of the experiments with uncontrolled dietary regimens, the short exposure to ethanol, low doses of ethanol and the failure to measure ethanol intake and/or concentrations in the blood. These concerns are also relevant for some of the studies that were published after 1988.

In a 2-year study, administration of ethanol to male mice in the drinking-water caused a dose-related increase in the incidence of hepatocellular adenomas and hepatocellular adenomas and carcinomas. In a lifetime study, administration of ethanol in the drinking-water resulted in an increase in the incidence of head and neck carcinomas in male and female rats and the incidence of forestomach carcinomas, testicular interstitial-cell adenomas and osteosarcomas of the head, neck and other sites in male rats. In another lifetime study, ethanol administered in the drinking-water induced mammary adenocarcinomas. In another study that used a genetically modified mouse model for intestinal cancer, administration of ethanol in the drinking-water increased

the incidence of intestinal tumours. Additional studies that encompassed oral and other routes of administration were also reviewed but were considered to be inadequate for the reasons noted above.

Many other studies were performed to determine whether ethanol modifies chemically induced carcinogenesis in various mouse and rat strains with a variety of carcinogens. Depending on the carcinogen and the animal model used, tumour-specific target organs included the mammary gland, oesophagus, forestomach, large intestine, liver, kidney, lung and thymus. Again, some of these studies were criticized because of the concerns mentioned above. However, in the majority of the studies, ethanol enhanced chemically induced carcinogenesis.

5.3.2 *Acetaldehyde*

Acetaldehyde was tested for carcinogenicity in rats by inhalation exposure and oral administration and in hamsters by inhalation exposure and intratracheal instillation. After inhalation exposure, acetaldehyde produced tumours of the respiratory tract, primarily adenocarcinomas and squamous-cell carcinomas of the nasal mucosa, in rats and laryngeal carcinomas in hamsters. Inhalation of acetaldehyde vapour enhanced the incidence of respiratory tract tumours induced by intratracheal instillation of benzo[*a*]pyrene. Intratracheal instillation of acetaldehyde did not increase tumour incidence in hamsters. Oral administration of acetaldehyde resulted in an increased incidence of tumours in several tissues. However, there was no obvious dose–response relationship.

Oral administration of acetaldehyde to rats did not potentiate the response induced by *N*-nitrosodiethylamine.

5.4 Mechanistic and other relevant data

5.4.1 *Ethanol*

Ethanol is absorbed rapidly from the upper gastrointestinal tract; a small fraction is cleared by first-pass metabolism, some of which probably occurs in the stomach and the remainder in the liver. Most of ethanol is eliminated in the liver, catalysed by alcohol dehydrogenases and to a much smaller degree by cytochrome P450 enzymes and catalase. The overall rate of elimination is affected to some extent by variation in alcohol dehydrogenase isozymes. Chronic consumption of alcoholic beverages induces cytochrome P450, but variants in this enzyme have not been clearly associated with differential susceptibility to alcoholism or ethanol-related pathology.

The presence of different alcohol dehydrogenase and aldehyde dehydrogenase isoenzymes determines tissue-specific differences in the metabolism of ethanol and acetaldehyde, and may contribute to tissue-specific susceptibilities to the toxicity of ethanol. The oesophagus and colon appear to express alcohol dehydrogenases (class IV (σ) alcohol dehydrogenase and alcohol dehydrogenase 1C, respectively), but have low

aldehyde dehydrogenase 2 activity, and hence may be susceptible to toxicity mediated by the metabolism of ethanol or exposure to acetaldehyde from other sources (saliva or microbes). Breast epithelium expresses class I alcohol dehydrogenase, but it is not clear whether it expresses aldehyde dehydrogenase 2; thus this tissue may also be susceptible to the oxidation products of ethanol.

Chronic ingestion of alcohol results in various adverse effects in the liver, such as fibrosis and cirrhosis. Although active alcohol dehydrogenase 1B and inactive aldehyde dehydrogenase 2 are a combination that protects against alcoholism, because of the undesired effects of accumulating acetaldehyde, polymorphisms in ethanol-metabolizing enzymes are unlikely to make a significant contribution to the development of alcoholic liver disease. The consumption of alcoholic beverages is detrimental in persons infected with the hepatitis C virus: alcoholic beverage drinking and the viral infection independently increase the risk for hepatocellular carcinoma.

In animal models, various types of ethanol-induced liver injury are observed that also occur in humans. Acute administration of ethanol causes hypoxia in the pericentral region of the liver lobule. Ethanol-induced liver pathology correlates with increased levels of cytochrome P450 2E1 and enhanced lipid peroxidation. Cytochrome P450 2E1-derived oxidants stimulate type I collagen synthesis in the liver and cause mitochondrial dysfunction and depolarization, which are key steps in apoptosis. Ethanol alters the permeability and microflora of the gut, which results in the release of endotoxins that can cause liver injury and inflammation.

The available data from molecular–genetic epidemiological studies suggest a positive association between the presence of *alcohol dehydrogenase 1B (*1/*1)* and the risk for upper aerodigestive tract cancer, but the mechanisms through which the functional polymorphism affects susceptibility to cancer have not been fully explained. The relationship between the *alcohol dehydrogenase 1B* genotype and cancer in other organs is inconclusive because the number of studies is small. Similarly, the evidence for a contribution of the *alcohol dehydrogenase 1C* polymorphism to the development of cancer in the upper aerodigestive tract is limited, and the relationship between the latter genotype and breast cancer is inconclusive because of the small number of studies.

Findings from studies that investigated the relationship between the *methylenetetrahydrofolate reductase* polymorphism *C677T* and the risk for colorectal cancer and adenoma indicate that high alcoholic beverage consumption increases the risk for colorectal cancer by influencing the metabolism of folate with respect to DNA methylation and DNA synthesis. A mechanistic interpretation regarding the role of polymorphisms of the methionine synthase and thymidylate synthase genes based on sparse data is difficult. The increased risk for breast, gastric and pancreatic cancer associated with the *methylenetetrahydrofolate reductase 677TT* genotype in persons with low folate and/or high alcoholic beverage intake suggests that alterations in the metabolism of folate may play a role in the occurrence of cancers at these sites.

Published results to date do not indicate that any particular DNA-repair gene variant has a dramatic effect on susceptibility to alcohol-related carcinogenesis, although

there are suggestions in the literature that genetic variation in the O^6-methylguanine–DNA methyltransferase gene, the X-ray repair cross-complementing gene (*XRCC-1*) and some nucleotide excision-repair genes may affect risk. With regard to the repair of oxidative DNA damage, two concordant studies showed an increased susceptibility to alcohol-related cancers in individuals who had the less active Cys 321 allele of the *oxoguanine glycosylase 1* gene. These results are of particular interest, since animal studies show that, in some cases, ethanol can increase oxidative DNA damage.

Ethanol has major effects on the metabolism and clearance of a variety of low-molecular-weight carcinogens and toxicants by cytochrome P450s 2E1, 1A1, 1A2, 2B6, 2C19 and 3A. In theory, ethanol may potentiate the tissue-specific effects of carcinogens by inducing cytochrome P450-dependent metabolism. However, most findings in experimental animals indicate that the more common mechanism is competitive inhibition of metabolism, especially in the liver, which results in increased dose delivery to peripheral target organs, an increase in DNA damage and enhancement of tumour formation, often five- to 20-fold. Such effects have been seen for many carcinogens and target organs. Evidence of this mechanism in humans is supportive but limited.

Alcoholic beverage consumption affects both male and female reproduction through the adverse regulation of levels of sex hormones and other effects on cells of the reproductive systems. There is a causal relationship between consumption of alcoholic beverages during pregnancy and the occurrence of adverse birth and developmental effects. Paternal exposure to alcoholic beverages has been associated with abnormalities in the offspring, such as decreases in birth weight and increases in ventricular septal defects. Animal models have convincingly supported the findings in humans; ethanol has deleterious effects on reproduction and causes skeletal and behavioural defects in the offspring of rodents when it is administered during gestation.

Numerous reports have shown that human alcoholics have a higher frequency of chromosomal aberrations, sister chromatid exchange and micronuclei in the peripheral lymphocytes and other cell types. Different types of DNA damage have been shown to occur in human tissues from subjects who consume alcoholic beverages; however, the relationship between oxidative stress-induced DNA lesions and alcoholic beverage consumption has not been well established.

Ethanol is not mutagenic in bacteria or *Drosophila*. It causes sister chromatid exchange in both lower organisms and mammalian cells, including human cells. The data from studies in animals suggest that ethanol causes DNA damage in target tissues.

5.4.2 *Acetaldehyde*

Acetaldehyde is formed metabolically from the oxidation of ethanol, and is further metabolized, predominantly by nicotinamide adenine dinucleotide-dependent aldehyde dehydrogenases, to acetic acid. The importance of aldehyde dehydrogenase in the oxidative pathway of ethanol is emphasized in drinkers of alcoholic beverages who are

deficient in this enzyme: the alcoholic flush reaction that they experience correlates with the accumulation of acetaldehyde in the blood.

In the absence of alcoholic beverage consumption, acetaldehyde ingested in food or generated by microbial fermentation is rapidly reduced to ethanol.

Acetaldehyde exerts toxic effects, mainly at the site of initial contact. Respiratory effects observed in studies in rats exposed to acetaldehyde by inhalation (for 13 weeks or 28 months) included degenerative changes in the olfactory and upper respiratory epithelium, metaplasia in the larynx and disturbances of the tracheal epithelium. When administered by intraperitoneal injection, acetaldehyde caused glycogenolysis, changes in the metabolic pathways and accumulation of lipids, cholesterol and free fatty acids in the liver. Effects on the pancreas and thyroid were also noted.

Acetaldehyde showed embryotoxic, fetotoxic and teratogenic effects in rats. In cultured cells of different origin, acetaldehyde affected lipid peroxidation, mitochondrial respiration and metabolism. In certain cell types, it reduced glutathione, increased intracellular calcium and induced DNA fragmentation, which are indicators of apoptosis.

The available data from molecular–genetic epidemiological studies provide ample evidence that the heterozygous *aldehyde dehydrogenase 2* genotype — which leads to the accumulation of acetaldehyde, e.g. in the blood, saliva and liver — contributes substantially to the development of oesophageal cancers (squamous-cell carcinomas) that are related to the consumption of alcoholic beverages.

While it is often difficult to differentiate clearly between the exact locations of tumours in the oropharyngolaryngeal area based on the available published data, there is strong evidence that the heterozygous *aldehyde dehydrogenase 2* genotype contributes to the development of cancers of the oropharyngolarynx as a whole that are related to the consumption of alcoholic beverages. The available epidemiological studies provide suggestive but inconclusive evidence for an association between the heterozygous *aldehyde dehydrogenase 2* genotype and hepatocellular carcinoma and inconclusive evidence for an association with colorectal cancer.

Acetaldehyde reacts with DNA to form various DNA adducts, and elevated levels of acetaldehyde-derived DNA adducts have been detected in white blood cells of individuals who are heavy alcoholic beverage drinkers. An important observation is that, with equivalent levels of tobacco smoking and consumption of alcoholic beverages, individuals who are deficient in aldehyde dehydrogenase 2 due the *aldehyde dehydrogenase 2*2* polymorphism had higher levels of acetaldehyde-related adducts in white blood cell DNA than individuals who have normal aldehyde dehydrogenase 2 activity. Aldehyde dehydrogenase 2-deficient individuals have been shown to be at higher risk for developing oesophageal cancer through alcoholic beverage consumption and also to have higher levels of acetaldehyde in the blood and saliva following alcoholic beverage drinking compared with aldehyde dehydrogenase 2-proficient individuals. Some of the DNA adducts that are increased after alcoholic beverage consumption are mutagenic in human cells. In addition, these adducts can undergo rearrangements in double-stranded DNA, which can result in the formation of DNA–protein cross-links

and DNA interstrand cross-links, which are mechanistically consistent with the generation of chromosomal aberrations. Elevated levels of chromosomal aberrations have been observed in human cells in culture after exposure to acetaldehyde as well as *in vivo* in human alcoholics.

6. Evaluation and Rationale

6.1 Carcinogenicity in humans

There is *sufficient evidence* in humans for the carcinogenicity of alcoholic beverages.

The occurrence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and female breast is causally related to the consumption of alcoholic beverages.

There is *evidence suggesting lack of carcinogenicity* in humans for alcoholic beverages and cancer of the kidney and non-Hodgkin lymphoma.

There is substantial mechanistic evidence in humans who are deficient in aldehyde dehydrogenase that acetaldehyde derived from the metabolism of ethanol in alcoholic beverages contributes to the causation of malignant oesophageal tumours.

6.2 Carcinogenicity in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethanol.

There is *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde.

Overall evaluation

Alcoholic beverages are *carcinogenic to humans (Group 1).*

Ethanol in alcoholic beverages is *carcinogenic to humans (Group 1).*

Rationale

The latter evaluation is based on (i) the epidemiological evidence, which showed little indication that the carcinogenic effects depend on the type of alcoholic beverage, (ii) the *sufficient evidence* that ethanol causes cancer in experimental animals; and (iii) the mechanistic evidence in humans who are deficient in aldehyde dehydrogenase that acetaldehyde derived from the metabolism of ethanol in alcoholic beverages contributes to the causation of malignant oesophageal tumours. Identification of ethanol as a known carcinogenic agent in alcoholic beverages does not rule out the possibility that other components may also contribute to their carcinogenicity.

Note added in proof:

In October 2009, the IARC Working Group for Monograph Volume 100E reviewed "Alcohol drinking" as a Group-1 agent. This Working Group considered that acetaldehyde is a genotoxic compound that is detoxified by aldehyde dehydrogenases (ALDH); that the *ALDH2*2* variant allele, which encodes an inactive enzyme, is prevalent in up to 30% of east-Asian populations; and that heterozygous carriers, who have about 10% enzyme activity, accumulate acetaldehyde and have considerably higher relative risks for alcohol-related oesophageal and head and neck cancers compared with individuals with the common alleles. The Working Group for Volume 100E concluded that "Acetaldehyde associated with alcoholic beverages" is *carcinogenic to humans* (Group 1).

ETHYL CARBAMATE

There appears to be no general consensus on a common trivial name for this substance: ethyl carbamate and urethane (or urethan) are both commonly used; however, a preference for ethyl carbamate was noted in the more recent literature. The name urethane is also sometimes applied to high-molecular-weight polyurethanes used as foams, elastomers and coatings. Such products are not made from and do not generate the chemical ethyl carbamate on decomposition. Due to this possible confusion, the term ethyl carbamate has been used in this monograph.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms*

CAS Registry No.*: 51–79–6*

Synonyms: Carbamic acid ethyl ester; ethylurethan; ethyl urethan; ethyl urethane; urethan; urethane

1.1.2 *Chemical formula and relative molecular mass*

$NH_2COOC_2H_5$ Relative molecular mass: 89.1

1.1.3 *Chemical and physical properties of the pure substance*

From Budavari (2000)

(a) Description: Colourless, almost odourless, columnar crystals or white granular powder; the pH of an aqueous solution is neutral

(b) Boiling-point: *182–184 °C*

(c) Melting-point: *48–50 °C*

(d) Solubility: Dissolves in water (1 g/0.5 mL), ethanol (1 g/0.8 mL), chloroform (1 g/0.9 mL), ether (1 g/1.5 mL), glycerol (1 g/2.5 mL) and olive oil (1 g/32 mL)

(e) Volatility: Sublimes readily at 103°C at 54 mm Hg; volatile at room temperature

1.1.4 *Technical products and impurities*

Trade names for ethyl carbamate include Leucothane, Leucethane and Pracarbamine.

The Chemical Catalogs Online database, produced by Chemical Abstracts Services, lists 37 suppliers for ethyl carbamate, which are predominantly situated in Europe, Japan and the USA. Technical grades with 98% purity as well as products with more than 99% purity (less than 0.1% ignitable residues) are available.

1.1.5 *Analysis*

The titration method described by Archer *et al*. (1948) was used to monitor patients who underwent therapy with ethyl carbamate. A gas chromatography–mass spectrometry (GC–MS) method to monitor ethyl carbamate in blood was developed by Hurst *et al*. (1990) to monitor the time course of elimination of ethyl carbamate in mice.

The methods developed to determine ethyl carbamate in various food matrices are summarized in Table 1.1; the analytical methodology was reviewed by Zimmerli and Schlatter (1991). GC coupled with MS seems to be the method of choice for this purpose. The overwhelming majority of methods involve quadrupole MS operating in selected-ion monitoring mode and the use of isotopically labelled internal standards. Validation data of collaborative studies are available (Dennis *et al*., 1990; Canas *et al*., 1994; Dyer, 1994; Hesford & Schneider, 2001; de Melo Abreu *et al*., 2005). In general, the validation results were judged to be satisfactory for the purpose of analysing ethyl carbamate in the lower microgram per kilogram range. The methods presented by Dyer (1994) and Canas *et al*. (1994) were adopted by the Association of Official Analytical Chemists International as part of their Official Methods. A collaborative analysis also led to the adoption of a method for the determination of ethyl carbamate in the European Community methods for the analysis of wine (European Commission, 1999).

The analysis of minor organic compounds in complex matrices, such as in spirit beverages, is difficult because of interferences by matrix components, even when extensive clean-up procedures are applied to the sample, e.g. extraction over diatomaceous earth columns, which is proposed by many authors. A possible approach to eliminate these interferences is the use of solid-phase extraction in combination with an improved chromatographic separation using multidimensional GC, as proposed by Jagerdeo *et al*. (2002) for the analysis of wine. However, this technique requires the time-consuming removal of ethanol before solid-phase extraction and specialized equipment consisting of GC with a flame-ionization detector and GC–MS, which are coupled using a cryo trap. As another approach, MS detection may be enhanced by application of tandem MS (MS–MS) to provide an improved sensitivity and specificity. Recently, it was demonstrated that low-cost bench-top triple quadruple mass spectrometers can be used in the routine analysis of ethyl carbamate in spirits (Lachenmeier *et al*., 2005a) or in bread (Hamlet *et al*., 2005).

Table 1.1 Methods for the analysis of ethyl carbamate in different matrices

Sample matrix	Internal standard	Extraction principle	Clean-up	Detection	Column	LOD (µg/L)	Reference
Alcoholic beverages	–	Dilution to 10% vol, dichloromethane extraction	–	GC–ECD	DBWAX-30W	Low µg/kg range	Bailey *et al.* (1986)
	Methyl carbamate	Dichloromethane extraction	Extrelut	GC-NPD	Durabond-Wax	20	Baumann & Zimmerli (1986a)
	–	Dilution to 5% alcohol	Chemtube or Extrelut	GC (1) TEA (2) ECD (3) MS	CP Wax 52 CB	 (1) 1 (2) 2–5 (3) 1	Dennis *et al.* (1986, 1988)
	1,4-Butanediol or *N*,*N*-dimethylformamide	Salting-out with potassium carbonate	–	GC-MS EI or PCI	Carbowax 20M	EI: 100 PCI: 10	Bebiolka & Dunkel (1987)
	–	Dichloromethane extraction	–	GC–ECD, GC–MS	DBWAX	ECD: 5–10 MS: 0.5	Conacher *et al.* (1987)
	–	Dichloromethane extraction	–	GC–MS	DBWAX	0.5	Lau *et al.* (1987)
	n-Butyl carbamate	Dichloromethane extraction	Extrelut	GC–MS	WCOT, DBWAX	10	Mildau *et al.* (1987)
	–	Dilution to 10% vol, dichloromethane extraction	–	Two-dimensional GC–FID	(1) CP-SIL 5 CB (2) CP-WAX 52	1	van Ingen *et al.* (1987)
	[^{13}C,^{15}N]-Ethyl carbamate	Dichloromethane extraction	Deactivated alumina	GC–TEA	DB-Wax	1.5	Canas *et al.* (1988)
	–	Dichloromethane extraction	–	GC–ion trap	Supelcowax 10	5	Clegg & Frank (1988)

Table 1.1 (continued)

Sample matrix	Internal standard	Extraction principle	Clean-up	Detection	Column	LOD (µg/L)	Reference
	Ethyl carbamate-d_5	Distillation, dichloromethane extraction	–	GC–MS	SGE BP 20	2-5	Funch & Lisbjerg (1988)
	tert-Butyl carbamate and *n*-butyl carbamate (GC–FID), [^{13}C,^{15}N]-ethyl carbamate	Dilution to 25% vol, dichloromethane extraction	Alumina clean-up	GC–FID GC–MS	DB-WAX Carbopack B/ Carbowax 20M	10-25 5	Pierce *et al*. (1988)
	Isopropyl carbamate	Dichloromethane extraction	–	Two-dimensional GC–TSD	BP-20, OV-1	1	Ma *et al*. (1995)
	–	Dilution to 20% vol	Derivatization with 9-xanthydrol	HPLC–fluorescence detection	HP AminoQuant	4.2	Herbert *et al*. (2002)
	Ethyl carbamate-d_5	Removal of ethanol	SPE (styrene–divinylbenzene copolymer)	GC–MS	HP-INNOWAX	3	Mirzoian & Mabud (2006)
Distilled spirits	Propyl carbamate	Evaporation with nitrogen	–	GC–MS	DB-Wax	10	Farah Nagato *et al*. (2000)
Grappa	Ethyl carbamate	Dichloromethane–ethyl acetate extraction	Derivatization with xanthydrol	GC–MS	DB 5	1	Giachetti *et al*. (1991)
Must and wine	–	–	–	FTNIR-screening	–	–	Manley *et al*. (2001)
Rice wine	Propyl carbamate	Chloroform extraction	Florisil	GC–MS	DB-Wax	–	Woo *et al*. (2001)
Spirits and mashes	–	Distillation	Chem-Elut 1020	GC–FID	(1) DB-Wax (2) DB-225	5	Wasserfallen & Georges (1987)

Table 1.1 (continued)

Sample matrix	Internal standard	Extraction principle	Clean-up	Detection	Column	LOD (µg/L)	Reference
Spirits	Pyrazole	Salting-out	–	GC–NPD	BC-CW 20 M	10	Adam & Postel (1987)
	n-Octanol	Ethyl acetate extraction	–	GC–FID	CP Wax 57 CB	10-20	Andrey (1987)
	tert-Butyl carbamate	Extraction with *n*-hexane–ethyl acetate mixture	Extrelut	GC–FID, GC–N-TSD	Stabilwax	50	Drexler & Schmid (1989)
	Propyl carbamate	–	–	GC–MS	FSOT	5	MacNamara *et al*. (1989)
	–	Salting-out	Filtration over activated carbon	GC–NPD, GC–FID	HP 19091 F-115 or Carbowax 20M	LOQ:1-5	Adam & Postel (1990)
	Ethyl carbamate-d_5	Dichloromethane extraction	Extrelut	GC–MS/MS	CP-wax	10	Lachenmeier *et al*. (2005a)
	–	–	–	FTIR screening	–	–	Lachenmeier (2005)
	Ethyl carbamate-d_5	Dilution 1:10	HS-SPME	GC–MS/MS	Stabilwax	30	Lachenmeier *et al*. (2006)
Whisky, sherry, port, wine	[^{13}C,^{15}N]-Ethyl carbamate	Dichloromethane extraction	–	GC–MS/MS CI.	Carbowax SP-10	1	Brumley *et al*. (1988)
Wines and spirits	[^{13}C,^{15}N]-Ethyl carbamate	Dichloromethane extraction	Florisil	GC–ECD, GC–MS/MS	Carbowax 20M Stabilwax		Cairns *et al*. (1987)
Wine	–	Chloroform extraction	Florisil	GC–ECD	GCQ, OV-17, Carbowax 1540	<100	Walker *et al*. (1974)

Table 1.1 (continued)

Sample matrix	Internal standard	Extraction principle	Clean-up	Detection	Column	LOD (µg/L)	Reference
	Propyl carbamate	Extraction with Soxhlet apparatus	–	GC–MS	DB-Wax	–	Fauhl & Wittkowski (1992)
	–	Dichloromethane extraction	Chem-Elut or Extrelut	GC–N-TEA	DB-Wax	1-2	Sen *et al*. (1992)
	Propyl carbamate	Dilution, dichloromethane extraction	Diatomaceous earth columns	GC–MS	Carbowax 20M	–	European Commission (1999)
	[^{13}C,^{15}N]-Ethyl carbamate	Removal of ethanol, dilution	SPE (styrene-divinylbenzene copolymer)	Two-dimensional GC–MS	HP-5MS DB-WAX	0.1	Jagerdeo *et al*. (2002)
	Propyl carbamate	–	MS–SPME	GC–MS	DB-Wax	9.6	Whiton & Zoecklein (2002)
Alcoholic beverages and foods	[^{13}C,^{15}N]-Ethyl carbamate	Dichloromethane extraction	–	GC–MI/FTIR	DBWAX-30W	10	Mossoba *et al*. (1988)
Alcoholic beverages, fermented foods	*n*-Butyl carbamate	Pre-extraction with petroleum ether, dichloromethane extraction	Deactivated alumina	GC–FID	DB-Wax	6,7	Wang *et al*. (1997); Wang & Gow (1998)
Bread	Ethyl carbamate-d_5	Dichloromethane extraction	Extrelut	GC–MS/MS	EC-WAX	0.6	Hamlet *et al*. (2005)
Fermented foods	–	Dichloromethane extraction	Acid–celite column	GC–MS	CBP-20	0.5	Hasegawa *et al*. (1990)
Fermented Korean foods and beverages	Propyl carbamate	Various procedures	Various procedures	GC–MS	DB-Wax	11	Kim *et al*. (2000)

Table 1.1 (continued)

Sample matrix	Internal standard	Extraction principle	Clean-up	Detection	Column	LOD (µg/L)	Reference
Soya sauce	Propyl carbamate	Dichloromethane extraction	Extrelut	GC–MS	DB-Wax	1	Fauhl *et al.* (1993)
	–	Dichloromethane extraction	Celite columns	GC–MS	Supelcowax	0.5	Matsudo *et al.* (1993)
Blood	–	Before and after alkaline hydrolysis	–	Titration with 0.1 N sodium thiosulfate	–	–	Archer *et al.* (1948)
	[^{13}C,^{15}N]-Ethyl carbamate	Dichloromethane extraction	Chem-Elut 1000M	GC–MS	DB-WAX, DB-1	20	Hurst *et al.* (1990)

CI., chemical ionization; ECD, electrolytic conductivity detector; EI, electron ionization; FID, flame ionization detection; FTIR, Fourier transform infrared spectroscopy; FTNIR, Fourier transform near-infrared spectroscopy; GC, gas chromatography; HPLC, high-performance liquid chromatography; LOD, limit of detection; MI, matrix isolation; MS, mass spectrometry; NPD, nitrogen/phosphorus detector; PCI, positive chemical ionization; SPME, solid-phase microextraction; TEA, thermal energy analyser; TSD, thermoionic-specific detection

Solid-phase microextraction has recently emerged as a versatile solvent-free alternative to conventional extraction procedures. Ethyl carbamate has been analysed by HS–solid-phase microextraction only in wine samples (Whiton & Zoecklein, 2002) and spirits (Lachenmeier *et al*., 2006).

The procedures that combine sample extraction and subsequent GC–MS or GC–MS–MS are regarded as references for the analysis of ethyl carbamate in alcoholic beverages (Lachenmeier, 2005). Increasing requirements and cost pressures have forced both government and commercial food-testing laboratories to replace traditional reference methods with faster and more economical systems. Fourier-transform infrared spectroscopy, in combination with multivariate data analysis, has shown great potential for expeditious and reliable screening analysis of alcoholic beverages. The analysis of ethyl carbamate found in wine samples using Fourier-transform near-infrared spectroscopy was evaluated by Manley *et al*. (2001). Fourier-transform infrared spectroscopy in combination with partial least squares regression was applied to the screening analysis of ethyl carbamate in stone-fruit spirits (Lachenmeier, 2005).

1.2 Production and use

Ethyl carbamate can be made by the reaction of ethanol and urea or by warming urea nitrate with ethanol and sodium nitrite (Budavari, 2000). Another possible method is via addition of ethanol to trichloroacetyl isocyanate (Kocovský, 1986).

Production of ethyl carbamate was predominantly reported in the first half of the twentieth century. Ethyl carbamate has been produced commercially in the USA for at least 30 years (Tariff Commission, 1945). A major use of methyl and ethyl carbamate has been for the manufacture of meprobamate (Adams & Baron, 1965), and the spectacular success of this drug as a tranquilizer in the 1950s resulted in a demand for the commercial production of these intermediates. Ethyl carbamate had been used as a crease-resistant finish in the textile industry, as a solvent, in hair conditioners, in the preparation of sulfamic acids, as an extractant of hydrocarbons from crude oil and as a food flavour-enhancing agent (Adams & Baron, 1965). No data on the present use of ethyl carbamate in industry were available to the Working Group.

Ethyl carbamate was used in medical practice as a hypnotic agent at the end of nineteenth century but this use was discontinued after barbiturates became available. It was also tested for the treatment of cancers (Paterson *et al*., 1946; Hirschboeck *et al*., 1948), or used as a co-solvent in water for dissolving water-insoluble analgesics used for post-operative pain (Nomura, 1975). Ethyl carbamate has also been used in human medicine as an antileukaemic agent at doses of up to 3 g per day for the treatment of multiple myeloma (Adams & Baron, 1965). No evidence was available to the Working Group that ethyl carbamate is currently used in human medicine.

Ethyl carbamate is widely used in veterinary medicine as an anaesthetic for laboratory animals (Hara & Harris, 2002).

1.3 Occurrence and exposure

The occurrence of and exposure to ethyl carbamate in food have been reviewed (Battaglia *et al*., 1990; Zimmerli & Schlatter, 1991).

Ethyl carbamate has been detected in many types of fermented foods and beverages. The levels in wine and beer are in the microgram per litre range (Tables 1.2 and 1.3). Higher levels have been found in spirits, especially stone-fruit spirits, up to the milligram per litre range (Table 1.4). Ethyl carbamate has also been found in bread (Table 1.5). It may occur in fruit and vegetable juices at very low concentrations (< 1 µg/L) (Table 1.6). Its occurrence in other fermented food products (most notably fermented Asian products, such as soy sauce) is shown in Table 1.7.

In the past 20 years, major research has been carried out to identify the precursors of ethyl carbamate (Table 1.8) and develop methods for its reduction. One of the most established sources of ethyl carbamate is urea, which may be formed during the degradation of arginine by yeast. Arginase hydrolyses l-arginine to l-ornithine and urea (Schehl *et al*., 2007), and urea is secreted by the yeast into the medium where it reacts with ethanol to form ethyl carbamate (Ough *et al*., 1988a; Kitamoto *et al*., 1991; An & Ough, 1993). The addition of urease has been shown to reduce the content of ethyl carbamate in wine and other fermented products (Kobashi *et al*., 1988; Ough & Trioli, 1988; Tegmo-Larsson & Henick-Kling, 1990; Kim *et al*., 1995; Kodama & Yotsuzuka, 1996).

Ethyl carbamate may also be formed from cyanide. This may explain its high concentrations in stone-fruit spirits. The removal of cyanogenic glycosides such as amygdalin in stone-fruit by enzymatic action (mainly β-glucosidase) leads to the formation of cyanide (Lachenmeier *et al*., 2005b). Cyanide is oxidized to cyanate, which reacts with ethanol to form ethyl carbamate (Wucherpfennig *et al*., 1987; Battaglia *et al*., 1990; MacKenzie *et al*., 1990; Taki *et al*., 1992; Aresta *et al*., 2001). The wide range of concentrations of ethyl carbamate in stone-fruit spirits reflects its light- and time-dependent formation after distillation and storage (Andrey, 1987; Mildau *et al*., 1987; Baumann & Zimmerli, 1988; Zimmerli & Schlatter, 1991; Suzuki *et al*., 2001).

1.4 Regulations, guidelines and preventive actions

Public health concern regarding ethyl carbamate in food, and especially in alcoholic beverages, began in 1985 when relatively high levels were detected by Canadian authorities in alcoholic beverages, mainly in spirit drinks imported from Germany (Conacher & Page, 1986). Subsequently, Canada established an ethyl carbamate guideline of 30 µg/L for table wines, 100 µg/L for fortified wines, 150 µg/L for distilled spirits and 400 µg/L for fruit spirits (Conacher & Page, 1986). The Canadian guidelines were adopted by many other countries. The *Codex alimentarius* gives no specific standards for ethyl carbamate in food.

Table 1.2 Occurrence of ethyl carbamate in wine and fortified wine

Product	Year	No. of samples	Ethyl carbamate (μg/L)		Reference
			Mean	Range	
Wine	1951–89	127	0–5	0–48.6	Sponholz *et al*. (1991)
Wine	1988				Clegg *et al*. (1988)
White wines		196		<10–>100	
Red wines		51		<10–100	
Sparkling wines		14		–	
Wine coolers		2		–	
Fortified wines					
Sherries		256		<10–>200	
Ports		57		<10–>200	
Vermouths		7		<10–200	
Sherry	1985–87	12	32–33	<5–60	Dennis *et al*. (1989)
Wine		31	6	1–18	
Wine	1993				Sen *et al*. (1993)
White wines		16		ND–24	
Red wines		7		1–14	
Sake		2		3–29	
Sherry		6		28–69	
Fortified wines	1988–90	14	30	7–61	Vahl (1993)
Wine		57	7	<3–29	
Italian wine	2000	90			Cerutti *et al*. (2000)
Red				6–22	
White				6–16	
Rosé				7–15	
Brazilian wine	2002				Francisquetti *et al*. (2002)
Cabernet Sauvignon		30	10.6	2–31.8	
Merlot		17	6.6	1.8–32.4	
Gamay		3	4.5	3.4–6.5	
Pinot blanc		5	7.4	2.7–10.1	
Generic reds		9	16.6	2.4–36.2	
Gewürztraminer		12	10.1	1.2–30.5	
Italian Riesling		10	13.0	1.0–39.1	
Chardonnay		5	19.3	1.7–70	
Semillon		3	14.5	3.5–20.5	
Generic whites		3	4.8	4.7–5.1	
Common reds		10	5.1	2.1–9	
Sparkling wines		17	7.6	2.1–24.6	
Spanish red wine	2004	36		0–25	Uthurry *et al*. (2004)
Wine	2006	3	4.9	1.7–11.7	Ha *et al*. (2006)

ND, not detected

Table 1.3 Occurrence of ethyl carbamate in beer

Product	Year	No. of samples	Ethyl carbamate (µg/L)		Reference
			Mean	Range	
Beer	1985–87	15	0.1–1.1	<1–1.8	Dennis *et al*. (1989)
Beer	1989				Canas *et al*. (1989)
Domestic		33	0.24	ND–0.8	
Imported		36	2.8	2.1–3.5	
Danish Beer	1988–90	50	3	<0.2–6.6	Vahl (1993)
Alcohol-free beer	1994	4	0.3	0.1–0.7	Groux *et al*. (1994)
Beer		5	2.7	0.9–4.7	Groux *et al*. (1994)
Beer	1997				Dennis *et al*. (1997)
Draught		20		<1	
Canned		26		0.4–2.5	
Bottled		51		<1–14.7	
Home-brewed beer		32		<1–9	
Beer	2006	6	0.5	0.5–0.8	Ha *et al*. (2006)

ND, not detected

However, the general standard for contaminants and toxins in foods demands that contaminant levels shall be as low as reasonably achievable and that contamination may be reduced by applying appropriate technology in food production, handling, storage, processing and packaging (FAO/WHO, 2008).

Many preventive actions to avoid ethyl carbamate formation in food and beverages have been proposed (Table 1.9). For beverages such as wine and sake, the preventive measures have concentrated on yeast metabolism, whereas for stone-fruit spirits, research has been centred on reducing the precursor, cyanide. In addition, measures of good manufacturing practice such as the use of high-quality, unspoiled raw materials and high standards of hygiene during fermentation and storage of the fruit mashes, mashing and distillation must be optimized. To avoid the release of cyanide, it is essential to avoid breaking the stones, to minimize exposure to light and to shorten storage time. Some authors have proposed the addition of enzymes to decompose cyanide or a complete de-stoning of the fruit before mashing. The mashes have to be distilled slowly with an early switch to the tailing-fraction. Further preventive actions are the addition of patented copper salts to precipitate cyanide in the mash, distillation using copper catalysts or the application of steam washers (Zimmerli & Schlatter, 1991).

Table 1.4 Occurrence of ethyl carbamate in spirits

Product	Year	No. of samples	Ethyl carbamate (µg/L)		Reference
			Mean	Range	
Canadian whiskey	1988	18		<50–150	Clegg *et al*. (1988)
Rum		20		<50–150	
Vodka		5		<50	
Gin		4		<50	
Scotch whisky		7		<50–150	
Bourbon whiskey		19		<50–>150	
Fruit spirits and liqueurs		123		<50–>400	
Scotch whisky	1985–87	11	44	19–90	Dennis *et al*. (1989)
Imported whiskey		7	69–70	<5–206	
Vodka		3	ND	ND[a]	
Gin		3	ND	ND[a]	
Fruit spirit		4	41–42	<5–139	
Port		4	18	14–21	
Liqueur		8	129	9–439	
Whisky	1993	6	75.7	26–247	Sen *et al*. (1993)
Rye		1		8	
Bourbon		4		44–208	
Vodka		1		ND	
Gin		1		0.5	
Rum		1		19	
Fruit spirit		3		104–2344	
Apricot spirit		1		11	
Armagnac		2		410–432	
Other brandies		3		25–28	
Spirits	1988–90	22	534	<5–5103	Vahl (1993)
Grappa	2000	6		75–190	Cerutti *et al*. (2000)
Fruit spirit	2006	7	196.7	3.5–689.9	Ha *et al*. (2006)
Whisky		5	20.1	13.9–30.0	
Cheongju		5	20.2	8.4–30.3	
Korean style spirits	2000	10	3.4	ND–15.4	Kim *et al*. (2000)
Stone–fruit spirits	1986–2004	631	1400	10–18 000	Lachenmeier *et al*. (2005b)

ND, not detected; [a] Detection limit at 5 µg/L

Table 1.5 Occurence of ethyl carbamate in bread

Product	Year	No. of samples	Ethyl carbamate (µg/kg)		Reference
			Mean	Range	
Bread	1988	9	ND	ND[a]	Dennis *et al*. (1989)
Bread	1989	30			Canas *et al*. (1989)
White			3.0	ND–8	
Wheat			1.2	ND–4	
Other			0.9	ND–4	
Bread	1993	12	3.1	1.6–4.8	Sen *et al*. (1993)
Light toast	1993	12	4.3	1.3–10.9	
Dark toast	1993	12	15.7	4.9–29.2	
Bread	1988–90	33	3.5	0.8–12	Vahl (1993)
Bread	1994	48	5.2	0.5–27	Groux *et al*. (1994)

ND, not detected; [a] Detection limit at 5 µg/kg

Table 1.6 Occurrence of ethyl carbamate in juices

Product	Year	No. of samples	Ethyl carbamate (µg/L)		Reference
			Mean	Range	
Freshly pressed grape juices	1990	15		19–54	Tegmo-Larsson & Henick-Kling (1990)
Apple and pear juice	1994	6	ND	ND[a]	Groux *et al*. (1994)
Citrus juice		7	0.1	0–0.1	
Grape juice		6	0.1	0–0.2	
Other fruit juices		8	0.1	0–0.2	
Vegetable juice		3	0.1	0–0.1	

ND, not detected; [a] Detection limit at 0.06 ppb = 0.06 µg/L

Table 1.7 Occurrence of ethyl carbamate in miscellaneous fermented foods

Product	Year	No. of samples	Ethyl carbamate (µg/kg)		References
			Mean	Range	
Cheese	1989	16	ND	ND	Canas *et al*. (1989)
Yoghurt		12	0.4	ND–4	
Tea		6	ND	ND	
Yoghurt	1988	9	0–1	<1–<1	
Cheese		19	0.6–5.1	<5–6	
Soya sauce	1993	10		ND–59	Sen *et al*. (1993)
Yoghurt and buttermilk		14		ND–0.4	
Yoghurt and other acidified milk products	1988–90	19	0.2	<0.1–0.3	Vahl (1993)
Kimchi	2000	20	3.5	ND–16.2	Kim *et al*. (2000)
Soy sauce					
Regular		5	14.6	ND–19.5	
Traditional type		15	17.1	ND–73.3	
Soybean paste		7	2.3	ND–7.9	
Vinegar		5	1.2	0.3–2.5	
Soju	2006	7	3.0	0.8–10.1	Ha *et al*. (2006)
Takju		7	0.6	0.4–0.9	

ND, not detected

Table 1.8 Precursors of ethyl carbamate in different food matrices and factors that influence its formation

Precursor	Food matrix	Reference
Diethyl dicarbonate (used as food additive)	Orange juice, white wine, beer	Löfroth & Gejvall (1971)
Carbamyl phosphate (produced by yeasts)	Wine, fermented foods, bread	Ough (1976a)
Diethyl dicarbonate (used as food additive)	Wine	Ough (1976b)
Cyanide, vicinal dicarbonyl compounds	Model systems	Baumann & Zimmerli (1986b)
Carbamyl phosphate and ethyl alcohol, light	Wine	Christoph *et al*. (1987)
Cyanide, benzaldehyde, light	Distilled products	Christoph *et al*. (1988)
Light	Distilled products	Baumann & Zimmerli (1988)
Urea	Wine	Ough & Trioli (1988)
Urea, citrulline, *N*-carbamyl α-amino acids, *N*-carbamyl β-amino acid, allantoin, carbamyl phosphate	White and red wines	Ough *et al*. (1988a)
Amino acids, urea, ammonia	Chardonnay juice fermentation	Ough *et al*. (1988b)
Urea, copper, carbamyl phosphate, citrulline	Wine	Sponholz *et al*. (1991)
Cyanate, cyanide, cyanohydrin, copper cyanide complexes	Grain whisky	Aylott *et al*. (1990)
Cyanide related species (cyanide, copper cyanide complex, lactonitrile, cyanate, thiocyanate)	Scotch grain whisky	MacKenzie *et al*. (1990)
Cyanide	Grain-based spirits	Cook *et al*. (1990)
Cyanide	Grain-based spirits	McGill & Morley (1990)
Temperature, light	Wine	Tegmo-Larsson & Spittler (1990)
Cyanate	Alcoholic beverages	Taki *et al*. (1992)
Yeast strain, arginine, urea	Fortified wine	Daudt *et al*. (1992)
Isocyanate	Wine distillates	Boulton (1992)
Cyanide, copper, light,	Stone-fruit distillates	Kaufmann *et al*. (1993)
Manufacturing conditions	Soya bean tempe	Nout *et al*. (1993)
Urea	Wine	An & Ough (1993)

Table 1.8 (continued)

Precursor	Food matrix	Reference
Urea, citrulline	Wine	Stevens & Ough (1993)
Urea	Wine	Kodama *et al*. (1994)
Citrulline, arginine degradation	Wine	Liu *et al*. (1994)
Yeast arginase activity	Port	Watkins *et al*. (1996)
Azodicarbonamide (used as food additive)	Bread, beer	Dennis *et al*. (1997)
Citrulline	Wine	Mira de Orduña *et al*. (2000)
Citrulline	Model fortified wines	Azevedo *et al*. (2002)
Arginine	Wine	Arena *et al*. (2002)
Arginine	Korean soy sauce	Koh *et al*. (2003)
Storage time, temperature	Wine	Hasnip *et al*. (2004)
Arginine, citrulline	Wine	Arena & Manca de Nadra (2005)
Cyanide	Stone-fruit spirits	Lachenmeier *et al*. (2005b)
Fruit types, fermentation conditions	Fruit mashes	Balcerek & Szopa (2006)
Selected yeasts, different conditions (temperature, pH)	Red wine	Uthurry *et al*. (2006)
Yeast strain, arginine	Stone-fruit distillates	Schehl *et al*. (2007)

Table 1.9 Procedures for reducing ethyl carbamate concentration in different food matrices

Procedure	Food matrix	Reference
Modification of vineyard procedures Use of commercial yeast strains Urease treatment	Wine	Butzke & Bisson (1997)
Use of non-arginine-degrading oenococci	Wine	Mira de Orduña *et al*. (2001)
Metabolic engineering of *Saccharomyces cerevisiae*	Wine	Coulon *et al*. (2006)
Malolactic fermentation with pure cultures at low pH values (<3.5)	Wine	Terrade & Mira de Orduña (2006)
Removal of urea with an acid urease	Sake	Kobashi *et al*. (1988)
Genetic engineering of yeast	Sake	Kitamoto *et al*. (1991)
Non-urea producing yeast	Sake	Kitamoto *et al*. (1993)
Non-urea producing yeast	Sake	Yoshiuchi *et al*. (2000)
Application of acid urease	Takju	Kim *et al*. (1995)
Application of acid urease	Sherry	Kodama & Yotsuzuka (1996)
Precipitation of cyanide (steam washer)	Stone-fruit distillates	Nusser *et al*. (2001)
Application of cyanide catalyst Optimization of distillation conditions	Stone-fruit distillates	Pieper *et al*. (1992a,b)
Dark storage Separation of cyanide	Stone-fruit distillates	Christoph & Bauer-Christoph (1998, 1999)
Complete prevention of ethyl carbamate by state-of-the-art production technology	Stone-fruit distillates	Lachenmeier *et al*. (2005b)
De-stoning of the fruits	Stone-fruit distillates	Schehl *et al*. (2005)
Automatic rinsing of the stills, copper catalysts, separation of tailings, no re-distillation of tailings	Stone-fruit distillates	Weltring *et al*. (2006)
Yeast with reduced arginase activity	Stone-fruit distillates	Schehl *et al*. (2007)

Research on ethyl carbamate in food has led to a significant reduction in its content during the past 20 years. The use of additives that might be precursors of ethyl carbamate has been forbidden in most countries. For stone-fruit spirits — the most problematic food group — the few large distilleries that produce for the mass market have all introduced the good manufacturing practices described above and produce stone-fruit distillates that have only traces of ethyl carbamate. The current problem of ethyl carbamate encompasses in particular small distilleries that have not introduced improved technologies (Lachenmeier *et al*., 2005b).

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2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Previous evaluation

Ethyl carbamate was evaluated by an IARC Working Group in February 1974 (IARC, 1974). It was also the subject of a very extensive review (Salmon & Zeise, 1991). Both reviews evaluated bioassays in which mice, rats and hamsters were exposed to ethyl carbamate by oral, dermal, subcutaneous and/or intraperitoneal routes.

Mice treated orally with ethyl carbamate had an increased incidence of lung adenomas, carcinomas and squamous-cell tumours, lymphomas (mainly lymphosarcomas), mammary gland adenocarcinomas and carcinomas, leukaemia and Harderian gland adenomas and angiomas. When oral administration was accompanied by topical application of the tumour promoter 12-*O*-tetradecanoylphorbol-13 acetate (TPA), the incidence of skin papillomas and squamous-cell carcinomas was significantly increased. Rats treated orally with ethyl carbamate had an increased incidence of Zymbal gland and mammary gland carcinomas. Hamsters treated orally with ethyl carbamate showed an increased incidence of skin melanotic tumours, forestomach papillomas, mammary gland adenocarcinomas, liver hepatomas, liver and spleen haemangiomas and carcinomas of the thyroid, ovary and vagina.

Topical application of ethyl carbamate to mice resulted in a significant increase in the incidence of lung adenomas and mammary gland carcinomas.

Subcutaneous administration of ethyl carbamate induced a significant increase in the incidence of lung adenomas in adult mice and hepatomas in newborn mice. When the treatment was followed by topical application of croton oil, a significant increase in the incidence of skin papillomas was observed.

Intraperitoneal administration of ethyl carbamate to adult mice resulted in a significant increase in the incidence of lung adenomas, hepatomas and skin papillomas. Similar treatment in newborn mice induced lymphomas, lung adenomas, hepatomas, Harderian gland tumours and stromal and epithelial tumours of the ovary.

Mice exposed transplacentally to ethyl carbamate developed an increased incidence of lung tumours, hepatomas and ovarian tumours.

Subsequent bioassays are summarized below.

3.1 Oral administration

3.1.1 *Mouse*

Groups of 50 male B6C3F$_1$ mice, 6 weeks of age, were given 0, 0.6, 3, 6, 60 or 600 ppm ethyl carbamate (> 99% pure) in the drinking-water for 70 weeks. Mice that survived more than 23 weeks were included in the analysis of tumours (i.e. effective number of mice). The effective number of mice was 49, 49, 48, 50, 50 and 44 for the 0-, 0.6-, 3-, 6-, 60- and 600-ppm ethyl carbamate dose groups, respectively. The mean survival of the 600-ppm dose group was significantly shorter than that of the control group (39.2 weeks versus 69.5 weeks, respectively; $P < 0.01$, Student's *t*-test). The other groups had mean survival times of ≥ 65.5 weeks. All mice were autopsied and histological examinations were conducted. Ethyl carbamate caused dose-related increases in the incidence of lung alveolar/bronchiolar adenomas and carcinomas, liver haemangiomas and angioasarcomas and heart haemangiomas. The incidence of lung alveolar/bronchiolar adenoma was 9/49 (18%), 4/49 (8%), 7/48 (15%), 8/50 (16%), 34/50 (68%) and 42/44 (95%) for the 0-, 0.6-, 3-, 6-, 60- and 600-ppm ethyl carbamate-treated groups, respectively; the increase at 60 and 600 ppm ethyl carbamate was significant ($P < 0.01$) compared with the control group. Lung alveolar/bronchiolar carcinoma was only observed in the 600-ppm ethyl carbamate-treated group (6/44; 14%), an incidence that was significant. Liver haemangioma occurred in the 60- and 600-ppm ethyl carbamate-treated groups (2/50 (4%) and 20/44 (45%), respectively), and the increase in the 600-ppm group was significant ($P < 0.01$). Liver angiosarcoma developed in the 6-, 60- and 600-ppm ethyl carbamate-treated groups at incidences of 2/50 (4%), 2/50 (4%) and 11/44 (25%), respectively; the latter was a significant increase compared with the control group ($P < 0.01$). Heart haemangioma occurred only in the mice treated with 600 ppm ethyl carbamate (4/44; 9%), an incidence that was significant ($P < 0.05$) (Inai *et al*., 1991).

Groups of 48 male and 48 female B6C3F$_1$ mice, 4 weeks of age, were given 0, 10, 30 or 90 ppm ethyl carbamate (> 99% pure) in the drinking-water for 104 weeks. The administration of ethyl carbamate caused a dose-dependent decrease in survival in both male and female mice, and the effect was significant at 30 and 90 ppm ethyl carbamate. Complete necropsies were performed on all mice and histological examinations were conducted. The incidence of tumours in males treated with 0-, 10-, 30- and 90-ppm, respectively, was: lung alveolar/bronchiolar adenomas or carcinomas, 5/48 (10%), 18/48 (37%), 29/47 (62%) and 37/48 (77%) (the increases at 10, 30 and 90 ppm ethyl carbamate were significant; $P < 0.05$); hepatocellular adenomas or carcinomas, 12/46 (26%), 18/47 (38%), 24/46 (52%) and 23/44 (52%) (the increases at 30 and

90 ppm ethyl carbamate were significant; $P < 0.05$); liver haemangiosarcomas, 1/46 (2%), 2/47 (4%), 5/46 (11%) and 13/44 (29%) (the increase at 90 ppm ethyl carbamate was significant; $P < 0.05$); Harderian gland adenomas or carcinomas, 3/47 (6%), 12/47 (25%), 30/47 (64%) and 38/47 (81%) (the increases at all three doses were significant; $P < 0.05$); skin squamous-cell papillomas or carcinomas, 0/47, 1/48 (2%), 3/47 (6%) and 6/48 (12%) (the increase at 90 ppm ethyl carbamate was significant; ($P < 0.05$); forestomach squamous-cell papillomas, 0/46, 2/47 (14%), 3/44 (7%) and 5/45 (11%) (the increase at 90 ppm ethyl carbamate was significant; $P < 0.05$); and heart haemangiosarcomas, 0/48, 0/48, 1/47 (2%) and 5/48 (10%) (the increase at 90 ppm ethyl carbamate was significant; $P < 0.05$). The incidence of tumours in female mice treated with 0-, 10-, 30- and 90-ppm, respectively, was: lung alveolar/bronchiolar adenomas or carcinomas, 6/48 (12%), 8/48 (17%), 28/48 (53%) and 39/47 (83%) (increases at 30 and 90 ppm ethyl carbamate were significant; $P < 0.05$); hepatocellular adenomas or carcinomas, 5/48 (10%), 11/47 (23%), 20/47 (43%) and 19/47 (40%) (the increases at 30 and 90 ppm ethyl carbamate were significant; $P < 0.05$); liver haemangiosarcoma, 0/48, 0/47, 1/47 (2%) and 7/47 (15%) (the increase at 90 ppm ethyl carbamate was significant; $P < 0.05$); mammary gland adenocarcinomas, 4/47 (8%), 3/46 (6%), 3/46 (6%) and 11/48 (23%) (the increase at 90 ppm ethyl carbamate was significant; $P < 0.05$); mammary gland adenoacanthomas, 0/47, 1/46 (2%), 1/46 (2%) and 11/48 (23%) (the increase at 90 ppm ethyl carbamate was significant; $P < 0.05$); Harderian gland adenomas or carcinomas, 3/48 (6%), 11/48 (23%), 19/48 (40%) and 30/48 (62%) (the increases at all three doses were significant; $P < 0.05$); and ovary granulosa-cell tumours, 0/48, 0/46, 2/46 (4%) and 5/39 (13%) (the increase at 90 ppm ethyl carbamate was significant; $P < 0.05$) (National Toxicology Program, 2004; Beland *et al*., 2005).

A study was conducted to compare the carcinogenicity of ethyl carbamate in mice that are proficient and deficient in cytochrome-P450 (CYP) 2E1. Groups of 28–30 male *Cyp2e1*+/+ and *Cyp2e1*–/– mice, 5–6 weeks of age, were administered by gavage 0, 1, 10 or 100 mg/kg body weight (bw) ethyl carbamate (purity, > 98%) once a day on 5 days per week for 6 weeks. The ethyl carbamate was dissolved in water and administered in a volume of 10 mL/kg bw. Twenty-four hours after the last treatment, 14–15 mice per group were killed. The remaining 14–15 mice per group were held for 7 months. Complete gross necropsy and microscopic examination were performed on all mice. Seven months after the end of treatment, liver tumours (haemangiomas and haemangiosarcomas) were observed in male *Cyp2e1*+/+ mice treated with 100 mg/kg bw ethyl carbamate (5/15 (33%) and 8/15 (53%) compared with 0/14 and 0/14, respectively, in control male *Cyp2e1*+/+ mice). The increased incidence was significant ($P < 0.05$ and < 0.01, respectively). Liver haemangioma was detected in a single *Cyp2e1*–/– mouse (1/15; 7%) treated with 100 mg/kg bw ethyl carbamate. The difference in the incidence of liver haemangiosarcomas was significant when *Cyp2e1*+/+ mice were compared with *Cyp2e1*–/– mice treated with 100 mg/kg bw ethyl carbamate (8/15 (53%) versus 0/15; $P = 0.0011$); the difference in the incidence of liver haemangioma was marginally significant (5/15 (33%) versus 1/15 (7%); $P = 0.0843$). In male *Cyp2e1*+/+ mice,

the incidence of bronchioalveolar adenoma was 0/14, 3/14 (21%), 14/14 (100%) and 14/15 (93%) in the control, low-dose, mid-dose and high-dose groups, and tumour multiplicities were 0, 1.0, 2.5 and 15.4 tumours/lung, respectively. The incidence of bronchioalveolar adenoma was significantly increased with doses of 10 and 100 mg/kg bw ethyl carbamate ($P < 0.01$) and there was a significant variation in the tumour multiplicity across doses ($P < 0.0001$). In the respective groups of male *Cyp2e1–/–* mice, the incidence of bronchioalveolar adenoma was 0/15, 0/15, 4/14 (29%) and 9/15 (60%), and tumour multiplicities were 0, 0, 1.0 and 2.4 tumours/lung. The incidence of bronchioalveolar adenoma was significantly increased with doses of 10 and 100 mg/kg bw ethyl carbamate ($P < 0.05$ and < 0.01; respectively). The difference in the incidence of bronchioalveolar adenoma was significant when *Cyp2e1+/+* mice were compared with *Cyp2e1–/–* mice treated with 10 and 100 mg/kg bw ethyl carbamate ($P = 0.0001$ and 0.04, respectively). The difference in the multiplicity of bronchioalveolar adenoma was also significant when *Cyp2e1+/+* mice were compared with *Cyp2e1–/–* mice treated with 10 and 100 mg/kg bw ethyl carbamate ($P = 0.0145$ and < 0.0001, respectively). A single case of bronchioalveolar carcinoma was detected in a *Cyp2e1+/+* mouse treated with 100 mg/kg bw ethyl carbamate. In male *Cyp2e1+/+* mice, the incidence of Harderian gland adenoma was 1/14 (7%), 4/14 (29%), 14/14 (100%) and 13/15 (87%) in control, low-dose, mid-dose and high-dose groups, respectively, and was significantly increased at 10 and 100 mg/kg bw ethyl carbamate ($P < 0.01$). That in male *Cyp2e1–/–* mice was 0/15, 1/15 (7%), 2/14 (14%) and 12/15 (80%), respectively and was significantly increased with the dose of 100 mg/kg bw ethyl carbamate ($P < 0.01$). The difference in the incidence of Harderian gland adenoma was significant when *Cyp2e1+/+* mice were compared with *Cyp2e1–/–* mice treated with 10 mg/kg bw ethyl carbamate ($P < 0.0001$) (Ghanayem, 2007).

3.1.2 *Monkey*

A group of neonatal cynomologus, rhesus and/or African green monkeys [sex, number and distribution not specified] was administered 250 mg/kg bw ethyl carbamate [purity not specified] orally in sterile water [volume not specified] on 5 days per week for 5 years. Thirty-two monkeys survived the first 6 months of treatment, at which time they typically were weaned. Some of the monkeys also received 7–10 weekly courses of whole-body radiation (50 rad per course). None of the monkeys survived after 5 years of treatment. Complete necropsies were performed on all animals. Six of the 32 (19%) monkeys developed one or more primary tumours. The tumours included adenocarcinoma of the lung, pancreas, bile ducts and small intestine, hepatocellular adenoma and carcinoma, haemangiosarcoma of the liver, ependymoma, pheochromocytoma, endocervical adenofibroma and squamous papilloma of the pouch. The specific incidences were not reported. Only two of the six (33%) monkeys that had malignant tumours had been irradiated. A concurrent control group did not appear to be included. Autopsy records were available for 373 breeders and ‘normal controls’.

Nineteen of these monkeys developed malignant and/or benign tumours. While some tumours occurred in both untreated and ethyl carbamate-treated monkeys (e.g. adenocarcinoma of the pancreas and intestine), hepatocellular adenoma and carcinoma and adenocarcinoma of the lung were only found in ethyl carbamate-treated monkeys (Thorgeirsson *et al*., 1994). [The Working Group noted the poor design and reporting of the study.]

3.2 Skin application

Mouse

A study was conducted to determine whether or not ethyl carbamate would act as an enhancer of skin carcinogenesis induced by 7,12-dimethylbenz[*a*]anthracene (DMBA). A group of 16 male and 16 female hairless *hr/hr* Oslo mice [age not specified] was treated topically once with 51.2 μg DMBA [purity not specified] in 100 μL acetone and were observed for 60 weeks. An additional group of the same number of mice was treated identically with DMBA and then, after a 2-week period, were treated topically twice a week for 50 weeks with 100 μL of a solution of 10% ethyl carbamate [purity not specified] in acetone. An additional group of the same number of mice was not treated with DMBA, but was treated with ethyl carbamate for a period of 60 weeks. Gross necropsies and histology were performed. Tumour rates (the percentage of tumour-bearing mice in relation to the number of mice alive at the appearance of the first tumour related to time) and yields (the cumulative occurrence of all skin tumours related to time) were analysed statistically. Mice treated with DMBA alone had a total of 21 skin tumours (primarily papillomas, but also carcinomas and atypical keratoacanthomas) in 11 mice and no lung adenomas; mice treated with ethyl carbamate alone had a total of eight skin tumours in five mice and 79 lung adenomas in 22 mice; and mice treated with DMBA and ethyl carbamate had a total of 60 skin tumours in 16 mice and 121 lung adenomas in 23 mice. Treatment with DMBA and ethyl carbamate induced a significantly higher number of skin tumours than treatment with DMBA alone (Iversen, 1991).

3.3 Inhalation exposure

Mouse

Groups of female JCL:ICR mice [number per group not specified], 28 days of age, were exposed to air containing 0.25 μg/mL ethyl carbamate [purity not specified] for 1, 3, 5 or 10 days or air containing 1.29 μg/mL ethyl carbamate for 0.25, 1, 2, 4 or 5 days. Groups of male JCL:ICR mice, 28 days of age, were exposed to air containing 0.25 μg/mL ethyl carbamate for 10 days (50 mice) or air containing 1.29 μg/mL

ethyl carbamate for 4 days (47 mice). Concurrent controls were exposed to air only. Female mice were killed 5 months after the exposure period and male mice were killed 12 months after the exposure period. Histological analyses were performed. Female mice exposed by inhalation to 0.25 μg/mL ethyl carbamate had a lung tumour incidence [tumour type not specified] and tumour multiplicity (tumours per lung) of 27/51 (53%) and 1.08 ± 0.39 (mean ± 95% confidence interval [CI]) after exposure for 1 day, 44/51 (86%) and 5.29 ± 1.28 after exposure for 3 days, 46/53 (87%) and 7.56 ± 2.05 after exposure for 5 days and 9/11 (82%) and 17.8 ± 4.6 after exposure for 10 days. In each of the exposed groups, the lung tumour incidence [$P < 0.0001$; one-tailed Fisher's exact test] and tumour multiplicity ($P < 0.05$) were significantly increased compared with the concurrent control group, which had values of 2/51 (4%) and 0.04, respectively. Female mice exposed by inhalation to 1.29 μg/mL ethyl carbamate had a lung tumour incidence [tumour type not specified] and tumour multiplicity of 38/79 (48%) and 0.67 ± 0.20 after exposure for 0.25 days, 37/40 (92%) and 10.7 ± 2.9 after exposure for 1 day, 66/70 (94%) and 18.6 ± 3.8 after exposure for 2 days, 81/86 (94%) and 10.6 ± 2.6 after exposure for 4 days and 18/18 (100%) and 12.2 ± 3.9 after exposure for 5 days. In each of the exposed groups, the lung tumour incidence [$P < 0.0001$; one-tailed Fisher's exact test] and tumour multiplicity ($P < 0.05$) were significantly increased compared with the concurrent control group, which had values of 2/51 (4%) and 0.04, respectively. Male mice exposed by inhalation to 0.25 μg/mL ethyl carbamate for 10 days had a lung adenocarcinoma incidence of 40/50 (80%), of which 11 (22%) showed signs of invasion or metastasis. Male mice exposed by inhalation to 1.29 μg/mL ethyl carbamate for 4 days had a lung adenocarcinoma incidence of 14/40 (35%). This group was composed of 47 mice, of which seven died within 7 days of being treated. In each of the exposed groups, the lung adenocarcinoma incidence was significantly increased ($P < 0.01$) compared with the control group, which had an incidence of 1/51 (2%). [The Working Group questioned the high incidence of adenocarcinomas associated with high survival.] The incidence of leukaemia in female mice exposed by inhalation to 0.25 μg/mL ethyl carbamate was 3/51 (6%) after exposure for 1 day, 2/51 (4%) after exposure for 3 days, 5/53 (9%) after exposure for 5 days and 0/11 after exposure for 10 days. The incidence of leukaemia in mice exposed for 5 days was significantly greater [$P = 0.0312$; one-tailed Fisher's exact test] than that in concurrent controls, which had an incidence of 0/51. Female mice exposed by inhalation to 1.29 μg/mL ethyl carbamate had an incidence of leukaemia of 2/79 (2%) after exposure for 0.25 days, 1/40 (2%) after exposure for 1 day, 12/70 (17%) after exposure for 2 days, 18/86 (21%) after exposure for 4 days and 3/18 (17%) after exposure for 5 days. The incidence in mice in each of the groups exposed for 2 or more days was significantly greater [$P \leq 0.0156$; one-tailed Fisher's exact test] than that in the concurrent control group, which had an incidence of 0/51. The incidence of leukaemia in male mice exposed by inhalation to 0.25 μg/mL ethyl carbamate for 10 days was 5/50 (10%). Male mice exposed by inhalation to 1.29 μg/mL ethyl carbamate for 4 days had an incidence of 8/40 (20%). In each of the exposed groups, the incidence of leukaemia was significantly increased [$P \leq 0.0264$;

one-tailed Fisher's exact test] compared with the control group, which had an incidence of 0/51. The incidence of uterine haemangioma in female mice exposed by inhalation to 1.29 μg/mL ethyl carbamate was 0/79 after exposure for 0.25 days, 1/40 (2%) after exposure for 1 day, 2/70 (3%) after exposure for 2 days, 8/86 (9%) after exposure for 4 days and 0/18 after exposure for 5 days. The incidence of uterine haemangioma in mice exposed for 4 days was significantly greater [$P = 0.0212$; one-tailed Fisher's exact test] than that in the concurrent control group, which had an incidence of 0/51. A single uterine haemangioma 1/51 (2%) was also observed in female mice exposed to 0.25 μg/mL ethyl carbamate for 3 days. The incidence of hepatoma in male mice exposed by inhalation to 0.25 μg/mL ethyl carbamate for 10 days was 6/50 (12%). In male mice exposed by inhalation to 1.29 μg/mL ethyl carbamate for 4 days, the incidence of hepatoma was 3/40 (7%). The incidence of hepatoma in the mice exposed to 0.25 μg/mL ethyl carbamate was marginally increased [$P = 0.0529$; one-tailed Fisher's exact test] compared with the control group, which had an incidence of 1/51 (2%) (Nomura *et al*., 1990).

3.4 Other exposures

3.4.1 *Pre-conception*

Mouse

A study was conducted to investigate whether pre-conception exposure of sperm cells to ethyl carbamate resulted in an increased risk for cancer in either untreated progeny or progeny treated with ethyl carbamate. Groups of 45 male CBA/JNCrj mice, 9 weeks of age, received two subcutaneous injections of 10 μL/g bw saline or 10 μL/g bw saline that contained 500 μg/kg bw ethyl carbamate (purity, > 99%) at a 24-hour interval. At 1, 3 and 9 weeks after treatment (i.e. at different stages of spermatogenesis), each male mouse was mated for 4 days with three untreated virgin 12-week-old female CBA/JNCrj mice. When the progeny were 6 weeks of age, one half was treated once with a subcutaneous injection of 10 μL/g bw saline and the other half was treated with 10 μL/g bw saline that contained 100 μg/kg bw ethyl carbamate. The mice were then kept for lifetime. The mean lifetime for the male mice, including the parental males, was 80–91 weeks, and that for the female mice, including the parental females, was 87–94 weeks. Statistical analyses indicated only sporadic differences in survival when ethyl carbamate-treated groups were compared with their appropriate control groups. Complete necropsies and histological examinations were conducted on all animals. Paternal treatment with ethyl carbamate caused a significant increase (98%) in the incidence of lung tumours (bronchioloalveolar adenomas and adenocarcinomas) in parental male mice compared with 22% in the 45 controls. Male F_1 mice treated with saline had a lung tumour incidence of 17–24% (71–135 mice per group); those treated with ethyl carbamate had a lung tumour incidence of 43–60% (83–124 mice per group). Paternal treatment had no consistent effect on lung-tumour incidence in

male F_1 mice. Male F_1 mice treated with ethyl carbamate had a significantly increased incidence of lung tumours [$P \leq 0.0004$; one-tailed Fisher's exact test], irrespective of the paternal treatment. Female F_1 mice treated with saline had a lung tumour incidence of 11–24% (59–111 mice per group) compared with 32–43% (81–104 mice per group) in those treated with ethyl carbamate. Paternal treatment with ethyl carbamate had no effect on the incidence of lung tumours in female F_1 mice. Female F_1 mice treated with ethyl carbamate had a significantly increased lung-tumour incidence [$P \leq 0.0168$; one-tailed Fisher's exact test], irrespective of the paternal treatment, with the exception of mice resulting from the 3-week mating of ethyl carbamate-treated F_0 male mice, which may be a spurious result. Paternal treatment with ethyl carbamate caused a significant increase (76%) in the incidence of liver tumours (hepatocellular adenomas and adenocarcinomas) in the parental male mice, compared with 53% in the 45 controls. Male F_1 mice treated with saline had a liver-tumour incidence of 54–66% compared with those treated with ethyl carbamate (56–70%). Paternal treatment with ethyl carbamate had no effect on the liver-tumour incidence in male F_1 mice. The incidence of liver tumours in male F_1 mice treated with ethyl carbamate did not differ from that in mice treated with saline, irrespective of the paternal treatment. Female F_1 mice treated with saline had a liver-tumour incidence of 2–7%; those treated with ethyl carbamate had a lung tumour incidence of 2–12%. Paternal treatment with ethyl carbamate had no consistent effect on lung-tumour incidence in female F_1 mice. Treatment of female F_1 mice with ethyl carbamate had no consistent effect on the incidence of liver tumours. Lymphomas and histocytic sarcomas occurred in both F_0 male mice (7%) and their F_1 offspring (5–14% in males; 11–20% in females). The haematopoietic tumour incidence was not affected by treatment with ethyl carbamate in either the F_0 male mice or their F_1 offspring of either sex (Mohr *et al*., 1999).

Male Swiss Cr:NIH(S) mice, 6 weeks of age [number not specified], received a single intraperitoneal injection of distilled water [volume not specified] or distilled water that contained 1.5 g/kg bw ethyl carbamate [purity not specified]. Two weeks later, each male mouse was housed with five 8-week-old female mice for an unspecified period of time. This timing was selected to ensure that the sperm used in fertilization would have been exposed postmeiotically, a stage of high sensitivity to pre-conception carcinogenic effects. Three weeks later, female mice that were visibly pregnant were housed individually and allowed to give birth. The offspring were weaned at 4 weeks. The experiment lasted until the last animal died, which was approximately 157 weeks after birth. Seventy-one per cent of the female mice placed with control male mice became pregnant. For the carcinogenesis study, 71 female offspring, arising from 23 litters, and 48 male offspring, arising from 14 litters, were used. These litters were the product of 11 sires. Sixty-six percent of the female mice placed with ethyl carbamate-treated male mice became pregnant. For the carcinogenesis study, 78 female offspring, arising from 20 litters, and 54 male offspring, arising from 20 litters, were used. These litters were the product of 12 sires. Paternal treatment with ethyl carbamate resulted in the induction of adrenal gland tumours in both the male and female offspring. The

incidence was 6/132 (5%), of which five were pheochromocytomas and one was a cortical adenoma. These tumours were not detected in the offspring (0/119) of control male mice that had been treated with distilled water. The increase in the incidence of both pheochromocytomas ($P = 0.039$) and total adrenal gland tumours [$P = 0.020$; one-tailed Fisher's exact test] was significant. Treatment with ethyl carbamate resulted in the induction of glandular stomach tumours in the male offspring. In the 54 male experimental mice, 10 (18%) glandular stomach lesions developed, of which three (6%) were adenomas, three were carcinomas and four (7%) were atypical hyperplasias. In the 48 male control mice, two (4%) adenomas developed. The increase in the incidence of combined neoplastic and non-neoplastic lesions was significant ($P = 0.024$) (Yu *et al*., 1999).

3.4.2 *Transplacental exposure*

Mouse

A group of 25 pregnant Swiss Webster mice, 10 weeks of age, received a single intravenous injection of 3.3 mmol/kg bw ethyl carbamate [purity not specified] in 250 μL phosphate-buffered saline on gestational day 14. A control group of 22 pregnant female mice of the same age received two injections (250 and 100 μL) of the phosphate-buffered saline only. An additional group of 30 virgin female mice was treated with 3.3 mmol/kg bw ethyl carbamate in phosphate-buffered saline and a further group of 29 virgin female mice was injected with phosphate-buffered saline alone. All injections were followed by a 'chaser' injection of 100 μL phosphate-buffered saline. Six months after the pregnant mice gave birth, the dams, their offspring and the virgin female mice were killed to determine lung-tumour incidence by gross analysis of the lungs. One control dam died before the scheduled killing. Survival in the offspring was not indicated. The incidence of lung adenomas in 21 control dams was 28.6%, with a tumour multiplicity of 0.33 tumours per mouse. The comparable values in the 96 male and 72 female offspring were 10.4% and 0.12 tumour per mouse and 16.6% and 0.19 tumour per mouse, respectively. The incidence of lung adenomas in 20 dams treated with ethyl carbamate was 95.0%, with a tumour multiplicity of 10.5 tumours per mouse. The comparable values in the 90 male and 70 female offspring were 45.0% and 0.96 tumour per mouse and 57.1% and 1.3 tumours per mouse, respectively. The incidence of lung adenomas in 29 control virgin females was 44.8%, with a tumour multiplicity of 0.75 tumour per mouse. The comparable values for 30 virgin females treated with ethyl carbamate were 100% and 6.2 tumours per mouse (Neeper-Bradley & Conner, 1992).

3.5 Metabolites of ethyl carbamate

Previous evaluation

During the review of ethyl carbamate by a previous IARC Working Group (IARC, 1974), the carcinogenicity of ethyl carbamate metabolites was considered briefly. The Working Group concluded that ethyl carbamate needed metabolism to exert its carcinogenicity. Bioassays have been conducted on several oxidized metabolites of ethyl carbamate, and these are summarized below.

3.5.1 *Oral administration*

Mouse

Groups of 20 or 25 male and 20 or 25 female Swiss mice, 2–3 months of age, were given a single oral dose of 25 mg ethyl carbamate [purity not specified] or 25 mg *N*-hydroxyethyl carbamate [purity not specified] in distilled water [volume not specified]. A control group of 46 mice remained untreated. Four days after the initial treatment, all groups received twice-weekly dermal applications of 5% croton oil in liquid paraffin [volume not specified]. The incidence and multiplicity of skin tumours were assessed after 20 and 40 weeks of croton-oil application; those of lung tumours were assessed after 40 weeks of croton-oil application. Histopathology was conducted on the lungs. Survival was ≥ 90% after 20 weeks and ≥ 80% after 40 weeks of croton oil application. After 20 weeks, the incidence and multiplicity (± standard deviation [SD]) of skin tumours were 16/18 (89%) and 1.5 ± 0.2 for mice treated with 25 mg ethyl carbamate and 12/25 (48%) and 0.7 ± 0.2 for mice treated with 25 mg *N*-hydroxyethyl carbamate versus 3/45 (7%) and 0.07 ± 0.05 for mice treated with croton oil only. The skin tumour incidence [$P \leq 0.0001$; one-tailed Fisher's exact test] and tumour multiplicity [$P < 0.001$; one-way ANOVA followed by SNK test] in each of the treatment groups were significantly increased compared with the croton oil control mice. The skin tumour incidence [$P = 0.0088$; two-tailed Fisher's exact test] and tumour multiplicity [$P < 0.001$; one-way ANOVA followed by SNK test] in mice treated with 25 mg ethyl carbamate were significantly greater than those in mice treated with the approximately equimolar amount of 25 mg *N*-hydroxyethyl carbamate. After 40 weeks of croton oil application, the incidence and multiplicity (± SD) of skin tumours were 16/18 (89%) and 1.6 ± 0.3 for mice treated with 25 mg ethyl carbamate and 19/20 (95%) and 1.5 ± 0.3 for mice treated with 25 mg *N*-hydroxyethyl carbamate versus 11/44 and 0.4 ± 0.1 for mice treated with croton oil only. The skin-tumour incidence [$P < 0.0001$; one-tailed Fisher's exact test] and tumour multiplicity [$P < 0.001$; one-way ANOVA followed by SNK test] in each of the treatment groups were significantly increased compared with the croton-oil control mice. After 40 weeks of croton-oil application, the incidence and multiplicity (± standard deviation) of lung tumours were 12/18 (67%) and 3.4 ± 1.3 for mice treated with 25 mg ethyl carbamate and 9/20 (45%) and 0.75 ± 0.3 for mice

treated with 25 mg *N*-hydroxyethyl carbamate versus 2/42 (5%) and 0.05 ± 0.03 for mice treated with croton oil only. The lung-tumour incidence [$P \leq 0.0003$; one-tailed Fisher's exact test] and tumour multiplicity [$P < 0.001$; one-way ANOVA followed by SNK test] in each of the treatment groups were significantly increased compared with the croton-oil control mice. The tumour multiplicity in mice treated with 25 mg ethyl carbamate was significantly greater than that in mice treated with the approximately equimolar amount of 25 mg *N*-hydroxyethyl carbamate [$P < 0.001$; two-tailed Fisher's exact test] (Berenblum *et al*., 1959).

3.5.2 *Dermal application*

Mouse

Groups of 40 female CD-1 mice, 6–8 weeks of age, were pretreated topically on the shaved back with 1.2 mg croton oil in 200 μL redistilled acetone. Eighteen to 24 hours later, each mouse was treated topically with 5 or 60 mg ethyl carbamate (> 99% pure by gas chromatography) or 5 mg vinyl carbamate (melting-point, 53–54°C; purity verified by elemental analysis, MS, infrared and nuclear magnetic resonance spectroscopy) in 200 μL acetone or the solvent alone. The application of the carbamate compounds or solvent was repeated 1 week later. One week after the second application, all mice were treated twice weekly with 900 μg croton oil in 150 μL acetone. The negative controls received the croton oil pre- and post-treatment, but were given the vehicle only with no carbamate. The experiment lasted 32 weeks, at which time ≥ 88% of the mice were still alive. All animals were subjected to gross necropsy. The lungs were fixed in formalin, and adenomas on the surface (≥ 1 mm in diameter) were counted. Representative tumours were fixed, sectioned and stained with haematoxylin and eosin. The incidence of skin papillomas and the average number of papillomas per mouse at 29 weeks were 1/40 (2%) and 0 for mice treated with the solvent, 10/40 (25%) and 0.3 for mice treated with a total of 10 mg ethyl carbamate, 19/40 (47%) and 3.4 for mice treated with a total of 120 mg ethyl carbamate and 23/35 (66%) and 4.5 for mice treated with a total of 10 mg vinyl carbamate. The incidence of skin papillomas in each of the treated groups was significantly greater than that in the control group [$P \leq 0.0035$; one-tailed Fisher's exact test]. The incidence of skin papillomas in the 10-mg vinyl carbamate-treated group was significantly greater than that in the approximately equimolar 10-mg ethyl carbamate-treated group [$P = 0.0004$; one-tailed Fisher's exact test]. The incidence of lung adenomas and the average number of lung adenomas per mouse at 32 weeks were 7/40 (17%) and 0.4 for mice treated with the solvent, 17/40 (42%) and 1.0 for mice treated with a total of 10 mg ethyl carbamate, 33/40 (82%) and 8.8 for mice treated with a total of 120 mg ethyl carbamate and 34/35 (97%) and 18.9 for mice treated with a total of 10 mg vinyl carbamate. The incidence of lung adenomas in each of the treated groups was significantly greater than that in the control group [$P \leq 0.0135$; one-tailed Fisher's exact test]. The incidence of lung adenomas in the 10-mg vinyl carbamate-treated

group was significantly greater than that in the approximately equimolar 10-mg ethyl carbamate-treated group [$P < 0.0001$; one-tailed Fisher's exact test] (Dahl *et al*., 1978).

In a second experiment, groups of 30–33 female CD-1 mice, 6–8 weeks of age, were treated topically on the shaved back with 1.2 mg croton oil in 200 μL redistilled acetone. Eighteen to 24 hour later, each mouse was treated topically with 2.5, 5 or 60 mg ethyl carbamate or 2.5 or 5 mg vinyl carbamate in 200 μL acetone or the solvent alone. The application of the carbamate compounds or solvent was repeated 1 week later. One week after the second application, all mice were treated twice weekly with 900 μg croton oil in 150 μL acetone. The experiment lasted 35 weeks, at which time ≥ 90% of the mice were still alive. The incidence of skin papillomas and the average number of papillomas per mouse at 32 weeks were 0/30 and 0 for mice treated with the solvent, 3/30 (10%) and 0.1 for mice treated with a total of 5 mg ethyl carbamate, 4/30 (13%) and 0.2 for mice treated with a total of 10 mg ethyl carbamate, 11/29 and 1.8 for mice treated with a total of 120 mg ethyl carbamate, 14/30 (38%) and 1.8 for mice treated with a total of 5 mg vinyl carbamate and 12/32 (37%) and 2.0 for mice treated with a total of 10 mg vinyl carbamate. The incidence of skin papillomas in the 120-mg ethyl carbamate-treated group and each of the vinyl carbamate-treated groups was significantly greater than that in the control group [$P \leq 0.0001$; one-tailed Fisher's exact test]. The incidence of skin papillomas in each of the vinyl carbamate-treated groups was significantly greater than that in the approximately equimolar ethyl carbamate-treated groups [$P \leq 0.0055$; one-tailed Fisher's exact test]. The incidence of lung adenomas and the average number of lung adenomas per mouse at 35 weeks were 15/27 (55%) and 0.9 for mice treated with the solvent, 13/28 (46%) and 0.9 for mice treated with a total of 5 mg ethyl carbamate, 16/30 (53%) and 1.0 for mice treated with a total of 10 mg ethyl carbamate, 24/29 (83%) and 7.3 for mice treated with a total of 120 mg ethyl carbamate, 27/30 (90%) and 4.5 for mice treated with a total of 5 mg vinyl carbamate and 32/32 (100%) and 12.0 for mice treated with a total of 10 mg vinyl carbamate. The incidence of lung adenomas in the 120-mg ethyl carbamate-treated group and each of the vinyl carbamate-treated groups was significantly greater than that in the control group [$P \leq 0.0268$; one-tailed Fisher's exact test]. The incidence of lung adenomas in each of the vinyl carbamate-treated groups was significantly greater than that in the approximately equimolar ethyl carbamate-treated groups [$P \leq 0.0004$; one-tailed Fisher's exact test] (Dahl *et al*., 1978).

Groups of 30 female CD-1 mice, 6–8 weeks of age, were treated topically on the shaved back with 2.5 μg TPA [purity not specified] in 100 μL acetone. Eighteen to 24 hours later, the mice received 5.8 or 11.5 μmol vinyl carbamate [purity not specified] or 5.8 or 11.5 μmol vinyl carbamate epoxide [purity not specified] in 200 μL acetone that contained 15% dimethyl sulfoxide (DMSO). The application of the vinyl carbamate and vinyl carbamate epoxide was repeated at weekly intervals for a total of five applications. This was then followed by twice weekly topical applications of 2.5 μg TPA in 100 μL acetone. Control mice were administered the solvent and TPA only. The experiment was terminated 22 weeks after the first application of vinyl carbamate

and vinyl carbamate epoxide. At this time, 95–100% of the mice were still alive. The average number of papillomas per mouse (± SD), as determined by gross examination, was 6.5 ± 5.2 for 5.8 μmol vinyl carbamate-treated, 10.5 ± 8.4 for 11.5 μmol vinyl carbamate-treated, 13.3 ± 9.2 for 5.8 μmol vinyl carbamate epoxide-treated, 13.8 ± 9.0 for 11.5 μmol vinyl carbamate epoxide-treated and 0.1 ± 0.3 for the solvent control animals. The average number of papillomas per mouse was significantly greater in each of the treated groups compared with the control group [$P < 0.001$; one-way ANOVA followed by SNK test] and significantly greater in the 5.8-μmol vinyl carbamate epoxide-treated group compared with the 5.8-μmol vinyl carbamate-treated group [$P < 0.001$; one-way ANOVA followed by SNK test] (Park *et al*., 1993).

In a second experiment, groups of 30 female CD-1 mice, 6–8 weeks of age, were treated topically on the shaved back with 2.5 μg TPA in 100 μL acetone. Eighteen to 24 hours later, the mice received applications of 1.15 or 11.5 μmol vinyl carbamate or 1.15 or 11.5 μmol vinyl carbamate epoxide in 200 μL acetone that contained 15% DMSO. Beginning 1 week after the treatment with vinyl carbamate or vinyl carbamate epoxide, the mice received twice-weekly topical applications of 2.5 μg TPA in 100 μL acetone. Control mice were given the solvent or TPA only. The experiment ended 22 weeks after the first application of vinyl carbamate and vinyl carbamate epoxide. At this time, 97–100% of the mice were still alive. The incidence of papillomas and the average number of papillomas per mouse (± SD), as determined by gross examination, were 56% and 0.9 ± 1.1 for 1.15 μmol vinyl carbamate-treated, 98% and 7.8 ± 5.1 for 11.5 μmol vinyl carbamate-treated, 93% and 5.2 ± 3.5 for 1.15 μmol vinyl carbamate epoxide-treated, 100% and 9.8 ± 4.7 for 11.5 μmol vinyl carbamate epoxide-treated and 7% and 0.07 ± 0.2 for the solvent control animals. The incidence of papillomas was significantly greater in each of the treated groups compared with the controls [$P < 0.0001$; one-tailed Fisher's exact test] and significantly greater in the 1.15-μmol vinyl carbamate epoxide-treated group compared with the 1.15-μmol vinyl carbamate-treated group [$P = 0.0011$; one-tailed Fisher's exact test]. With the exception of the group treated with 1.15 μmol vinyl carbamate, the average number of papillomas per mouse was significantly greater in each of the treated groups compared with the controls [$P < 0.05$; one-way ANOVA followed by SNK test]. The average number of papillomas per mouse was significantly greater in the 1.15- and 11.5-μmol vinyl carbamate epoxide-treated groups compared with the 1.15- and 11.5-μmol vinyl carbamate-treated groups, respectively [$P \leq 0.027$; one-way ANOVA followed by SNK test] (Park *et al*., 1993).

In a third experiment, groups of 30 female CD-1 mice [age not specified] were treated topically on the shaved back once a week with vinyl carbamate or vinyl carbamate epoxide in 200 μL acetone that contained 15% DMSO at the following doses: 11.5 μmol at weeks 1 and 2, 5.7 μmol at weeks 3 and 4 and 3.8 μmol from weeks 5 to 32. The mice were kept for an additional 10 weeks after the last treatment. Control mice were given the solvent only. Survival was not indicated. Thirty-two weeks after the first application of vinyl carbamate and vinyl carbamate epoxide, the incidence of papillomas and the average number of papillomas per mouse (± SD), as determined by gross

examination, were 4% and 0.03 ± 0.2 for vinyl carbamate-treated, 96% and 4.6 ± 2.6 for vinyl carbamate epoxide-treated and 0% and 0.0 ± 0.0 for the solvent control animals. The incidence of papillomas [$P < 0.0001$; one-tailed Fisher's exact test] and the average number of papillomas per mouse [$P < 0.001$; one-way ANOVA followed by SNK] in the vinyl carbamate epoxide-treated group were significantly greater than those in both the vinyl carbamate-treated and control groups. Twelve mice that received vinyl carbamate epoxide also had epidermoid carcinomas compared with none in the vinyl carbamate-treated or solvent control groups, a difference that was significant [$P = 0.0001$; one-tailed Fisher's exact test]. Forty-two weeks after the first application of vinyl carbamate and vinyl carbamate epoxide, malignant tumours were detected in both groups (two mammary adenocarcinomas, one lymphoblastic lymphoma, one haemangioma and one epidermoid carcinoma in mice treated with vinyl carbamate and 18 epidermoid carcinomas, four keratoacanthomas, three squamous-cell fibrosarcomas and one thymic lymphoma in mice treated with vinyl carbamate epoxide). None of the control mice had malignant tumours (Park *et al*., 1993).

3.5.3 *Subcutaneous or intramuscular administration*

(a) Mouse

Weanling female albino mice [number not specified] were given a subcutaneous injection of 100 μL water containing 12 mg ethyl carbamate [purity not specified] or equimolar amounts of *N*-hydroxyethyl carbamate [purity not specified]. The treatment was repeated 4 days later. The treatment of the control group was not specified and the effect of treatment upon survival was not indicated. Five months after treatment, the mice were killed and adenomas on the surface of the lung were counted. The number sof lung adenomas observed grossly was 434 in 28 mice treated with ethyl carbamate, 159 in 35 mice administered *N*-hydroxyethyl carbamate and six in 30 control mice (Miller *et al*., 1960).

In a second experiment, weanling female albino mice [number not specified] were treated in a manner identical to that described for the previous experiment. Four and a half months after treatment, the mice were killed and adenomas on the surface of the lung were counted. The number of lung adenomas was 90 in 18 mice treated with ethyl carbamate, 30 in 20 mice administered *N*-hydroxyethyl carbamate and two in an unspecified number of control mice (Miller *et al*., 1960).

Newborn SWR/J mice [age, sex and number not specified], weighing 1.1–1.7 g, were given a single subcutaneous injection of 2 μmol/g bw ethyl carbamate [purity not specified] or *N*-hydroxyethyl carbamate (purified by redistillation) in 50 μL/g bw distilled water. The experiment lasted 10 weeks, at which time the incidence of lung adenomas was assessed. Histology was conducted on questionable tumours. No differences in body weights were observed. Survival was not specified and there was no control group. The mean number of adenomas per mouse (95% CI) was 2.3 (1.8–2.7) in

mice treated with 2 μmol/g bw ethyl carbamate and 0.4 (0.0–0.9) in mice treated with 2 μmol/g bw *N*-hydroxyethyl carbamate (Kaye & Trainin, 1966).

(b) Rat

Groups of 12 female Sprague-Dawley rats [age not specified] were given 10 weekly intramuscular injections in the left hind leg of 250 μL trioctanoin or 250 μL trioctanoin that contained 1.15 or 2.30 μmol vinyl carbamate [purity not specified] or vinyl carbamate epoxide [purity not specified]. At 17–18 months, the incidence of injection-site sarcomas and mammary gland tumours was determined. The incidence of injection-site sarcomas was 0/12 for the 1.15-μmol vinyl carbamate-treated group, 1/11 (9%) for the 1.15-μmol vinyl carbamate epoxide-treated group, 0/12 for the 2.30-μmol vinyl carbamate-treated group, 4/11 (36%) for the 2.30-μmol vinyl carbamate epoxide-treated group and 0/11 for the control group. The incidence of injection-site sarcomas was significantly increased in the 2.30-μmol vinyl carbamate epoxide-treated group compared with the 2.30-μmol vinyl carbamate-treated group and the control group [$P < 0.045$; one-tailed Fisher's exact test]. The incidence and total number of mammary gland tumours were 3/12 (25%) and six for the 1.15-μmol vinyl carbamate-treated group, 1/11 (9%) and three for the 1.15-μmol vinyl carbamate epoxide-treated group, 3/11 (27%) and eight for the 2.30-μmol vinyl carbamate-treated group, 6/11 (54%) and 16 for the 2.30-μmol vinyl carbamate epoxide-treated group and 3/11 (27%) and seven for the control group (Park *et al*., 1993).

3.5.4 *Intraperitoneal administration*

(a) Mouse

Groups of 18–30 male or female Swiss mice, 2–3 months of age, were administered a single intraperitoneal injection of 10 mg ethyl carbamate [0.11 mmol] or 11.8 mg *N*-hydroxyethyl carbamate [0.11 mmol] in saline [volume not specified], or 5 or 25 mg *N*-hydroxyethyl carbamate in distilled water [volume not specified]. A control group of 46 mice remained untreated. Four days after the initial treatment, all groups received twice weekly dermal applications of 5% croton oil in liquid paraffin [volume not specified]. The incidence and multiplicity of skin tumours were assessed after 20 and 40 weeks of croton oil application; those of lung tumours were assessed after 40 weeks of croton oil application. Histopathology was conducted on the lungs. Survival was ≥ 97% after 20 weeks of croton oil application and ≥ 80% after 40 weeks of croton oil application. After 20 weeks of croton oil application, the incidence and multiplicity (± SD) of skin tumours were 14/30 (47%) and 0.6 ± 0.1 for mice treated with 10 mg ethyl carbamate, 3/29 (10%) and 0.1 ± 0.05 for mice treated with 11.8 mg *N*-hydroxyethyl carbamate, 14/20 (70%) and 1.0 ± 0.2 for mice treated with 25 mg *N*-hydroxyethyl carbamate and 4/18 (22%) and 0.3 ± 0.1 for mice treated with 5 mg *N*-hydroxyethyl carbamate versus 3/45 (7%) and 0.07 ± 0.05 for mice treated with

croton oil only. The skin tumour incidence was significantly increased in mice treated with 10 mg ethyl carbamate or 25 mg *N*-hydroxyethyl carbamate compared with the croton oil control mice [$P \leq 0.0001$; one-tailed Fisher's exact test]. The tumour multiplicity was significantly increased in all treatment groups [$P < 0.001$; one-way ANOVA followed by SNK test], with the exception of the mice treated with 11.8 mg *N*-hydroxyethyl carbamate. The incidence [$P = 0.0034$; two-tailed Fisher's exact test] and multiplicity [$P < 0.001$; one-way ANOVA followed by SNK test] of skin tumours in mice treated with 10 mg ethyl carbamate were significantly greater than those in mice treated with 11.8 mg *N*-hydroxyethyl carbamate. After 40 weeks of croton oil application, the incidence and multiplicity (± SD) of skin tumours were 18/30 (60%) and 0.9 ± 0.2 for mice treated with 10 mg ethyl carbamate, 6/28 (21%) and 0.2 ± 0.1 for mice treated with 11.8 mg *N*-hydroxyethyl carbamate, 17/18 (95%) and 1.9 ± 0.2 for mice treated with 25 mg *N*-hydroxyethyl carbamate and 8/18 (44%) and 0.25 ± 0.05 for mice treated with 5 mg *N*-hydroxyethyl carbamate versus 11/44 (25%) and 0.4 ± 0.1 for mice treated with croton oil only. The incidence [$P \leq 0.0026$; one-tailed Fisher's exact test] and multiplicity [$P < 0.001$; one-way ANOVA followed by SNK test] of skin tumours were significantly increased in mice treated with 10 mg ethyl carbamate or 25 mg *N*-hydroxyethyl carbamate compared with the croton oil control mice. The incidence [$P = 0.0037$; two-tailed Fisher's exact test] and multiplicity [$P < 0.001$; one-way ANOVA followed by SNK test] of skin tumours in mice treated with 10 mg ethyl carbamate were significantly greater than those in mice treated with 11.8 mg *N*-hydroxyethyl carbamate. After 40 weeks of croton oil application, the incidence and multiplicity (± SD) of lung tumours were 23/26 (88%) and 2.8 ± 0.5 for mice treated with 10 mg ethyl carbamate, 5/26 (19%) and 0.3 ± 0.1 for mice treated with 11.8 mg *N*-hydroxyethyl carbamate, 11/18 (6%) and 0.8 ± 0.2 for mice treated with 25 mg *N*-hydroxyethyl carbamate and 5/18 (28%) and 0.4 ± 0.1 for mice treated with 5 mg *N*-hydroxyethyl carbamate versus 2/42 (5%) and 0.05 ± 0.03 for mice treated with croton oil only. The lung-tumour incidence was significantly increased in mice treated with 10 mg ethyl carbamate or 25 mg *N*-hydroxyethyl carbamate compared with the croton-oil control mice [$P < 0.0001$; one-tailed Fisher's exact test]. Lung tumour multiplicity was significantly increased in all treatment groups [$P < 0.001$; one-way ANOVA followed by SNK test]. The incidence [$P < 0.0001$; two-tailed Fisher's exact test] and multiplicity [$P < 0.001$; one-way ANOVA followed by SNK test] of lung tumours in mice treated with 10 mg ethyl carbamate were significantly greater than those in mice treated with 11.8 mg *N*-hydroxyethyl carbamate (Berenblum *et al*., 1959).

Groups of 20 female Holtzman mice, 10 weeks of age, received an intraperitoneal injection of 200 µL water that contained 15 mg ethyl carbamate [0.17 mmol; purity not specified] or 17.7 mg *N*-hydroxyethyl carbamate [0.17 mmol; purity not specified]. A second, identical injection was given 4 hours later. After 1 week, the backs of the mice were shaved and 300 µL acetone that contained 0.3% croton oil was applied topically once a week for 18 weeks. There was no control group. After 18 weeks, 12/19 (63%) surviving mice treated with ethyl carbamate had a total of 33 skin papillomas and 9/18

(50%) surviving mice treated with *N*-hydroxyethyl carbamate had a total of 25 skin papillomas. [The incidence did not differ between the groups; $P = 0.3175$, one-tailed Fisher's exact test.] The mice were killed after 22 weeks, at which time 11/19 (58%) surviving mice treated with ethyl carbamate had a total of 57 lung adenomas and eight of 18 surviving mice treated with *N*-hydroxyethyl carbamate had a total of 29 lung adenomas. [The incidence did not differ between the groups; $P = 0.3127$, one-tailed Fisher's exact test] (Miller *et al*., 1960).

Groups of 22–25 female weanling SWR/J mice, 9–10 weeks of age, were given a single intraperitoneal injection of 5 or 10 μmol/g bw ethyl carbamate [purity not stated] or *N*-hydroxyethyl carbamate (purified by redistillation) in distilled water. The ethyl carbamate was administered as a 5 or 10% or 5-mM solution; the *N*-hydroxyethyl carbamate was given as a 5-mM solution. Additional groups that received 10 μmol/g bw ethyl carbamate or *N*-hydroxyethyl carbamate were also given 50 μg/g bw 2-diethylaminoethyl-2,2-diphenylpentanoate hydrochloride (SKF-525A) [purity not specified] dissolved in distilled water at a concentration of 5 mg/mL. Controls received injections of the same volume of 0.9% saline. SKF-525A inhibits the conversion of *N*-hydroxyethyl carbamate to ethyl carbamate. The experiment lasted 10 weeks, at which time the incidence of lung adenomas was assessed. Histology was conducted on questionable tumours. There were no differences in body weights, and survival was ≥ 88%. The incidence of adenomas and the mean number of adenomas per survivor (95% CI) were 57% and 1.0 (0.5–1.6) in mice treated with 5 μmol/g bw ethyl carbamate, 27% and 0.4 (0.1–0.7) in mice treated with 5 μmol/g bw *N*-hydroxyethyl carbamate, 100% and 4.0 (2.9–5.1) in mice treated with 10 μmol/g bw ethyl carbamate, 75% and 1.9 (1.2–2.5) in mice treated with 10 μmol/g bw *N*-hydroxyethyl carbamate, 96% and 4.1 (3.0–5.1) in mice treated with 10 μmol/g bw ethyl carbamate and 50 μg/g bw SKF-525A and 62% and 0.6 (0.4–0.9) in mice treated with 10 μmol/g bw *N*-hydroxyethyl carbamate and 50 μg/g bw SKF-525A. The incidence of adenomas [$P = 0.0127$; two-tailed Fisher's exact test] and mean number of adenomas per survivor in mice treated with 10 μmol/g bw *N*-hydroxyethyl carbamate were significantly lower than those in mice treated with 10 μmol/g bw ethyl carbamate. The mean number of adenomas per survivor in mice treated with 10 μmol/g bw *N*-hydroxyethyl carbamate and 50 μg/g bw SKF-525A was significantly lower than that in mice treated with 10 μmol/g bw *N*-hydroxyethyl carbamate alone (Kaye & Trainin, 1966).

Groups of 40–42 female CD-1 mice, 6–8 weeks of age, were treated topically on the shaved back with 1.2 mg croton oil in 200 μL redistilled acetone. Eighteen to 24 hours later, each mouse received a single intraperitoneal injection of 65 μg/g bw ethyl carbamate (> 99% pure by gas chromatography) or vinyl carbamate (melting point, 53–54°C, purity verified by elemental analysis, MS, infrared and nuclear magnetic resonance spectroscopy) in 5 μL/g bw 0.87% saline or the solvent alone. An additional group received two intraperitoneal injections of 1.0 mg/g bw ethyl carbamate in 5 μL/g bw 0.9% saline at a 1-week interval. One week after the last application, all mice were treated topically twice a week with 900 μg croton oil in 150 μL acetone.

The experiment lasted 28 weeks, at which time ≥ 63% of the mice were still alive. All animals were subjected to gross necropsy. The lungs were fixed in formalin and adenomas on the surface (≥ 1 mm in diameter) were counted. Representative tumours were fixed, sectioned and stained with haematoxylin and eosin. The incidence and the average number of skin papillomas per mouse at 25 weeks were 1/41 (2%) and 0 for mice treated with the solvent, 5/41 (12%) and 0.2 for mice treated with 65 μg/g bw ethyl carbamate, 24/37 (65%) and 5.4 for mice treated with a total of 2 mg/g bw ethyl carbamate and 15/26 (58%) and 3.9 for mice treated with 65 μg/g bw vinyl carbamate. The incidence of skin papillomas in the 2-mg/g bw ethyl carbamate-treated group and the 65-μg/g bw vinyl carbamate-treated group was significantly greater than that in the control group [$P < 0.0001$; one-tailed Fisher's exact test]. The incidence of skin papillomas in the 65-μg/g bw vinyl carbamate-treated group was significantly greater than that in the approximately equimolar 65-μg/g bw ethyl carbamate-treated group [$P = 0.0001$; one-tailed Fisher's exact test]. The incidence and the average number of lung adenomas per mouse at 28 weeks were 4/41 (10%) and 0.2 for mice treated with the solvent, 14/39 (36%) and 0.6 for mice treated with 65 μg/g bw ethyl carbamate, 30/32 (94%) and 28.3 for mice treated with a total of 2 mg/g bw ethyl carbamate and 24/26 (93%) and 19.2 for mice treated with 65 μg/g bw vinyl carbamate. The incidence of lung adenomas in each of the treated groups was significantly greater than that in the control group [$P \leq 0.0051$; one-tailed Fisher's exact test]. The incidence of lung adenomas in the 65-μg/g bw vinyl carbamate-treated group was significantly greater than that in the approximately equimolar 65-μg/g bw ethyl carbamate-treated group [$P < 0.0001$; one-tailed Fisher's exact test] (Dahl *et al*., 1978).

In a second experiment, groups of 20 or 33 female A/Jax mice, 6–8 weeks of age, were given a single intraperitoneal injection of 32 or 65 μg/g bw ethyl carbamate or vinyl carbamate in 5 μL/g bw 0.9% saline or 500 μg/g bw ethyl carbamate in 5 μL 0.9% saline or the solvent alone. The experiment lasted 22 weeks. At this time, survival was ≥ 95% in all groups except for the 65-μg/g bw vinyl carbamate-treated group, in which survival was 65%. The incidence of lung adenomas and the average number of lung adenomas per mouse were 3/20 (15%) and 0.2 for mice treated with the solvent, 15/20 (75%) and 0.8 for mice treated with 32 μg/g bw ethyl carbamate, 17/20 (85%) and 1.7 for mice treated with 65 μg/g bw ethyl carbamate, 19/19 (100%) and 17.4 for mice treated with 500 μg/g bw ethyl carbamate, 33/33 (100%) and 42.3 for mice treated with 32 μg/g bw vinyl carbamate and 13/13 (100%) and 19.1 for mice treated with 65 μg/g bw vinyl carbamate. The incidence of lung adenomas in each of the treated groups was significantly greater than that in the control group [$P \leq 0.0002$; one-tailed Fisher's exact test]. The incidence of lung adenomas in the 32-μg/g bw vinyl carbamate-treated group was significantly greater than that in the approximately equimolar 32-μg/g bw ethyl carbamate-treated group [$P = 0.0054$; one-tailed Fisher's exact test] (Dahl *et al*., 1978).

In a third experiment, groups of 20 or 30 female A/Jax mice, 6–8 weeks of age, received a single intraperitoneal injection of 16, 32 or 65 μg/g bw vinyl carbamate in 5 μL/g bw 0.9% saline or the solvent alone. The experiment lasted 28 weeks. At this time,

survival was ≥ 85% in all groups except for the 65-μg/g bw vinyl carbamate-treated, in which survival was 27%. The incidence of lung adenomas and the average number of lung adenomas per mouse were 5/17 (29%) and 0.4 for mice treated with the solvent, 20/20 (100%) and 20.0 for mice treated with 16 μg/g bw vinyl carbamate, 19/19 (100%) and 35.2 for mice treated with 32 μg/g bw vinyl carbamate and 8/8 (100%) and 21.4 for mice treated with 65 μg/g bw vinyl carbamate. The incidence of lung adenomas in each of the treated groups was significantly greater than that in the control group [$P \leq 0.0012$; one-tailed Fisher's exact test] (Dahl *et al*., 1978).

In a fourth experiment, groups of nine to 20 female A/Jax mice, 6–8 weeks of age, were given five intraperitoneal injections of 10 μg/g bw ethyl carbamate, a single intraperitoneal injection of 500 μg/g bw ethyl carbamate, 10 intraperitoneal injections of 5 μg/g bw vinyl carbamate, five intraperitoneal injections of 10 μg/g bw vinyl carbamate or a single intraperitoneal injection of 16 μg/g bw vinyl carbamate. Multiple injections were given at weekly intervals. The compounds were dissolved in 5 μL/g bw 0.9% saline. The control group received 10 weekly injections of the solvent alone. The experiment lasted 20 weeks and all animals survived. The incidence and the average number of lung adenomas per mouse were 3/14 (21%) and 0.4 for mice treated with the solvent, 15/20 (75%) and 1.2 for mice treated with five injections of 10 μg/g bw ethyl carbamate, 9/9 (100%) and 19.3 for mice treated with a single injection of 500 μg/g bw ethyl carbamate, 19/19 (100%) and 25.2 for mice treated with 10 injections of 5 μg/g bw vinyl carbamate, 20/20 (100%) and 53.2 for mice treated with five injections of 10 μg/g bw vinyl carbamate and 20/20 (100%) and 25.2 for mice treated with a single injection of 16 μg/g bw vinyl carbamate. The incidence of lung adenomas in each of the treated groups was significantly greater than in the control group [$P \leq 0.0028$; one-tailed Fisher's exact test]. The incidence of lung adenomas in the mice that received five injections of 10 μg/g bw vinyl carbamate was significantly greater than that in mice that received five injections of approximately equimolar 10 μg/g bw ethyl carbamate [$P = 0.0236$; one-tailed Fisher's exact test] (Dahl *et al*., 1978).

Male and female C57BL/6J × C3H/HeJ F_1 mice (B6C3F_1 mice) [initial number not specified], 1 day of age, were administered eight twice-weekly intraperitoneal injections of 46, 91, 136 or 5625 nmol/g bw ethyl carbamate [purity not specified], 46, 91 or 136 nmol/g bw vinyl carbamate [purity not specified but assessed by melting-point, infrared spectroscopy, MS, high-performance liquid chromatography and GC] or the solvent (5 μL/g bw 0.9% saline). Most (> 90%) of the mice survived the treatment, and 18–25 mice of each sex from each group were weaned. The study was terminated when the mice were 15–16 months old. All animals were subjected to gross necropsy. All tumours were fixed, sectioned and stained with haematoxylin and eosin. The incidence and multiplicity (± SD) of liver tumours (hepatomas) in male and female mice were, respectively: 6/25 (24%) and 0.2 ± 0.4 and 0/24 and 0.0 ± 0.0 for mice that received the solvent; 14/25 (56%) and 0.8 ± 0.9 and 2/23 (9%) and 0.1 ± 0.3 for mice that received 46 nmol/g bw ethyl carbamate; 22/25 (88%) and 2.5 ± 1.4 and 6/22 (27%) and 0.4 ± 0.9 for mice that received 91 nmol/g bw ethyl carbamate; 22/25 (88%) and 2.5 ± 1.9 and

8/23 (35%) and 0.8 ± 1.6 for mice that received 136 nmol/g bw ethyl carbamate; 9/9 (100%) and 3.1 ± 1.4 and 7/10 (70%) and 4.8 ± 5.1 for mice that received 5625 nmol/g bw ethyl carbamate; 15/19 (79%) and 3.6 ± 3.2 and 16/19 (84%) and 5.9 ± 3.9 for mice that received 46 nmol/g bw vinyl carbamate; 13/14 (93%) and 7.9 ± 9.6 and 17/19 (89%) and 2.5 ± 1.6 for mice that received 91 nmol/g bw vinyl carbamate; and 14/18 (78%) and 6.6 ± 5.8 and 10/12 (83%) and 5.6 ± 6.0 for mice that received 136 nmol/g bw vinyl carbamate. All groups, except for female mice treated with 46 nmol/g bw ethyl carbamate, had an increased multiplicity of hepatomas compared with their respective control groups. Also, equimolar doses of vinyl carbamate increased tumour multiplicity compared with equimolar doses of ethyl carbamate. Thymic lymphomas were only observed with 5625 nmol/g bw ethyl carbamate and 91 and 136 nmol/g bw vinyl carbamate. The incidence in male and female mice was, respectively, 5/17 (29%) and 9/20 (45%) for mice that received 5625 nmol/g bw ethyl carbamate, 3/19 (16%) and 4/21 (19%) for mice that received 91 nmol/g bw vinyl carbamate and 9/23 (39%) and 6/19 (32%) for mice that received 136 nmol/g bw vinyl carbamate. The increased incidence of thymic lymphomas compared with the respective control groups was significant in each of these groups, with the exception of male mice treated with 91 nmol/g bw vinyl carbamate. The incidence of thymic lymphomas in male and female mice treated with 136 nmol/g bw vinyl carbamate and female mice treated with 91 nmol/g bw vinyl carbamate was also significantly greater than that in the respective groups treated with an equimolar dose of ethyl carbamate. The incidence of lung adenomas in male and female mice was, respectively: 1/25 (4%) and 0/25 for mice that received the solvent; 0/25 and 2/24 (8%) for mice that received 46 nmol/g bw ethyl carbamate; 4/25 (16%) and 4/22 (22%) for mice that received 91 nmol/g bw ethyl carbamate; 2/25 (8%) and 6/23 (26%) for mice that received 136 nmol/g bw ethyl carbamate; 5/17 (29%) and 9/20 (45%) for mice that received 5625 nmol/g bw ethyl carbamate; 10/19 (53%) and 15/19 (79%) for mice that received 46 nmol/g bw vinyl carbamate; 15/19 (79%) and 16/21 (76%) for mice that received 91 nmol/g bw vinyl carbamate; and 10/23 (43%) and 10/19 (53%) for mice that received 136 nmol/g bw vinyl carbamate. All groups treated with vinyl carbamate (males and females combined) and the group treated with 5625 nmol/g bw ethyl carbamate had an increased incidence of lung adenomas compared with the control group. Also, equimolar doses of vinyl carbamate increased lung tumour incidence compared with equimolar doses of ethyl carbamate. The incidence of Harderian gland tumours in male and female mice was, respectively: 0/25 and 0/25 for mice that received the solvent; 0/25 and 1/24 (4%) for mice that received 46 nmol/g bw ethyl carbamate; 0/25 and 0/22 for mice that received 91 nmol/g bw ethyl carbamate; 2/25 (8%) and 3/23 (9%) for mice that received 136 nmol/g bw ethyl carbamate; 3/17 (18%) and 3/20 (15%) for mice that received 5625 nmol/g bw ethyl carbamate; 4/19 (21%) and 6/19 (32%) for mice that received 46 nmol/g bw vinyl carbamate; 0/19 and 5/21 (24%) for mice that received 91 nmol/g bw vinyl carbamate; and 1/23 (4%) and 4/19 (21%) for mice that received 136 nmol/g bw vinyl carbamate. Only female mice treated with vinyl carbamate and the male mice treated with 46 nmol/g bw vinyl carbamate had an

increased incidence of Harderian gland tumours compared with their respective control groups. Also, male and female mice treated with 46 nmol/g bw vinyl carbamate and female mice treated with 91 nmol/g bw vinyl carbamate had an increased Harderian gland tumour incidence compared with the respective groups treated with equimolar doses of ethyl carbamate (Dahl *et al*., 1980).

In a second experiment, groups of 30 female A/J mice, 6–8 weeks of age, received a single intraperitoneal injection of 3 or 6 μmol/g bw [ethyl-$^{1}H_5$]ethyl carbamate or [ethyl-$^{2}H_5$]ethyl carbamate (melting-point, 46–47 °C, satisfactory elemental analysis, mass spectrum) or the solvent (5 μL/g bw 0.9% saline). The experiment ended 5 months later, at which time most (≥ 87%) of the mice were still alive. The incidence and multiplicity (± SD) of lung adenomas were 8/30 (27%) and 0.3 ± 0.1 for mice that received the solvent; 30/30 (100%) and 5.3 ± 2.4 for mice that received 3 μmol/g bw [ethyl-$^{1}H_5$] ethyl carbamate; 26/26 (100%) and 4.7 ± 2.6 for mice that received 3 μmol/g bw [ethyl-$^{2}H_5$]ethyl carbamate; 29/29 (100%) and 10.9 ± 6.8 for mice that received 6 μmol/g bw [ethyl-$^{1}H_5$]ethyl carbamate; and 30/30 (100%) and 9.6 ± 4.4 for mice that received 6 μmol/g bw [ethyl-$^{2}H_5$]ethyl carbamate. The tumour multiplicity in mice that received [ethyl-$^{1}H_5$]ethyl carbamate did not differ statistically from that observed in mice that received equimolar doses of [ethyl-$^{2}H_5$]ethyl carbamate (Dahl *et al*., 1980).

In a third experiment, a group of 17–20 female A/J mice, 6–8 weeks of age, were administered a single intraperitoneal injection of 4000 nmol/g bw ethyl carbamate, 4000 nmol/g bw *N*-hydroxyethyl carbamate [purity not specified], 150 nmol/g bw vinyl carbamate or the solvent (5 μL/g bw 0.9% saline). Additional groups were pretreated immediately before injection with the carbamate test compounds with intraperitoneal injections of 40 nmol/g bw 2-(2,4-dichloro-6-phenyl)phenoxyethylamine (DPEA), an inhibitor of cytochrome-P450 (CYP). Mice in some of the DPEA-treated groups received seven additional intraperitoneal injections of DPEA at 2-hour intervals. The experiment was terminated 7 months later, at which time most of the mice were still alive. The incidence and multiplicity (± SD) of lung adenomas were 2/19 (10%) and 0.1 ± 0.3 for mice that received the solvent, 18/18 (100%) and 7.1 ± 3.7 for mice that received 4000 nmol/g bw ethyl carbamate, 17/19 (89%) and 4.0 ± 2.3 for mice that received 4000 nmol/g bw *N*-hydroxyethyl carbamate, and 15/15 (100%) and 11.3 ± 3.4 for mice that received 150 nmol/g bw vinyl carbamate. Treatment with a total dose of 320 nmol/g bw DPEA significantly decreased the tumour multiplicity in mice that received 4000 nmol/g bw *N*-hydroxyethyl carbamate (2.4 ± 1.6 versus 4.0 ± 2.3) (Dahl *et al*., 1980).

In a fourth experiment, groups of 10, 15 or 20 female A/J mice, 6–8 weeks of age, received a single intraperitoneal injection of 1120 or 5620 nmol/g bw ethyl carbamate, 950 or 4760 nmol/g bw *N*-hydroxyethyl carbamate, 57 or 115 nmol/g bw vinyl carbamate or the solvent (5 μL/g bw 0.9% saline). The experiment was terminated 6.5 months later, at which time most (> 90%) of the mice were still alive. The incidence and multiplicity (± SD) of lung adenomas were 7/15 (47%) and 0.7 ± 0.1 for mice that received the solvent, 14/15 (93%) and 3.7 ± 2.4 for mice that received 1120 nmol/g

bw ethyl carbamate, 15/15 (100%) and 17.9 ± 4.3 for mice that received 5620 nmol/g bw ethyl carbamate, 12/15 (80%) and 1.5 ± 1.0 for mice that received 950 nmol/g bw *N*-hydroxyethyl carbamate, 14/14 (100%) and 7.8 ± 3.8 for mice that received 4760 nmol/g bw *N*-hydroxyethyl carbamate, 9/10 (90%) and 3.7 ± 3.6 for mice that received 57 nmol/g bw vinyl carbamate, and 14/15 (93%) and 6.4 ± 3.1 for mice that received 115 nmol/g bw vinyl carbamate (Dahl *et al*., 1980).

In a fifth experiment, groups of 13–20 female A/J mice, 6–8 weeks of age, were given a single intraperitoneal injection of 2000 or 4000 nmol/g bw ethyl carbamate or *N*-hydroxyethyl carbamate, 75 or 150 nmol/g bw vinyl carbamate or the solvent (5 μL/g bw 0.9% saline). The experiment was terminated 6.5 months later, at which time most (> 80%) of the mice were still alive. The incidence and multiplicity (± SD) of lung adenomas were 7/16 (44%) and 0.7 ± 0.1 for mice that received the solvent, 15/15 (100%) and 4.3 ± 2.1 for mice that received 2000 nmol/g bw ethyl carbamate, 14/14 (100%) and 9.5 ± 3.6 for mice that received 4000 nmol/g bw ethyl carbamate, 10/15 (67%) and 1.1 ± 1.1 for mice that received 2000 nmol/g bw *N*-hydroxyethyl carbamate, 18/19 (95%) and 3.2 ± 2.2 for mice that received 4000 nmol/g bw *N*-hydroxyethyl carbamate, 19/19 (100%) and 3.8 ± 2.2 for mice that received 75 nmol/g bw vinyl carbamate, and 19/19 (100%) and 12.1 ± 4.0 for mice that received 150 nmol/g bw vinyl carbamate. Tumour multiplicity in mice treated with ethyl carbamate was significantly higher than that in mice treated with equimolar doses of *N*-hydroxyethyl carbamate [$P \leq 0.002$; one-way ANOVA followed by SNK test] (Dahl *et al*., 1980).

A study was conducted to determine whether vinyl carbamate showed the same strain-specific tumorigenicity patterns as ethyl carbamate. Specifically, groups of male and female A/J, C3HeB/FeJ (C3H) and C57BL/6J mice, 3–5 months of age, received single intraperitoneal injections of 100 μL 0.9% saline solution that contained 30, 100, 300 and 1000 mg/kg bw ethyl carbamate (≥ 99% pure) or 1, 3, 10, 30 and 60 mg/kg bw vinyl carbamate (≥ 99% pure). Two control groups, one untreated and the other injected with 100 μL 0.9% saline were available. The groups comprised 32 mice (16 males and 16 females), except for the C3H and C57BL/6J groups treated with 60 mg/kg bw vinyl carbamate, which comprised 16 mice (eight males and eight females). All animals were killed 24 weeks after the injection. At the end of the experiment, 26–32 mice were alive in each of the groups (14 and 16, respectively, in the C3H and C57BL/6J groups treated with 60 mg/kg bw vinyl carbamate). Only mice that survived to the end of the experiment were used to assess the extent of tumorigenicity. The incidence of lung tumours was determined by gross examination of the lungs using a dissecting microscope. The incidence and multiplicity (± SD) of lung tumours in A/J mice were: untreated control, 25% and 0.3 ± 0.54 tumours/mouse; 0.9% saline control, 28% and 0.4 ± 0.71 tumours/mouse; 30-mg/kg ethyl carbamate-treated, 71% and 0.9 ± 0.75 tumours/mouse; 100-mg/kg ethyl carbamate-treated, 94% and 1.7 ± 0.96 tumours/mouse; 300-mg/kg ethyl carbamate-treated, 100% and 7.3 ± 2.86 tumours/mouse; 1000-mg/kg ethyl carbamate-treated, 100% and 29.5 ± 7.67 tumours/mouse; 1-mg/kg vinyl carbamate-treated, 33% and 0.4 ± 0.68 tumours/mouse; 3-mg/kg vinyl carbamate-treated, 81% and 1.4 ± 1.08

tumours/mouse; 10-mg/kg vinyl carbamate-treated, 100% and 7.2 ± 4.16 tumours/mouse; 30-mg/kg vinyl carbamate-treated, 100% and 43.0 ± 12.33 tumours/mouse; and 60-mg/kg vinyl carbamate-treated, 100% and 40.2 ± 14.07 tumours/mouse. The incidence and multiplicity (± SD) of lung tumours in C3H mice were: untreated control, 3% and 0.0 ± 0.19 tumours/mouse; 0.9% saline control, 3% and 0.0 ± 0.17 tumours/mouse; 30-mg/kg ethyl carbamate-treated, 3% and 0.0 ± 0.19 tumours/mouse; 100-mg/kg ethyl carbamate-treated, 6% and 0.1 ± 0.25 tumours/mouse; 300-mg/kg ethyl carbamate-treated, 14% and 0.2 ± 0.47 tumours/mouse; 1000-mg/kg ethyl carbamate-treated, 23% and 0.3 ± 0.70 tumours/mouse; 1-mg/kg vinyl carbamate-treated, 0% and 0.0 ± 0.00 tumours/mouse; 3-mg/kg vinyl carbamate-treated, 0% and 0.0 ± 0.00 tumours/mouse; 10-mg/kg vinyl carbamate-treated, 20% and 0.4 ± 1.00 tumours/mouse; 30-mg/kg vinyl carbamate-treated, 47% and 0.8 ± 1.06 tumours/mouse; and 60-mg/kg vinyl carbamate-treated, 43% and 0.6 ± 0.76 tumours/mouse). The incidence and multiplicity (± SD) for lung tumours in C57BL/6J mice were: untreated control, 6% and 0.1 ± 0.25 tumours/mouse; 0.9% saline control, 3% and 0.0 ± 0.18 tumours/mouse; 30-mg/kg ethyl carbamate-treated, 13% and 0.1 ± 0.34 tumours/mouse; 100-mg/kg ethyl carbamate-treated, 13% and 0.1 ± 0.34 tumours/mouse; 300-mg/kg ethyl carbamate-treated, 23% and 0.3 ± 0.71 tumours/mouse; 1000-mg/kg ethyl carbamate-treated, 66% and 1.2 ± 1.39 tumours/mouse; 1-mg/kg vinyl carbamate-treated, 7% and 0.1 ± 0.40 tumours/mouse; 3-mg/kg vinyl carbamate-treated, 13% and 0.1 ± 0.34 tumours/mouse; 10-mg/kg vinyl carbamate-treated, 9% and 0.1 ± 0.42 tumours/mouse; 30-mg/kg vinyl carbamate-treated, 78% and 1.7 ± 1.53 tumours/mouse; and 60-mg/kg vinyl carbamate-treated, 100% and 6.1 ± 2.91 tumours/mouse. Lung-tumour incidence was significantly greater than that in the 0.9% saline control group in A/J mice with all doses of ethyl carbamate and ≥ 3 mg/kg vinyl carbamate, in C3H mice with doses of 1000 mg/kg ethyl carbamate and ≥ 10 mg/kg vinyl carbamate and in C57BL/6J mice with doses of ≥ 300 mg/kg ethyl carbamate and ≥ 30 mg/kg vinyl carbamate [$P \leq 0.04$; one-tailed Fisher's exact test]. In all three strains, lung tumour incidence with 30 mg/kg vinyl carbamate was significantly greater than that with the approximately equimolar dose of 30 mg/kg ethyl carbamate [$P \leq 0.001$; one-tailed Fisher's exact test]. Lung tumour multiplicity was significantly greater than that in the 0.9% saline control group in A/J mice with doses of ≥ 300 mg/kg ethyl carbamate and ≥ 10 mg/kg vinyl carbamate, in C3H mice with doses of ≥ 10 mg/kg vinyl carbamate and in C57BL/6 mice with doses of 1000 mg/kg ethyl carbamate and ≥ 30 mg/kg vinyl carbamate [$P < 0.05$; one-way ANOVA, followed by Dunnett's test, respectively]. In all three strains, lung tumour multiplicity with 30 mg/kg vinyl carbamate was significantly greater than that with the approximately equimolar dose of 30 mg/kg ethyl carbamate [$P < 0.0001$; one-way ANOVA followed by SNK test] (Allen *et al*., 1986).

Groups of male A/J mice [number not specified], 6 weeks of age, were administered a single intraperitoneal injection of 60 mg/kg bw vinyl carbamate [purity not specified] in 100 μL tricaprylin or the solvent alone. Interim killings were performed at 7, 8, 10, 12 and 14 months of age. The overall survival was not specified. Lungs were fixed

and examined histologically. The number of mice examined and the mean number of lung lesions (hyperplasias, adenomas and/or carcinomas) per mouse (± standard error [SE]) were four and 0.00 ± 0.00 for control mice and nine and 36.89 ± 4.46 for vinyl carbamate-treated mice killed at 7 months of age, five and 0.00 ± 0.00 for control and 12 and 31.25 ± 2.90 for vinyl carbamate-treated mice killed at 8 months of age, 11 and 36.73 ± 1.93 for vinyl carbamate-treated mice killed at 10 months of age (no control mice were sacrified at 10 months), 19 and 0.58 ± 0.14 for control and eight and 39.50 ± 3.58 for vinyl carbamate-treated mice killed at 12 months of age, 10 and 0.80 ± 0.33 for control and 44 and 37.34 ± 1.06 for vinyl carbamate-treated mice killed at 14 months of age. At each time-point (for which control animals were available), the number of lesions per mouse was significantly greater in the vinyl carbamate-treated animals [$P < 0.001$; Student's *t*-test] compared with the control group. At 7, 8, 10, 12 and 14 months, hyperplasias accounted for 32%, 8%, 2%, 2% and ~0%, respectively, of the lesions in the vinyl carbamate-treated mice, the relative contribution of adenomas was 66%, ~90%, ~82%, ~52% and 45%, respectively, and the relative contribution of carcinomas was 2%, 2%, ~16%, ~46% and 55%, respectively (Foley *et al*., 1991).

A group of 55 male and 50 female C57Bl/10J mice, 4–6 weeks of age, received intraperitoneal injections of 6 mg/kg bw vinyl carbamate (purity, > 99%) in 10 µL/g bw sterile physiological saline once a week for 35 weeks. A group of 10 male and 10 female control mice remained untreated. Five vinyl carbamate-treated mice of each sex were killed at 5 weeks; the remaining mice formed the main body of the study. Male mice treated with vinyl carbamate weighed significantly less than control males beginning at week 14, and weighed 76% of the control males by 57 weeks. The body weight of the female mice was not affected by treatment with vinyl carbamate. There were few unscheduled early deaths during the 35-week treatment period; however, ~70% of the mice either died or were removed due to morbidity by the time the experiment was terminated at week 59. Gross necropsy was performed and histopathology was conducted. Treatment with vinyl carbamate resulted in the formation of hepatocellular adenomas (2/49 (4%) males and 1/45 (2%) females), hepatocellular carcinomas (8/49 (16%) males and 9/45 (20%) females), liver haemangiosarcomas (30/49 (6%) males and 25/45 (56%) females), liver haemangiomas (31/49 (63%) males and 24/45 (53%) females) and liver histiocytic sarcomas (6/49 (12%) males and 1/45 (2%) females). The incidence of liver haemangiosarcoma and liver hemangioma was significantly increased in both sexes compared with the control group [$P \leq 0.0015$; one-tailed Fisher's exact test] (Wright *et al*., 1991).

Groups of 30–50 female A/Jax mice, 6–8 weeks of age, received a single intraperitoneal injection of 5 µL/g bw trioctanoin or 5 µL/g bw trioctanoin that contained 34 or 68 nmol/g bw vinyl carbamate [purity not specified] or vinyl carbamate epoxide [purity not specified]. At 6 months, the mice were killed, the lungs were fixed in buffered formalin and the number of adenomas (> 1 mm in diameter) was determined. The number of mice that survived to the end of the experiment was 30/30 for the 34-nmol/g bw vinyl carbamate-treated group, 19/30 for the 34-nmol/g bw vinyl

carbamate epoxide-treated group, 30/30 for the 68-nmol/g bw vinyl carbamate-treated group, 15/50 for the 68-nmol/g bw vinyl carbamate epoxide-treated and 28/30 for the solvent-treated control group. The incidence of lung adenomas and the average number of lung adenomas per mouse (± SD) were 26/30 (87%) and 2.0 ± 1.4 for the 34-nmol/g bw vinyl carbamate-treated group, 16/19 (84%) and 1.4 ± 1.9 for the 34-nmol/g bw vinyl carbamate epoxide-treated group, 30/30 (100%) and 4.4 ± 2.5 for the 68-nmol/g bw vinyl carbamate-treated group, 13/15 (87%) and 3.8 ± 2.8 for the 68-nmol/g bw vinyl carbamate epoxide-treated group and 9/28 (32%) and 0.3 ± 0.5 for the solvent-treated control group. The incidence of lung adenomas in each of the treated groups was significantly greater than that in the control group [$P \leq 0.0007$; one-tailed Fisher's exact test]. The average number of lung adenomas per mouse was greater in the groups treated with 68 nmol/g bw vinyl carbamate and vinyl carbamate epoxide than in the control group [$P \leq 0.001$; one-way ANOVA followed by SNK test] (Park *et al*., 1993).

In a second study, groups of 26–29 male B6C3F1 mice, 12 days of age, received a single intraperitoneal injection of 10 µL trioctanoin or 10 µL/g bw trioctanoin that contained 1400 nmol/g bw ethyl carbamate, 29 nmol/g bw vinyl carbamate or 4.8, 12 or 24 nmol/g bw vinyl carbamate epoxide. At 9 months of age, the mice were killed and the number of hepatomas (> 2 mm in diameter and visible on the surface) were determined. The number of mice that survived to the end of the experiment was 28/28 for the 1400-nmol/g bw ethyl carbamate-treated, 29/29 for the 29 nmol/g bw vinyl carbamate-treated, 29/29 for the 4.8-nmol/g bw vinyl carbamate epoxide-treated, 5/27 for the 12-nmol/g bw vinyl carbamate epoxide-treated, 4/26 for the 24-nmol/g bw vinyl carbamate epoxide-treated and 29/29 for the solvent-treated control animals. The incidence of hepatomas and the average number of hepatomas per mouse (± SD) were 100% and 12.1 ± 3.5 for the 1400-nmol/g bw ethyl carbamate-treated group, 96% and 11.3 ± 5.0 for the 29-nmol/g bw vinyl carbamate-treated group, 28% and 0.4 ± 0.9 for the 4.8-nmol/g bw vinyl carbamate epoxide-treated group, 60% and 8.8 ± 9.1 for the 12-nmol/g bw vinyl carbamate epoxide-treated group, 100% and 49.0 ± 5.4 for the 24-nmol/g bw vinyl carbamate epoxide-treated group and 10% and 0.1 ± 0.3 for the solvent-treated control group. With the exception of the 4.8-nmol/g bw vinyl carbamate epoxide-treated group, the incidence of hepatomas [$P \leq 0.03$; one-tailed Fisher's exact test] and the average number of hepatomas per mouse [$P < 0.05$; one-way ANOVA followed by Dunnett's test] were greater in each of the treatment groups compared with the control group (Park *et al*., 1993).

Groups of 25 male NIH strain A mice, 6 weeks of age, were given single intraperitoneal injections of 10 mL/kg bw isotonic saline alone or containing 1.12, 4.6 or 11.2 mmol/kg bw 2-hydroxyethyl carbamate (purity not stated but assessed by melting-point, GC, nuclear magnetic resonance spectroscopy and MS) or 1.12 or 4.6 mmol/kg bw ethyl carbamate [purity not stated]. The mice were maintained for 16 weeks after the injection, at which time the incidence and multiplicity of lung adenomas was assessed. The incidence of lung adenomas (> 1 mm) was determined by gross examination using a dissecting microscope; representative tumours were sectioned

and examined histologically. With the exception of one mouse in the 4.6-mmol ethyl carbamate-treated group, all mice survived to the end of the experiment. No tumours were observed grossly outside of the lungs. The incidence and multiplicity (± SE) of lung adenomas were: 4/25 (16%) and 0.16 ± 0.07 tumours/mouse for the 1.12-mmol/kg bw 2-hydroxyethyl carbamate-treated group; 7/25 (28%) and 0.32 ± 0.11 tumours/mouse for the 4.6-mmol/kg bw 2-hydroxyethyl carbamate-treated group; 7/25 (28%) and 0.32 ± 0.11 tumours/mouse for the 11.2-mmol/kg bw 2-hydroxyethyl carbamate-treated group; 23/25 (92%) and 3.3 ± 0.3 tumours/mouse for the 1.12-mmol/kg bw ethyl carbamate-treated group; and 24/24 (100%) and 13.5 ± 0.8 tumours/mouse for the 4.6-mmol/kg bw ethyl carbamate-treated group; versus 1/25 (4%) and 0.04 ± 0.04 tumours/mouse for the control group. The incidence in each of the treated groups was significantly greater than that in the control group. The tumour multiplicity in the groups treated with ethyl carbamate was significantly greater than that in the control group. The incidence [$P < 0.0001$; two-tailed Fisher's exact test] and multiplicity [$P < 0.001$; one-way ANOVA followed by SNK test] in the ethyl carbamate-treated groups were significantly greater than those in the respective 2-hydroxyethyl carbamate-treated groups (Mirvish *et al*., 1994).

Male and female C57BL/6J × BALB/cJ mice ($B6CF_1$) [number not specified], 15 days of age, were administered a single intraperitoneal injection of 30 nmol/kg bw vinyl carbamate [purity not specified] in saline [volume not specified]. Subgroups of mice were killed at selected intervals from 30 to 122 weeks of age. Overall survival was not specified. Lungs were examined histologically. In those killed at 6–12 months of age, the number of mice examined, the percentage incidence of lung tumours (alveolar/bronchiolar adenomas or carcinomas) and number of tumours per mouse were: three, 0% and none for male control mice; three, 0% and none for female control mice; six, 0% and none for male vinyl carbamate-treated mice; and three, 0% and none for female vinyl carbamate-treated mice. For those killed at 12–18 months of age, the values were: 10, 30% and 0.40 for male control mice, 10, 10% and 0.20 for female control mice; 15, 33% and 0.40 for male vinyl carbamate-treated mice; and 15, 40% and 0.67 for female vinyl carbamate-treated mice. For those killed at 18–24 months of age, the values were: 27, 22% and 0.30 for male control mice; 47, 13% and 0.13 for female control mice; 65, 46% and 0.71 for male vinyl carbamate-treated mice; and 111, 45% and 0.76 for female vinyl carbamate-treated mice. The incidence of lung tumours was significantly greater in male and female vinyl carbamate-treated mice than in male and female control mice [$P = 0.0264$ and 0.0001, respectively; one-tailed Fisher's exact test]. For those killed at > 24 months of age, the values were: 42, 50% and 0.64 for male control mice; 45, 27% and 0.47 for female control mice; and 20, 45% and 1.0 for male vinyl carbamate-treated mice. For the entire experiment, the values were: 82, 37% and 0.48 for male control mice; 105, 18% and 0.28 for female control mice; 106, 41% and 0.68 for male vinyl carbamate-treated mice; and 129, 43% and 0.73 for female vinyl carbamate-treated mice. The incidence of lung tumours was significantly greater in female vinyl carbamate-

treated mice compared with female control mice [$P = 0.0001$; one-tailed Fisher's exact test] (Massey *et al*., 1995).

An experiment was conducted with $CB6F_1$-Tg *HRAS2* mice (*HRAS2* mice), a hemizygous transgenic mouse strain that carries the human prototype *c-Ha-RAS* gene, and their non-transgenic (non-Tg) littermates. Groups of 31 male and 29 female *HRAS2* and 31 male and 31 female non-Tg mice, 7 weeks of age, received a single intraperitoneal injection of 60 mg/kg bw vinyl carbamate [purity not specified] in 10 mL/kg bw sterile 0.9% saline. Control groups consisting of 10 male and 10 female *HRAS2* and 10 male and 10 female non-Tg mice received a single injection of the solvent. The experiment lasted 16 weeks. Nine male and nine female *HRAS2* mice that were treated with vinyl carbamate died before the end of the experiment. Mean body weights of both sexes of non-Tg mice treated with vinyl carbamate were significantly lower than their respective control non-Tg mice. Complete necropsy was performed. Target tissues (forestomach, lung and spleen) and any gross lesions were examined histopathologically. Statistical comparisons of differences in incidence and multiplicity between *HRAS2* and non-Tg mice were conducted using the one-tailed Fisher's exact test and Student's *t*-test, respectively. The percentage of mice killed 16 weeks after treatment with lung adenomas and the mean number of adenomas (± SD)/mouse were 100% and 14.76 ± 5.36 for male vinyl carbamate-treated *HRAS2* mice, 10.0% and 0.10 ± 0.32 for male solvent-treated *HRAS2* mice, 88.5% and 2.92 ± 2.10 for male vinyl carbamate-treated non-Tg mice, 0% and 0.0 ± 0.0 for male solvent-treated non-Tg mice, 100% and 20.53 ± 7.54 for female vinyl carbamate-treated *HRAS2* mice, 0% and 0.0 ± 0.0 for female solvent-treated *HRAS2* mice, 96.2% and 3.19 ± 1.55 for female vinyl carbamate-treated non-Tg mice and 0% and 0.0 ± 0.0 for female solvent-treated non-Tg mice. In both male and female *HRAS2* and non-Tg mice, the incidence of lung adenomas [$P < 0.0001$] and the mean number of adenomas/mouse [$P < 0.001$] were significantly greater in the mice treated with vinyl carbamate than in their respective control groups. In both male and female *HRAS2* mice treated with vinyl carbamate, the mean number of adenomas/mouse was significantly greater than that in male and female non-Tg mice treated with vinyl carbamate. The percentage of mice with lung carcinomas and the mean number of carcinomas (± SD)/mouse were 47.1% and 0.65 ± 0.79 for male vinyl carbamate-treated *HRAS2* mice, 0% and 0.0 ± 0.0 for male solvent-treated *HRAS2* mice, 3.9% and 0.04 ± 0.20 for male vinyl carbamate-treated non-Tg mice, 0% and 0.0 ± 0.0 for male solvent-treated non-Tg mice, 53.3% and 0.67 ± 0.72 for female vinyl carbamate-treated *HRAS2* mice, 0% and 0.0 ± 0.0 for female solvent-treated *HRAS2* mice, 0% and 0.0 ± 0.0 for female vinyl carbamate-treated non-Tg mice and 0% and 0.0 ± 0.0 for female solvent-treated non-Tg mice. In both male and female *HRAS2* mice, the incidence of lung carcinomas [$P \leq 0.01$] and the mean number of carcinomas/mouse [$P \leq 0.015$] were significantly greater in the mice treated with vinyl carbamate than in their respective control groups. In both male and female *HRAS2* mice treated with vinyl carbamate, the incidence of carcinomas and the mean number of carcinomas/mouse were significantly greater than those in male and

female non-Tg mice treated with vinyl carbamate. The percentage of mice with lung adenomas and carcinomas, and the mean number of adenomas and carcinomas (± SD)/mouse were 100% and 15.41 ± 5.43 for male vinyl carbamate-treated *HRAS2* mice, 10.0% and 0.10 ± 0.32 for male solvent-treated *HRAS2* mice, 88.5% and 2.96 ± 2.18 for male vinyl carbamate-treated non-Tg mice, 0% and 0.0 ± 0.0 for male solvent-treated non-Tg mice, 100% and 21.20 ± 7.59 for female vinyl carbamate-treated *HRAS2* mice, 0% and 0.0 ± 0.0 for female solvent-treated *HRAS2* mice, 96.2% and 3.19 ± 1.55 for female vinyl carbamate-treated non-Tg mice and 0% and 0.0 ± 0.0 for female solvent-treated non-Tg mice. In both male and female *HRAS2* and non-Tg mice, the incidence of adenomas and carcinomas [$P < 0.0001$] and the mean number of adenomas and carcinomas/mouse [$P < 0.001$] were significantly greater in the mice treated with vinyl carbamate compared with their respective controls. In both male and female *HRAS2* mice treated with vinyl carbamate, the mean number of adenomas and carcinomas/mouse was significantly greater than that in the male and female non-Tg mice treated with vinyl carbamate. The percentage of mice with spleen haemangiosarcomas and the mean number of spleen haemangiosarcomas (± SD)/mouse were 91% and 2.88 ± 1.50 for male vinyl carbamate-treated *HRAS2* mice, 10% and 0.10 ± 0.32 for male solvent-treated *HRAS2* mice, 0% and 0.0 ± 0.0 for male vinyl carbamate-treated non-Tg mice, 0% and 0.0 ± 0.0 for male solvent-treated non-Tg mice, 86% and 2.13 ± 1.46 for female vinyl carbamate-treated *HRAS2* mice, 10% and 0.10 ± 0.32 for female solvent-treated *HRAS2* mice, 0% and 0.0 ± 0.0 for female vinyl carbamate-treated non-Tg mice and 0% and 0.0 ± 0.0 for female solvent-treated non-Tg mice. In both male and female *HRAS2* mice, the incidence of spleen haemangiosarcomas [$P < 0.0001$] and mean number of spleen haemangiosarcomas/mouse [$P < 0.001$] were significantly greater in the mice treated with vinyl carbamate than in their respective control groups. In both male and female *HRAS2* mice treated with vinyl carbamate, the mean number of spleen haemangiosarcomas/mouse and incidence of spleen haemangiosarcomas were significantly greater than those in male and female non-Tg mice treated with vinyl carbamate. The percentage of mice with lung haemangiosarcomas was 11.8% for male vinyl carbamate-treated *HRAS2* mice, 0% for male solvent-treated *HRAS2* mice, 0% for male vinyl carbamate-treated non-Tg mice, 0% for male solvent-treated non-Tg mice, 20.0% for female vinyl carbamate-treated *HRAS2* mice, 0% for female solvent-treated *HRAS2* mice, 0% for female vinyl carbamate-treated non-Tg mice and 0% for female solvent-treated non-Tg mice. In female *HRAS2* mice treated with vinyl carbamate, the incidence of lung haemangiosarcomas was significantly greater than that in female non-Tg mice treated with vinyl carbamate. Male *HRAS2* mice treated with vinyl carbamate had a 5% incidence of forestomach papillomas and a 14% incidence of forestomach squamous-cell carcinomas. Female *HRAS2* mice treated with vinyl carbamate had a 5% incidence of forestomach squamous-cell carcinomas. These were not significantly elevated compared with the other treatment groups, in which papillomas and squamous-cell carcinomas were not detected. A low incidence of haemangiosarcomas of

the submandibular gland, epididymis and omentum (5%) was also detected in male vinyl carbamate-treated *HRAS2* mice only (Mitsumori *et al*., 1997).

A study was conducted to compare the prevalence of liver neoplasms among five strains of mice. Groups of male mice, 15 days of age, received a single intraperitoneal injection of either 100 µL saline or 100 µL saline that contained vinyl carbamate [stated as pure]. The strains of mice (amount of vinyl carbamate administered and number of mice examined) were B6D2F$_1$ (control, 64 mice; 30 nmol vinyl carbamate, 130 mice), B6C3F$_1$ (control, 138 mice; 30 nmol vinyl carbamate, 70 mice; 150 nmol vinyl carbamate, 128 mice), C3H (control, 73 mice; 30 nmol vinyl carbamate, 181 mice; 150 nmol vinyl carbamate, 139 mice), B6CF$_1$ (control, 97 mice; 30 nmol vinyl carbamate, 114 mice) and C57BL/6 (control, 166 mice; 30 nmol vinyl carbamate, 107 mice; 150 nmol vinyl carbamate, 231 mice). Three to five mice per group were killed at 3–5-week intervals. The first killing of B6C3F$_1$, C57BL/6 and C3H mice was performed at 36 days of age; that of B6D2F$_1$ and B6CF$_1$ mice was performed at 190 days of age. The final killing was conducted when six or fewer mice per group remained; this ranged between 448 and 869 days of age. Overall survival was not indicated. Representative sections from liver masses and lung metastases were examined histologically. The incidence of mice with hepatocellular adenoma, hepatocellular carcinoma and hepatocellular adenoma or carcinoma were: B6D2F$_1$ (control, 6.3%, 7.8% and 14.1%; 30-nmol vinyl carbamate-treated, 37.7%, 38.5% and 59.2%), B6C3F$_1$ (control, 8.0%, 5.1% and 12.3%; 30-nmol vinyl carbamate-treated, 70.0%, 34.3% and 72.9%; 150-nmol vinyl carbamate-treated, 45.3%, 28.1% and 45.3%), C3H (control, 2.7%, 5.5% and 8.2%; 30-nmol vinyl carbamate-treated, 47.5%, 21.5% and 48.6%; 150-nmol vinyl carbamate-treated, 56.1%, 33.8% and 59.7%); B6CF$_1$ (control, 5.2%, 3.1% and 7.2%; 30-nmol vinyl carbamate-treated, 15.8%, 10.5% and 22.8%) and C57BL/6 (control, 1.8%, 0.6% and 2.4%; 30-nmol vinyl carbamate-treated, 34.6%, 18.7% and 43.9%; 150-nmol vinyl carbamate-treated, 43.3%, 22.5% and 46.8%). The incidence of hepatocellular adenoma, hepatocellular carcinoma and hepatocellular adenoma or carcinoma in each of the groups treated with vinyl carbamate was significantly greater than that in the respective control groups [$P \leq 0.03$; one-tailed Fisher's exact test] (Takahashi *et al*., 2002).

Groups of 9–10 male C57BL/6 mice, 6–8 weeks of age, were injected intraperitoneally once or twice with 60 µg/g bw vinyl carbamate [purity not specified] dissolved in saline [volume not specified]. Mice injected once were killed 12 months later; mice that received two injections were dosed at a 1-week interval and killed 6 months after the second injection. No control mice were available. Lung tumours were evaluated histologically. In mice that received a single injection of vinyl carbamate, the incidence of lung adenomas was 5/10 (50%), with a multiplicity (± SE) of 0.50 ± 0.17 tumours/mouse. Lymphoid nodules, which were indistinguishable from epithelial adenomas, were also observed at an incidence of 2/10 (20%) and a multiplicity of 0.20 ± 0.13 tumours/mouse. In mice that received two injections of vinyl carbamate, the incidence of lung adenomas and lymphoid nodules was 1/9 (11%) and 1/9 (11%), with multiplicities of 0.11 ± 0.21 and 0.11 ± 0.21 tumours/mouse, respectively (Miller *et al*., 2003).

(b) Rat

Groups of male and female Fischer rats [initial number not specified], 1 day of age, were given 10 twice-weekly intraperitoneal injections of 92 or 3370 nmol/g bw ethyl carbamate [purity not specified] or five weekly or 10 twice-weekly intraperitoneal injections of 92 nmol/g bw vinyl carbamate (purity not specified but assessed by melting-point, infrared spectroscopy, MS, high-performance liquid chromatography and GC) or 10 twice-weekly intraperitoneal injections of the solvent (10 μL/g bw 0.9% saline). Most of the rats survived the treatment and 17–20 of each sex from each group were weaned. An additional group received five weekly intraperitoneal injections of 380 nmol/g bw vinyl carbamate. Most of these rats died within 3 weeks of being treated, but those remaining were allocated to the experiment. The study was terminated when the rats were 22–23 months old. All animals were subjected to gross necropsy. All tumours were fixed, sectioned and stained with haematoxylin and eosin. The incidence of hepatic carcinomas (mostly mixed hepatocellular-cholangiocellular carcinomas, with a few hepatocellular or cholangiocellular carcinomas) in the male and female rats, respectively, was 0/20 and 0/19 for 10 injections of the solvent, 3/20 (15%) and 0/20 for 10 injections of 92 nmol/g bw ethyl carbamate, 3/18 (17%) and 6/17 (35%) for 10 injections of 3370 nmol/g bw ethyl carbamate, 6/19 (32%) and 4/19 (21%) for five injections of 92 nmol/g bw vinyl carbamate, 6/18 (33%) and 10/20 (50%) for 10 injections of 92 nmol/g bw vinyl carbamate and 8/10 (80%) and 2/3 (67%) for five injections of 380 nmol/g bw vinyl carbamate, and that in all treated groups (males and females combined) was significantly increased compared with the control group, with the exception of rats that received 10 injections of 92 nmol/g bw ethyl carbamate, and that in the group that received 10 injections of 92 nmol/g bw vinyl carbamate was significantly greater than the incidence in the group that received 10 injections of 92 nmol/g bw ethyl carbamate. The incidence of ear duct carcinomas in male and female rats, respectively, was 1/20 (5%) and 0/19 for 10 injections of the solvent, 2/20 (10%) and 0/20 for 10 injections of 92 nmol/g bw ethyl carbamate, 4/18 (22%) and 1/17 (6%) for 10 injections of 3370 nmol/g bw ethyl carbamate, 1/19 (5%) and 2/19 (10%) for five injections of 92 nmol/g bw vinyl carbamate, 4/18 (22%) and 2/20 (10%) for 10 injections of 92 nmol/g bw vinyl carbamate and 4/10 (40%) and 1/3 (33%) for five injections of 380 nmol/g bw vinyl carbamate. The incidence of ear duct carcinomas (males and females combined) was significantly increased in the groups that received 10 injections of 92 nmol/g bw vinyl carbamate and five injections of 380 nmol/g bw vinyl carbamate compared with controls. The incidence of neurofibrosarcomas of the ear lobe in male and female rats, respectively, was 0/20 and 0/19 for 10 injections of the solvent, 0/20 and 0/20 for 10 injections of 92 nmol/g bw ethyl carbamate, 1/18 (5%) and 0/17 for 10 injections of 3370 nmol/g bw ethyl carbamate, 5/19 (26%) and 2/19 (10%) for five injections of 92 nmol/g bw vinyl carbamate, 4/18 (22%) and 1/20 (5%) for 10 injections of 92 nmol/g bw vinyl carbamate and 0/10 and 1/3 for five injections of 380 nmol/g bw vinyl carbamate. The incidence of neurofibrosarcomas of the ear lobe (males and females

combined) was significantly increased in the groups that received five and 10 injections of 92 nmol/g bw vinyl carbamate compared with controls. In addition, the incidence was increased in rats that received 10 injections of 92 nmol/g bw vinyl carbamate compared with rats that received 10 injections of 92 nmol/g bw ethyl carbamate. A low incidence of a variety of other tumours was also observed (Dahl *et al*., 1980).

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4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

Data on the absorption, distribution, metabolism and excretion of ethyl carbamate in experimental animals have been reviewed (National Toxicology Program, 2004). Ethyl carbamate is rapidly distributed in body water after administration; it accumulates somewhat more slowly in adipose tissue than in other organs. Earlier studies with labelled ethyl carbamate indicated that it was largely oxidized to carbon dioxide. Its metabolism was suggested to proceed via an esterase reaction that released ethanol, carbon dioxide and ammonia. The rate of elimination was reported to be lower in newborn than in adult mice, which was attributed to the lack of microsomal esterase.

Human CYP2E1 was shown to be a major catalyst of the oxidation of both ethyl carbamate and vinyl carbamate in experiments with human liver microsomes (Guengerich & Kim, 1991; Guengerich *et al.*, 1991). Furthermore, when human liver microsomes were incubated with nicotinamide adenine dinucleotide phosphate (NADPH) and ethyl carbamate, the products vinyl carbamate, 2-hydroxyethyl carbamate and ethyl *N*-hydroxycarbamate were detected (Guengerich & Kim, 1991). The formation of 1,N^6-ethenoadenosine from adenosine in the presence of ethyl carbamate and vinyl carbamate was demonstrated in these studies and it was noted that this reaction was considerably slower with ethyl carbamate. In a separate study, Forkert *et al.* (2001) showed that the metabolism of vinyl carbamate in human lung microsomes is mediated by lung microsomal CYP2E1. Together, these studies suggest that, in human liver, ethyl carbamate can be converted to its proximate DNA-reactive metabolites, a mechanism similar to that suggested to play a role in carcinogenesis in rodents. [The Working

Group noted that (i) experimental evidence suggests great similarities between rodents and humans in the metabolic activation pathways of ethyl carbamate in target tissues (liver and lung); and (ii) the formation of the same proximate carcinogens that are DNA-reactive and thought to play a major role in ethyl carbamate-induced carcinogenesis in rodents probably also occurs in human cells.]

Ethyl carbamate is metabolized by CYP2E1. *N*-Hydroxylation products have carcinogenic properties, but are less potent than ethyl carbamate itself, and *N*-hydroxyethyl carbamate can be converted to ethyl carbamate (Dahl *et al.*, 1978, 1980; National Toxicology Program, 2004). *N*-Hydroxy derivatives are excreted in the urine as glucuronide and other conjugates. Oxidation of ethyl carbamate to vinyl carbamate, and thence to vinyl carbamate epoxide is thought to account for its carcinogenic properties (National Toxicology Program, 2004).

Yamamoto *et al.* (1988) reported that co-administration of ethanol with ethyl carbamate resulted in delayed clearance of ethyl carbamate and its metabolism to carbon dioxide in male mice; ethanol inhibited the metabolism of ethyl carbamate by liver homogenates. Carlson (1994) also found that ethanol inhibited the metabolism of ethyl carbamate, and that the CYP2E1 inhibitor, diethyldithiocarbamate, substantially reduced the metabolism of ethyl carbamate to carbon dioxide in rats.

Hoffler *et al.* (2003) examined the metabolism of ethyl carbamate in *CYP2E1*-knockout mice and in mice that had been treated with the CYP inhibitor, 1-aminobenzotriazole, and concluded that 96% of the metabolism of radiolabelled ethyl carbamate was mediated by CYP2E1. 1-Aminobenzotriazole also markedly inhibited the metabolism of ethyl carbamate in wild-type mice, and inhibited the residual metabolism in knockout mice. It was suggested that both the oxidation of ethyl carbamate to vinyl carbamate and the subsequent generation of the epoxide are catalyzed by CYP2E1.

Hoffler *et al.* (2005) studied the effects of administration of ethyl carbamate to *CYP2E1*-knockout mice for 6 weeks. The appearance of micronucleated erythrocytes was reduced in the knockout mice. Cell proliferation demonstrated by the appearance of K_i-67, was increased in the lung and liver of ethyl carbamate-treated wild-type mice, but not in the knockout animals. It was concluded that metabolism of ethyl carbamate via CYP2E1 was required for its genotoxicity.

These reports suggest that there are important interactions between ethanol and ethyl carbamate. The ability of ethanol to inhibit the clearance of ethyl carbamate suggests that it does so by competing for metabolic conversion by CYP2E1. Since chronic use of ethanol induces CYP2E1, prior chronic ethanol consumption could be predicted to increase the carcinogenicity of ethyl carbamate (as reported for mice treated with ethanol for 3 days; National Toxicology Program, 2004). Simultaneous exposure to ethanol and ethyl carbamate was reported in several studies to reduce the carcinogenicity of the latter (National Toxicology Program, 2004). However, in a 2-year toxicity study (National Toxicology Program, 2004), there was only a weak interaction between ethanol (0, 2.5 and 5% ethanol) and ethyl carbamate when the two compounds

were co-administered *ad libitum* in the drinking-water to mice (see Section 4.4.2(*b*)(i) of the monograph on Alcoholic beverage consumption.).

4.2 Toxic effects

4.2.1 *Humans*

A clinical trial of ethyl carbamate in patients with leukaemia (32 cases) and other types of somatic cancer (13 cases) involved oral administration of doses of 1–6 g per day for 5 to 109 days (Paterson *et al.*, 1946). The total dose varied by patient from 26 to 390 g. Nausea, vomiting and diarrhoea were reported as common side-ffects. Leukopoenia was observed in patients with somatic tumours, while the observed sharp fall in white cell counts was considered to be a beneficial effect in patients with leukaemia. These health effects were reversible when treatment with ethyl carbamate was discontinued. Similar side-effects were observed by Hirschboeck *et al.* (1948) in patients who took 0.5–2 g ethyl carbamate orally in capsules. When administered intramuscularly (2–4 mL of a 50% solution [1–2 g]), dizziness and drowsiness were also reported. No reports of the possible adverse health effects of ethyl carbamate when it was used as a co-solvent in Japanese patients (doses estimated to be 10–50 mg/kg bw; Nomura, 1975a) are available.

4.2.2 *Experimental systems*

Ethyl carbamate is known to induce acute toxic reactions in rodents. In female C57BL/6J mice that received subcutaneous injections of 4000 mg/kg bw ethyl carbamate for 12 days, spleen and thymus weights and circulating leukocyte levels were reduced (Luebke *et al.*, 1987). The immunocompetence of treated mice was also severely compromised, as measured by the delayed hypersensitivity reaction.

Female B6C3F_1 mice that received a total dose of 4000 mg/kg bw ethyl carbamate by intraperitoneal injection over 14 days also had lower spleen and thymus weights than the controls, but peripheral blood cell counts were not affected (Luster *et al.*, 1982). The presence of micronuclei in peripheral blood cells of mice following administration of ethyl carbamate supports the possibility that blood-forming organs are targets for the toxicity of ethyl carbamate (Bruce & Heddle, 1979). The hypnotic and anaesthetic properties of ethyl carbamate suggest neuropharmacological effects, which may become significant when the chemical is co-administered with ethanol (Salmon & Zeise, 1991).

Various toxic effects were reported in studies of ethyl carbamate administered for 13 weeks in the drinking-water or in 5% ethanol to rats and mice (National Toxicology Program, 1996). Increased lethality was observed in rats that received more than ~300 mg/kg bw ethyl carbamate. Ethyl carbamate was much more toxic in mice; all mice that received more than 1000 mg/kg bw and many that were given ~300 mg/kg died

before the end of the study. Animals in the high-dose groups had lower body weights, reduced water consumption and exhibited thinness, abnormal posture and ruffled fur. Leukopoenia (primarily lymphocytopoenia) was also observed in rats and mice that received doses of ethyl carbamate of ~20 mg/kg bw and ~300 mg/kg bw, respectively.

In separate 4-week and 2-year studies in which male and female B6C3F_1 mice were administered 10–90 mg/kg bw ethyl carbamate in the drinking-water or in 5% ethanol (National Toxicology Program, 2004), no adverse effects on body weight or water consumption were noted at 4 weeks, but increased lethality and decreases in body weight were observed in high-dose groups in the 2-year study.

In a study of ethyl carbamate in the drinking-water conducted by Inai *et al.* (1991), survival of male B6C3F_1 mice exposed to 100 mg/kg bw ethyl carbamate for 70 weeks was decreased, but not that of mice exposed to less than 10 mg/kg bw. A similar decrease in survival of NMRI mice exposed to concentrations of up to 12.5 mg/kg bw ethyl carbamate per day in the drinking-water began at approximately 85 weeks into the study (Schmähl *et al.*, 1977).

Acute oral administration of 1000 mg/kg bw ethyl carbamate in water to Swiss albino mice led to loss of consciousness for up to 5 hours (Abraham *et al.*, 1998).

Atrophy of the spleen and thymus was reported in BALB/c mice that received intraperitoneal injections of 200 and 400 mg/kg bw ethyl carbamate for 7 days (Cha *et al.*, 2000, 2001).

4.3 Reproductive toxicity and teratogenicity

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

(a) Teratogenic effects

(i) *Prenatal and transplacental (gestational) exposures*

Takaori *et al.* (1966) investigated the teratogenic response of Wistar rats to 1000 mg/kg bw ethyl carbamate given orally at different times during gestation: during 7 successive days of the first, second or third trimester, on 2 successive days during organogenesis or as a single dose on the 8th or 9th day of gestation. Fetal body weight was decreased in all treated groups compared with that of controls. The mean number of resorbed fetuses was increased in the animals treated during the first and second trimesters; a smaller increase occurred in animals treated during the third trimester. No gross malformations were apparent in the fetuses of dams treated in either the first or third trimester, but dams treated on days 8–13 of gestation produced offspring without tails and one with exencephaly. Offspring of animals treated during either trimester had increased incidences of skeletal malformations, which were most pronounced

when treatment occurred during days 6–12. In rats treated with two consecutive doses of ethyl carbamate (1000 mg/kg bw), similar observations were reported. The most pronounced effects were a decrease in placental weight, a decrease in the number of live fetuses, an increase in the number of resorbed fetuses and an increased incidence of skeletal malformations.

Ferm and Hanover (1966) injected ethyl carbamate once intraperitoneally or intravenously into female hamsters on gestation day 8 and the fetuses were taken 1–3 days later. An intravenous dose of 200 mg/kg bw led to abnormalities in 33% of the fetuses examined. Higher doses of 400, 800 or 1200 mg/kg bw given by either route produced fetotoxicity, as well as fetal abnormalities. The malformations reported were exencephaly, *spina bifida*, convoluted cardiac tubes, non-closing of neural folds and marked degeneration of the anterior neural tube.

Single intraperitoneal doses of 500–3000 mg/kg bw ethyl carbamate were injected into pregnant Syrian hamsters on day 8 of gestation, and fetuses were examined for malformations on day 13 of gestation (DiPaolo & Elis, 1967). Ethyl carbamate was lethal to pregnant dams at the 3000-mg/kg bw dose. At lower doses, a dose-dependent increase in the number of dead or resorbed fetuses was observed. Malformations (exencephaly, microcephaly, encephalocele) were detected in up to 10% of fetuses, although no dose-dependent effect was found.

Sinclair (1950) observed that female mice became infertile when injected subcutaneously with ethyl carbamate at a dose of 1500 mg/kg bw. Injection of 750 mg/kg bw ethyl carbamate into pregnant mice on day 7 of gestation caused abortions and lethal central nervous system defects in fetuses. Failure of the brain to close and degeneration of the brain and spinal cord were also seen in fetuses produced by mothers that were treated with the same dose on day 8 of gestation.

Nishimura and Kuginuki (1958) reported that intraperitoneal injection of 1500 mg/kg bw ethyl carbamate into pregnant mice during gestation days 3–9 led to fetal toxicity, but not malformations. Injection on days 7–8 caused resorption of all fetuses. After injection on days 9–12, fetal malformations (short tails and skeletal malformations) were found.

A single injection of 1500 mg/kg bw ethyl carbamate to CBA and C3HeB mice on day 8.5 of gestation induced exencephaly in both CBA and C3HeB fetuses, although marked strain differences were noted (Tutikawa & Harada, 1972).

Fetal malformations developed in the offspring of female ICR/Jcl mice administered ethyl carbamate by subcutaneous injection as early as day 5 of gestation with a high dose of 1500 mg/kg bw and on day 10 with lower doses of 500–1000 mg/kg bw (Nomura, 1974). An increased incidence of preimplantation loss and of early and late deaths was also reported in this study, but only with the high dose (1500 mg/kg bw) of ethyl carbamate.

Subcutaneous administration of 1000 mg/kg bw ethyl carbamate to pregnant ICR/Jcl mice on day 17 of gestation caused embryonic deaths and malformations (skeletal defects and cleft palate) in the offspring (Nomura, 1975b). Three subcutaneous

injections of 150 mg/kg bw ethyl carbamate to pregnant ICR/Jcl mice on days 9, 10 and 11 led to a significant increase in fetal malformations (Nomura, 1975a).

Nomura (1977) gave a single subcutaneous injection of 1000 mg/kg bw ethyl carbamate to pregnant ICR/Jcl mice on day 9, 10, or 11 of gestation. Cleft palates were the only anomaly seen in the offspring of animals treated on day 9. Polydactyly, cleft palates, tail anomalies and open eyelids were seen after treatment on day 10. Syndactyly, tail anomalies and cleft palates occurred after treatment on day 11. In a separate study, a single subcutaneous injection of 1000 mg/kg bw ethyl carbamate to pregnant ICR/Jcl mice on gestational day 10 led to fetal malformations such as cleft palates, tail anomalies and polydactyly (Nomura, 1983).

Nakane and Kameyama (1986) studied the teratogenicity of ethyl carbamate in CL/Fr mice, a strain that is characterized by a 30% incidence of spontaneous cleft lip with associated cleft palate in the offspring. Pregnant CL/Fr mice were treated with various doses of ethyl carbamate on different days of pregnancy. In the groups treated with 250, 500 and 750 mg/kg bw ethyl carbamate on day 9 of pregnancy, the frequency of cleft lip/palate decreased to 18%, 14% and 11% of term fetuses, respectively. In the group treated with 1000 mg/kg bw ethyl carbamate on day 9, the frequency of cleft lip/palate decreased to 6%, but isolated cleft palate was observed in 23% of term fetuses. Most fetuses in the same group had severe tail anomalies and showed marked loss in body weight.

Treatment of NMRI mice with a single intraperitoneal injection of 800 mg/kg bw ethyl carbamate on day 14 of gestation caused an increased incidence of polydactylism, cleft palate and microphthalmia in fetuses (Burkhard & Fritz-Niggli, 1987).

Treatment of ICR mice with a single subcutaneous injection of 1500 mg/kg bw ethyl carbamate on gestation day 10 resulted in cleft palate in approximately two-thirds of fetuses evaluated at gestation day 14 (Sharova *et al.*, 2003). The fetal weight:placental weight ratio was not changed by treatment with ethyl carbamate in this study; however, treatment resulted in lower weight of both clefted and morphologically normal fetuses.

(ii) *Parental exposures*

Maternal exposures

Nomura (1975b) observed that, when female ICR/Jcl mice received 1500 mg/kg bw ethyl carbamate and were subsequently mated with untreated males at 1–10-week intervals, dominant lethality was higher than that in controls at 2–3-week intervals. Malformed fetuses (open eyelids, kinky tails, cleft palates and dwarfism) were observed at a significantly higher incidence than in controls, and a higher incidence of malformations was observed in the offspring of ethyl carbamate-exposed females than in those of ethyl carbamate-exposed males.

Nomura (1982) administered a single subcutaneous injection of 1000 or 1500 mg/kg bw ethyl carbamate to female ICR mice; the mice were subsequently mated with untreated males (9 weeks). A significant increase in developmental anomalies was

detected in both 19-day-old fetuses and 7-day-old offspring at both doses with no clear dose–response.

In a subsequent study, Nomura (1988) reported a single subcutaneous injection of 1000–2000 mg/kg bw ethyl carbamate to female mice led to a dose-dependent increase in the incidence of phenotypic anomalies (cleft palate, dwarfism, tail anomalies, open eyelid) in the progeny from subsequent matings. It was noted that immature oocytes of 21-day-old females (mated 10 weeks after exposure) were more sensitive than mature oocytes, but no differences were observed in the anomalies detected after birth.

Paternal exposures

Jackson *et al.* (1959) injected male Wistar rats intraperitoneally with five daily doses of 250 mg/kg bw ethyl carbamate and reported no reduction in litter size following mating with unexposed females for up to 6 weeks after treatment.

Bateman (1967) injected male mice intraperitoneally with 1500 mg/kg bw ethyl carbamate and allowed them to mate with unexposed females. Females in the cage were changed each week for up to 9 weeks after treatment of the males. No significant effect on the number of implants, or early or late deaths was observed at any of the time-points. The study also attempted to increase exposure to ethyl carbamate through injections of 1500 mg/kg bw on 3 successive days. However, most males did not survive beyond 2 weeks after treatment. Nevertheless, no significant effect on the number of implants or early or late deaths was observed in embryos from pregnancies that occurred up to 3 weeks after treatment of the males.

Kennedy *et al.* (1973) administered a single intraperitoneal injection of 50 or 100 mg/kg bw ethyl carbamate to male mice and mated them with untreated virgin females that were changed weekly for 6 weeks. Females were sacrificed 1 week after removal from the breeding cage, and their uterine contents were evaluated for numbers of embryos, implantations and resorptions (early and late). The authors reported that genetic damage, as manifested by dominant lethal mutations, did not occur.

Nomura (1975b) administered a single subcutaneous injection of 1500 mg/kg bw ethyl carbamate to male mice, 9 weeks of age, and subsequently mated the mice with untreated females (9 weeks). Dominant lethality was significantly different from that in controls at all experimental stages. A significantly higher incidence of malformed fetuses (open eyelids, kinky tails, cleft palates and dwarfism) was observed after treatment than in controls.

Nomura (1982) administered a single subcutaneous injection of 1500–2000 mg/kg bw ethyl carbamate to male ICR mice and subsequently mated the mice with untreated females (9 weeks). No dominant lethality was detected at any stage of embryonic development. A significant increase in developmental anomalies was detected in both 19-day-old fetuses and 7-day-old offspring after both doses with no clear dose–response.

Russell *et al.* (1987) administered a single intraperitoneal injection of 1750 mg/kg bw ethyl carbamate to male (101 × C3H)F_1 mice that were then mated with unexposed females. Litter sizes from successive conceptions made in any of the first 7 weeks gave no indication of induced dominant lethality.

Nomura (1988) reported that paternal exposure to a single subcutaneous injection of 1000–2000 mg/kg bw ethyl carbamate led to a nonlinear dose-dependent increase in the incidence of phenotypic anomalies (cleft palate, dwarfism, tail anomalies, open eyelid) in F_1 progeny. It was noted that anomalies were induced more effectively in the F_1 fetuses by treatment at the stage of spermatozoa rather than at that of spermatogonia.

Edwards *et al.* (1999) treated male CD-1 mice with ethyl carbamate, either acutely by intraperitoneal injection of 1250 and 1750 mg/kg bw, or subchronically in the drinking-water at 190 mg/kg bw for 10 weeks and 370 mg/kg bw for 9 weeks. One week after the end of each treatment, male mice were mated with untreated females. No genetic effect of acute treatment with ethyl carbamate on male germ cells, as indicated by dominant lethality, was observed. No skeletal or other malformations were observed following acute paternal exposure. A significant increase in post-implantation deaths was observed only after acute administration of ethyl carbamate (1750 mg/kg) and the authors suggested that this was possibly due to perinatal mortality, since no such increase occurred in the dominant lethal part of the study. No effects were observed in offspring of males treated subchronically with ethyl carbamate in the drinking-water.

(iii) *Postnatal exposures*

Increased tumour incidence is the most frequently reported effect of perinatal exposure to ethyl carbamate. These studies are described in detail in Section 3.

(b) Effects on male and female reproductive systems

Russell *et al.* (1987) administered a single intraperitoneal injection of 1750 mg/kg bw ethyl carbamate to male (101 × C3H)F_1 mice. Cytotoxic effects on male reproduction were evident from a slight reduction in the numbers of certain types of spermatogonia in seminiferous tubule cross-sections and a borderline decrease in the number of litters conceived during the 8th and 9th weeks after treatment.

Nomura (1988) reported that a single subcutaneous injection of 1000 or 1500 mg/kg bw ethyl carbamate to male mice did not decrease their fertility for up to 180 days after exposure.

Yu *et al.* (1999) reported no significant decreases in the total number of litters or the average number of offspring born per litter when male NIH Swiss mice were exposed intraperitoneally to 1500 mg/kg bw ethyl carbamate and mated with unexposed females 2 weeks later.

A 13-week study of ethyl carbamate administered in the drinking-water to Fischer 344/N rats (National Toxicology Program, 1996) reported that the only parameter affected in the reproductive system in males was lowered epididymal spermatozoal motility and concentration in the 78- and 287-mg/kg bw groups. When ethyl carbamate was administered in a 5% ethanol vehicle, the responses were similar to those with the drinking-water vehicle. The length of the estrous cycle of female rats that received 201 mg/kg bw ethyl carbamate in 5% ethanol was longer than that of the controls. This

effect was not observed when ethyl carbamate was added to the drinking-water at a dose of 332 mg/kg bw, but was observed with a dose of 525 mg/kg bw.

A 13-week study of ethyl carbamate administered in the drinking-water to B6C3F_1 mice (National Toxicology Program, 1996) reported that minimal to mild degeneration occurred in the testes of males administered ~1500 mg/kg bw. Degeneration of the seminiferous tubules, characterized by loss of germ cells and the presence of a few to numerous spermatid giant cells within tubule lumens, was observed in five males that received ~1500 mg/kg bw. The histopathological changes in the testis were considered to be secondary to the debilitated condition of the mice, as these changes occurred only in mice that died early. Epididymal spermatozoal concentration was generally lower in exposed males than in the controls, and the difference was significant in the 30- and 191-mg/kg bw groups. Spermatozoal motility was also lower in males in the 191-mg/kg bw group than in controls. In females, minimal to mild degeneration occurred in the ovaries at doses above 1500 mg/kg bw. The degenerative changes in the ovarian follicles consisted of greater amounts of cell debris within developing follicles than that observed in control females. The histopathological changes in the ovaries were considered to be secondary to the debilitated condition of the mice, as these changes occurred only in mice that died early. In seven females in the 511-mg/kg bw group, the ovaries were smaller than those of the controls as a result of decreased numbers of follicles and *corpora lutea* and the flattening of interstitial cells and females in this group had effectively ceased to have an estrous cycle. In nine females, no cyclicity was demonstrated, while in the remaining female, the percentage of diestrous smears was doubled.

In the same study (National Toxicology Program, 1996), when ethyl carbamate was administered in 5% ethanol, the effects on epididymal spermatozoal concentration in male mice did not appear to be enhanced. Spermatozoal motility was lower in males in the 370-mg/kg bw group. It was noted that, if 5% ethanol had any effect on the toxicity of ethyl carbamate in the male reproductive system in mice, this may have been masked due to the lower fluid (and therefore ethyl carbamate) consumption in that study. In females, the 5% ethanol vehicle appeared to enhance ethyl carbamate-induced ovarian atrophy. Other effects produced with the water vehicle were also observed when 5% ethanol was used as a vehicle.

Non-neoplastic lesions of the reproductive system in female B6C3F_1 mice were assessed in a 2-year study (National Toxicology Program, 2004). In the uterus of females exposed to increasing concentrations of ethyl carbamate in drinking-water that contained 0% or 2.5% ethanol, the incidence of angiectasis (dilated vascular spaces lined by a single layer of essentially normal endothelial cells) and thrombosis had a positive trend, and was significantly increased in females exposed to ~3 and 12 mg/kg bw ethyl carbamate. In female mice that received ethyl carbamate in 5% ethanol vehicle, no significant effect on these parameters was observed. Haemorrhage from large areas of uterine angiectasis was the cause of death in five females (one exposed to ~3 mg/kg bw and four exposed to ~10 mg/kg bw ethyl carbamate). No significant effects of ethyl carbamate on the male reproductive system were reported in this study.

In the study by Edwards *et al.* (1999), some of the male mice treated acutely with an intraperitoneal injection of 1750 mg/kg bw ethyl carbamate exhibited partial infertility; however, none of the mice treated with 1250 mg/kg bw had adverse effects on reproductive ability. Similarly, no effects on fertility were noted when male mice were treated with ethyl carbamate in the drinking-water at 190 mg/kg bw for 10 weeks or 370 mg/kg bw for 9 weeks.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems (see Table 4.1 for details and references)*

Ethyl carbamate is a weak mutagen in prokaryotes (*Bacillus subtilis, Escherichia coli* and *Salmonella typhimurium*). It appears to be a weak mutagen in fungi, and its mutagenicity and genotoxicity vary greatly in different tester strains. Ethyl carbamate is clearly mutagenic *in vivo* in *Drosophila* and induces sex-linked recessive lethal mutations and reciprocal translocations in germ cells.

The results of in-vitro clastogenicity tests with ethyl carbamate in mammalian systems vary among assays; the infrequent positive responses appeared most often with high doses and with exogenous metabolic activation in specific cell types under stringent conditions. Most of the data indicate that ethyl carbamate is inefficient in causing point mutations in mammalian cells *in vitro*.

A limited number of studies was performed to assess the clastogenicity of ethyl carbamate in human cells *in vitro*, and showed that ethyl carbamate induces sister chromatid exchange in human lymphocytes and causes DNA damage (measured as unscheduled DNA synthesis) in human fibroblasts *in vitro*. However, it was reported that ethyl carbamate does not induce micronucleus formation in human lymphocytes or cause chromosomal aberrations in human germ cells *in vitro*. Furthermore, no effect of ethyl carbamate on gene mutations was observed in a human lymphoblastoid cell line.

Results from in-vivo somatic cell assays with ethyl carbamate in mammalian species were generally positive. Chromosomal aberrations, sister chromatid exchange, gene mutation, DNA damage and micronucleus formation were induced with a wide range of doses and in a large number of experimental model organisms (mice, rats and hamsters) and tissues (liver, bone marrow and lungs). Classical clastogenic effects such as chromosomal aberrations were less dose-dependent than sister chromatid exchange. In studies that also assessed the ability of ethyl carbamate to induce cancer, a poor correlation was found between its carcinogenicity and clastogenicity. Ethyl carbamate also induced point mutations in somatic cells *in vivo*.

Table 4.1 Genetic and related effects of ethyl carbamate

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Bacillus subtillis, M45 *rec*$^-$, differential toxicity	(+)[c]	(+)[c]	2000	Ashby & Kilbey (1981)
Escherichia coli polA$^-$, differential toxicity	–	–	2500	Ashby & Kilbey (1981)
Escherichia coli WP2-WP100, differential toxicity	NT	–	2000	Mamber *et al*. (1983)
Escherichia coli recA$^-$, differential toxicity	(+)[d]	(+)[d]	2000	Ashby & Kilbey (1981)
Escherichia coli gal operon, reverse mutation	NT	–	2000	Ashby & Kilbey (1981)
Escherichia coli PQ37 SOS, reverse mutation	–	–	1000	Dayan *et al*. (1987)
Escherichia coli WP2 *uvrA*, reverse mutation	NT	(+)[e]	25	Bridges *et al*. (1981)
Escherichia coli WP2 *uvrA*, reverse mutation	–	NT	5340	Pai *et al*. (1985)
Escherichia coli K12 *uvrB/recA*, DNA repair host-mediated assay	–	–	50163	Hellmér & Bolcsfoldi (1992)
Salmonella typhimurium TA100, TA1535, TA1537, TA98, reverse mutation	–	–	10000	McCann *et al*. (1975)
Salmonella typhimurium TA100, TA1535, reverse mutation	–	–	400	Dahl *et al*. (1978)
Salmonella typhimurium TA100, TA1535, TA1536, TA1537, TA98, reverse mutation	–	–	125	Simmon (1979a)
Salmonella typhimurium TA100, reverse mutation	–	–	13	Dahl *et al*. (1980)
Salmonella typhimurium TA100, reverse mutation	NT	(+)[e]	25	Bridges *et al*. (1981)
Salmonella typhimurium TA100, TA1537, TA98, TA97, reverse mutation	–	–	10000	National Toxicology Program (1996)
Salmonella typhimurium TA100, TA102, TA98, reverse mutation	–	+	5000	Hübner *et al*. (1997)

Table 4.1 (continued)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA1535, reverse mutation	–	+	6666	National Toxicology Program (1996)
Salmonella typhimurium YG7108pin3ERb5, reverse mutation	–	NT	10000	Emmert *et al*. (2006)
Salmonella typhimurium TA98, frame shift mutation	–	–	400	Dahl *et al*. (1978)
Salmonella typhimurium TA98, frame shift mutation	NT	(+)[e]	25	Bridges *et al*. (1981)
Salmonella typhimurium TA98, frame shift mutation	(+)[f]	NT	500	Flückiger-Isler *et al*. (2004)
Salmonella typhimurium RS112, DEL recombination	+	+	20000	Galli & Schiestl (1998)
Saccharomyces cerevisiae D3, mitotic recombination	–	–	50000	Simmon (1979b)
Saccharomyces cerevisiae D4, mitotic recombination	–	–	333 µg/plate	Jagannath *et al*. (1981)
Saccharomyces cerevisiae T1, T2, mitotic recombination	–	–	1000	Kassinova *et al*. (1981)
Saccharomyces cerevisiae JD1, mitotic recombination	+	+	150	Sharp & Parry (1981)
Saccharomyces cerevisiae D7, mitotic recombination	–	–	4800	Zimmermann & Scheel (1981)
Saccharomyces cerevisiae XV185-14C, reversion	–	(+)	889	Mehta & von Borstel (1981)
Saccharomyces cerevisiae D6, aneuploidy	–	–	600	Parry & Sharp (1981)
Saccharomyces cerevisiae YB110, chromosomal translocation	+	NT	75000	Hübner *et al*. (1997)
Schizosaccharamyces pombe P1, forward mutation	–	–	4.6	Loprieno (1981)
Aspergillus nidulans, aneuploidy	+	NT	20000	Crebelli *et al*. (1986)
Aspergillus nidulans, forward mutation	–	NT	40000	Crebelli *et al*. (1986)
Neurospora crassa, aneuploidy	–	NT	100	Griffiths *et al*. (1986)
Drosophila melanogaster, sex-linked recessive lethal mutation	+		267000	Vogt (1948)
Drosophila melanogaster, sex-linked recessive lethal mutation	+		222750	Oster (1958)

Table 4.1 (continued)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Drosophila melanogaster, sex-linked recessive lethal mutation	+		10000	Knaap & Kramers (1982)
Drosophila melanogaster, somatic mutation and recombination	+		445	Frölich & Würgler (1990)
Drosophila melanogaster, somatic mutation and recombination	+		1800	Graf & van Schaik (1992)
Drosophila melanogaster, somatic mutation and recombination	+		890	Osaba *et al*. (1999)
Drosophila melanogaster, somatic mutation and recombination	+		445	Dogan *et al*. (2005)
Drosophila melanogaster, genetic crossing-over or recombination	+		225	Nivard & Vogel (1999)
DNA strand breaks, rat hepatocytes *in vitro*	+	NT	8900	Sina *et al*. (1983)
Unscheduled DNA synthesis, Holtzman rat hepatocytes *in vitro*	–	NT	890	Sirica *et al*. (1980)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	–	–	3000	Jotz & Mitchell (1981)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	NT	–	11000	Amacher & Turner (1982)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	–	–	5000	Sofuni *et al*. (1996)
Sister chromatid exchange, Chinese hamster DON cells *in vitro*	+	NT	890	Abe & Sasaki (1977)
Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	–	–	25	Popescu *et al*. (1977)
Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	–	–	20000	Allen *et al*. (1982)
Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro*	–	–	1000	Evans & Mitchell (1981)
Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro*	–	–	100	Perry & Thompson (1981)
Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro*	+	+	500	National Toxicology Program (1996)
Sister chromatid exchange, mouse embryo cells *in vitro*	–	NT	8900	Itoh & Matsumoto (1984)
Micronucleus formation, Chinese hamster ovary (CHO) cells *in vitro*	–	NT	5000	Aardema *et al*. (2006)

Table 4.1 (continued)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Micronucleus formation, Chinese hamster lung (CHL) cells *in vitro*	–	NT	5000	Wakata *et al*. (2006)
Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro*	–	–	5000	National Toxicology Program (1996)
Chromosomal aberrations, mouse embryo cells *in vitro*	+	NT	8.9	Itoh & Matsumoto (1984)
Cell transformation, mouse fibroblast C3H2K cells	–	NT	100	Yoshikura & Matsushima (1981)
Cell transformation, C3H 10T1/2 mouse cells	–	–	25000	Allen *et al*. (1982)
Cell transformation, baby hamster kidney (BHK21) cells	–	+	5750	Daniel & Dehnel (1981)
Cell transformation, baby hamster kidney (BHK21) cells	NT	+	200	Styles (1981)
Unscheduled DNA synthesis, HeLa cells *in vitro*	NT	+	0.9	Martin *et al*. (1978)
Unscheduled DNA synthesis, human fibroblasts *in vitro*	+	+	0.8	Agrelo & Amos (1981)
Unscheduled DNA synthesis, HeLa cells *in vitro*	+	+	100	Martin & McDermid (1981)
Gene mutation, human lymphoblastoid TK6 cells, *HGPRT* and *TK* loci *in vitro*	–	–	12500	Hübner *et al*. (1997)
Sister chromatid exchange, human lymphocytes *in vitro*	+	–	8.9	Csukás *et al*. (1979)
Sister chromatid exchange, human lymphocytes *in vitro*	+	–	890	Csukás *et al*. (1981)
Micronucleus formation, human lymphocytes *in vitro*	–	NT	5000	Clare *et al*. (2006)
Chromosomal aberrations, human germ cells *in vitro*	–	NT	1000	Kamiguchi & Tateno (2002)
DNA strand breaks, Sprague-Dawley rat hepatocytes *in vivo*	–		500 ip	Petzold & Swenberg (1978)
DNA strand breaks, Sprague-Dawley rat brain cells *in vivo*	+		25 ip	Petzold & Swenberg (1978)
Unscheduled DNA synthesis, mouse germline cells *in vivo*	+		750 ip	Sotomayor *et al*. (1994)

Table 4.1 (continued)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Gene mutation, Chinese hamster lung cells, *in vivo*	+		1000 ip	Dean & Hodson-Walker (1979)
Gene mutation, mouse germline cells *in vivo*	–		1750 ip	Russell *et al*. (1987)
Gene mutation, mouse lung, liver and spleen cells *lacZ* operon *in vivo*	+		900 ip	Williams *et al*. (1998)
Sister chromatid exchange, mouse somatic cells *in vivo*	+		50 ip	Roberts & Allen (1980)
Sister chromatid exchange, mouse germline cells *in vivo*	+		400 ip	Roberts & Allen (1980)
Sister chromatid exchange, mouse somatic cells *in vivo*	+		193 inh and iv	Cheng *et al*. (1981a)
Sister chromatid exchange, mouse somatic cells *in vivo*	+		392 ip	Cheng *et al*. (1981b)
Sister chromatid exchange, mouse bone-marrow cells *in vivo*	+		400 ip	Allen *et al*. (1982)
Sister chromatid exchange, mouse somatic cells, alveolar macrophages and bone-marrow *in vivo*	+		300 ip	Conner & Cheng (1983)
Sister chromatid exchange, mouse bone-marrow cells *in vivo*	+		150 ip	Dragani *et al*. (1983)
Sister chromatid exchange, mouse somatic cells, lymphocytes, alveolar macrophages and bone-marrow *in vivo*	+		300 ip	Goon & Conner (1984)
Sister chromatid exchange, mouse bone-marrow cells *in vivo*	+		400 ip	Sharief *et al*. (1984)
Sister chromatid exchange, mouse lymphocytes *in vivo*	+		200 ip	Neft *et al*. (1985)
Sister chromatid exchange, mouse bone-marrow cells *in vivo*	+		300 ip	Sozzi *et al*. (1985)
Sister chromatid exchange, mouse lung cells *in vivo*	+		1000 ip	Allen *et al*. (1986)
Sister chromatid exchange, mouse fetal liver and bone-marrow cells *in vivo*	+		100 iv	Neeper-Bradley & Conner (1989, 1990)
Sister chromatid exchange, mouse somatic cells, skin and bone-marrow *in vivo*	+		0.6 ip or skin	Barale *et al*. (1992)

Table 4.1 (continued)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Sister chromatid exchange, rat bone-marrow cells *in vivo*	+		400 ip	Sharief *et al.* (1984)
Sister chromatid exchange, Chinese and Syrian golden hamster bone-marrow cells *in vivo*	+		400 ip	Sharief *et al*. (1984)
Micronucleus formation, mouse polychromatic erythrocytes *in vivo*	+		178 ip	Wild (1978)
Micronucleus formation, mouse polychromatic erythrocytes *in vivo*	+		615 ip	Salamone *et al*. (1981)
Micronucleus formation, mouse bone-marrow polychromatic erythrocytes *in vivo*	+		200 ip	Tsuchimoto & Matter (1981)
Micronucleus formation, mouse bone-marrow polychromatic erythrocytes *in vivo*	+		1000 sc	Aldovini & Ronchese (1983)
Micronucleus formation, mouse bone-marrow polychromatic erythrocytes *in vivo*	+		900 po	Ashby *et al*. (1990)
Micronucleus formation, mouse bone-marrow polychromatic erythrocytes *in vivo*	+		400 ip	Holmstrom (1990)
Micronucleus formation, mouse skin cells *in vivo*	+		2 ip	He *et al.* (1991)
Micronucleus formation, mouse bone-marrow polychromatic erythrocytes *in vivo*	+		400 po × 3	Westmoreland *et al*. (1991)
Micronucleus formation, mouse bone-marrow polychromatic erythrocytes *in vivo*	+		500 ip	Balansky *et al*. (1992)
Micronucleus formation, mouse bone-marrow polychromatic and normochromatic erythrocytes *in vivo*	+		990 ip	Sanderson & Clark (1993)
Micronucleus formation, mouse bone-marrow polychromatic erythrocytes *in vivo*	+		500 ip	Balansky (1995)

Table 4.1 (continued)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Micronucleus formation, mouse bone-marrow polychromatic erythrocytes *in vivo*	+		1000 ip	Choy *et al*. (1995, 1996)
Micronucleus formation, mouse bone-marrow polychromatic erythrocytes *in vivo*	+		25 ip	Adler *et al*. (1996)
Micronucleus formation, mouse polychromatic and normochromatic erythrocytes *in vivo*	+		200 po	National Toxicology Program (1996)
Micronucleus formation, mouse bone-marrow polychromatic erythrocytes *in vivo*	+		1000 po	Abraham *et al*. (1998)
Micronucleus formation, mouse peripheral blood normochromatic erythrocytes *in vivo*	+		400 ip	Balansky & De Flora (1998)
Micronucleus formation, mouse peripheral blood normochromatic erythrocytes *in vivo*	+		600 po, 12 wk	Director *et al*. (1998)
Micronucleus formation, mouse bone-marrow polychromatic erythrocytes *in vivo*	+		900 ip	Williams *et al*. (1998)
Micronucleus formation, mouse peripheral blood reticulocytes *in vivo*	+		500 ip	Kim *et al*. (1999)
Micronucleus formation, mouse peripheral blood polychromatic and normochromatic erythrocytes *in vivo*	+[g]		10 po 5 d/wk, 6 wk	Hoffler *et al.* (2005)
Micronucleus formation, rat polychromatic erythrocytes *in vivo*	–		2500 ip	Trzos *et al*. (1978)
Micronucleus formation, rat polychromatic erythrocytes *in vivo*	+		600 po	Westmoreland *et al*. (1991)
Micronucleus formation, rat germline spermatid cells *in vivo*	–		500 ip	Adler *et al*. (1996)
Chromosomal aberrations, mouse somatic bone-marrow, thymus and spleen cells *in vivo*	+		1000 sc	Kurita *et al*. (1969)

Table 4.1 (continued)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Chromosomal aberrations, mouse bone-marrow and spleen cells *in vivo*	+		500 sc	Miyashita *et al*. (1987)
Chromosomal aberrations, mouse somatic skin and bone-marrow cells *in vivo*	+		600 skin	Barale *et al*. (1992)
Chromosomal aberrations, mouse blood and bone-marrow somatic cells *in vivo*	–		600 po, 12 wk	Director *et al*. (1998)
Chromosomal aberrations, rat bone-marrow cells *in vivo*	+		100 ip	Topaktaş *et al*. (1996)
Dominant lethal mutation, rats	–		250 ip × 5	Jackson *et al*. (1959)
Dominant lethal mutation, mice	–		1500 ip	Bateman (1967)
Dominant lethal mutation, mice	–		1200 ip	Epstein *et al*. (1972)
Dominant lethal mutation, mice	–		100 ip	Kennedy *et al*. (1973)
Dominant lethal mutation, mice	–		2250 ip	Nomura (1982)
Dominant lethal mutation, mice	–		1750 ip	Adler *et al*. (1996)
Sperm morphology, mice	–		1000 ip × 5	Wyrobek & Bruce (1975)
Sperm morphology, mice	–		1000 ip × 5	Topham (1981)

[a] +, positive; (+), weak positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro formations, µg/mL; in-vivo formations, mg/kg bw/day; d, day; inh, inhalation; ip, intraperitoneal; iv, intravenous; po, oral; sc, subcutaneous; wk, week

[c] Two of 7 formations weakly positive without exogenous metabolic system (S9) and 1 of 7 formations weakly positive with S9

[d] Four of 7 formations negative without exogenous metablic system (S9) and two of 7 formations weakly positive with S9

[e] Positive in some, but not all formations performed at different laboratories

[f] One of 5 formations strongly positive

[g] Effect largely absent in*CYP2E1*-null mice

Some reports have indicated that ethyl carbamate can cause DNA damage in mammalian cells *in vitro* and *in vivo*. Ethyl carbamate and/or its metabolites can bind to nucleic acids *in vivo*. Boyland and Williams (1969) showed that, after intraperitoneal injection of radiolabelled ethyl or carboxyethyl carbamate to mice, liver and lung RNA were labelled. It was also noted that the ability of ethyl carbamate to bind to nucleic acids correlates with its organ-, sex- and strain-specific carcinogenic potency (Fossa *et al*., 1985). Sotomayor *et al.* (1994) administered 10–1000 mg/kg bw [^{3}H]ethyl carbamate to male mice intraperitoneally and measured DNA binding and unscheduled DNA synthesis in the liver and testis 12 hours later. A linear increase in the binding of labelled ethyl carbamate to DNA was detected in both organs, although the binding increased more rapidly in the liver at lower doses. Unscheduled DNA synthesis was elevated in early spermatids only with the 750-mg/kg bw dose.

Ribovich *et al.* (1982) demonstrated that 1,N^{6}-ethenoadenosine and 3,N^{4}-ethenocytidine were formed in the RNA of liver after intraperitoneal administration of radiolabelled [ethyl-1,2-^{3}H]ethyl carbamate to mice. Following single and multiple intraperitoneal injections of ethyl carbamate or its metabolites, vinyl carbamate or vinyl carbamate oxide, the formation of 1,N^{6}-ethenodeoxyadenosine and 3,N^{4}-ethenodeoxycytidine was increased in the liver and lung DNA of several mouse strains (Fernando *et al*., 1996). Vinyl carbamate was about threefold more potent in inducing etheno-DNA adducts in either the liver or lung. Recently, Beland *et al*. (2005) reported that the levels of 1,N^{6}-ethenodeoxyadenosine in hepatic DNA were increased by exposure to ethyl carbamate (90 ppm [90 µg/mL], 4 weeks in the drinking-water) but were lower when 5% ethanol served as the vehicle. In the same study, neither ethyl carbamate nor ethanol affected the levels of 1,N^{6}-ethenodeoxyadenosine or 3,N^{4}-ethenodeoxycytidine in lung DNA.

It was also suggested that *N*-7-(2-oxoethyl)guanine may be a key DNA adduct formed after exposure to ethyl carbamate (Scherer *et al*., 1986). These authors also showed that vinyl carbamate is a much more potent inducer of this adduct than ethyl carbamate. Svensson (1988) reported the formation of 2-oxoethyl haemoglobin and the DNA adduct *N*-7-(2-oxoethyl)guanine in mice treated with ethyl carbamate and the number of protein adducts increased linearly with dose. The *N*-7-(2-oxoethyl)guanine adduct is not considered to be pro-mutagenic but it was suggested that it may lead to cross-linking in DNA (Conner & Cheng, 1983), a mechanism that may be involved in the sister chromatid exchange induced by ethyl carbamate in multiple test systems.

4.5 Mechanistic considerations

The following are potential mechanisms that are not mutually exclusive.

4.5.1 *Genotoxicity*

The carcinogenicity of ethyl carbamate is thought to be mediated via a bioactivation pathway in which it is oxidized sequentially by CYP2E1 to vinyl carbamate and vinyl carbamate epoxide (Dahl *et al.*, 1978). Vinyl carbamate epoxide is a DNA-reactive species that can yield promutagenic etheno-DNA adducts. In support of this hypothesis, vinyl carbamate has been shown to induce more hepatocellular carcinomas than ethyl carbamate (Dahl *et al.*, 1980) and vinyl carbamate epoxide is more hepatocarcinogenic than vinyl carbamate (Park *et al.*, 1993). DNA adducts indicative of exposure to vinyl carbamate epoxide have been detected in the liver DNA of mice treated with ethyl carbamate (Beland *et al.*, 2005), vinyl carbamate and vinyl carbamate epoxide (Fernando *et al.*, 1996). In addition, hepatocellular adenomas and carcinomas induced in $B6C3F_1$ mice by ethyl and vinyl carbamate have a characteristic increase in CAA to CTA mutations at codon 61 of the H-*Ras* oncogene compared with CAA to AAA mutations that are typically found in spontaneous tumours (Wiseman *et al.*, 1986; Dragani *et al.*, 1991). Such mutations are consistent with the formation of 1,N^6-ethenodeoxyadenosine, which has been shown to lead to A→T transversion mutations (Levine *et al.*, 2000). In addition, it has been suggested that a potential DNA-cross-linking alkylating adduct, *N*-7-(2-oxoethyl)guanine, may be formed after exposure to ethyl carbamate *in vivo* (Scherer *et al.*, 1986).

4.5.2 *Cell proliferation*

Treatment with ethyl carbamate has been shown to induce cell proliferation in mouse lung (Yano *et al.*, 1997, 2000) and liver (Beland *et al.*, 2005). Cell proliferation can occur either as a regenerative response to cytotoxicity or via the induction of other molecular pathways. In the mouse lung, ethyl carbamate has been purported to act via the induction of ornithine decarboxylase and subsequent polyamine accumulation (Yano *et al.*, 1997), which are events that are thought to be involved in stimulation of the cell cycle. The proliferative effects of ethyl carbamate in the liver seem to be sex-specific, since hepatocellular proliferation was observed only in female mice (Beland *et al.*, 2005). The fact that female mice in the same study had a greater relative increase in the incidence of hepatocellular tumours following administration of ethyl carbamate may suggest that formation of the genotoxic metabolites of ethyl carbamate (see above), coupled with a greater rate of cell replication, contributes to the tumour response. It was shown that ethyl carbamate-induced increases in cell proliferation in the liver and lung are dependent on CYP2E1 because no effect was observed in *CYP2E1*-null mice (Hoffler *et al.*, 2005).

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5. Summary of Data Reported

5.1 Exposure data

Ethyl carbamate may be formed naturally as a result of fermentation and has been detected in a variety of fermented foods and alcoholic beverages. Ethyl carbamate can also be made commercially by various reactions with ethanol. It was formerly used in medical practice as a hypnotic agent, for the treatment of cancer, in particular multiple myeloma, or in analgesics. There is no evidence that ethyl carbamate is currently used in human medicine. It is used as an anaesthetic in veterinary medicine.

The levels of ethyl carbamate in wine and beer are usually below 100 µg/L, whereas higher levels (in the milligram per litre range) have been found in some stone-fruit spirits. Levels in foods have been regulated and significantly reduced during the past 20 years.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

In many studies, mice treated orally with ethyl carbamate demonstrated an increased incidence of lung adenomas, carcinomas and squamous-cell tumours, lymphomas (mainly lymphosarcomas), mammary gland adenocarcinomas, carcinomas and adenoacanthomas, leukaemias, forestomach squamous-cell papillomas or carcinomas, heart haemangiosarcomas, liver haemangiomas and haemangiosarcomas, Harderian gland adenomas or carcinomas and angiomas. Subcutaneous administration of ethyl carbamate to adult and newborn mice induced significant increases in the incidence of lung adenomas and hepatomas, respectively. Topical application of ethyl carbamate to mice resulted in a significant increase in the incidence of lung adenomas

and mammary gland carcinomas. Mice exposed by inhalation to ethyl carbamate had an increased incidence of lung adenocarcinomas, leukaemias and uterine haemangiomas. Intraperitoneal administration of ethyl carbamate to adult mice resulted in a significant increase in the incidence of lung adenomas, hepatomas and skin papillomas. Similar treatment in newborn mice induced lymphomas, lung adenomas, hepatomas, Harderian gland tumours and stromal and epithelial tumours of the ovary. Mice exposed transplacentally to ethyl carbamate developed an increased incidence of lung tumours, hepatomas and ovarian tumours. Mice born after pre-conception exposure of the sires to ethyl carbamate had an increased incidence of pheochromocytomas and adrenal gland tumours.

In one study, oral administration of ethyl carbamate to mice deficient in CYP2E1 resulted in a lower incidence of liver haemangiomas and haemangiosarcomas, lung bronchioalveolar adenomas and carcinomas, and Harderian gland adenomas than that in mice proficient in CYP2E1. In other studies, when the administration of ethyl carbamate was accompanied by topical application of the tumour promoter, 12-*O*-tetradecanoylphorbol-13-acetate, the incidence of skin papillomas and squamous-cell carcinomas was significantly increased. When the treatment with ethyl carbamate was followed by topical application of croton oil, a significant increase in the incidence of skin papillomas resulted. Topical application of ethyl carbamate to mice previously treated with 7,12-dimethylbenz[*a*]anthracene resulted in a significant increase in the incidence of skin tumours.

Rats treated orally with ethyl carbamate had an increased incidence of Zymbal gland carcinomas and mammary gland carcinomas.

Hamsters treated orally with ethyl carbamate showed an increased incidence of skin melanotic tumours, forestomach papillomas, mammary gland adenocarcinomas, liver hepatomas, liver and spleen haemangiomas, and thyroid, ovarian and vaginal carcinomas.

In one study, hepatocellular adenomas and carcinomas and adenocarcinomas of the lung were observed in monkeys treated orally with ethyl carbamate.

The carcinogenicity of ethyl carbamate has been compared with that of *N*-hydroxyethyl carbamate, 2-hydroxyethyl carbamate, vinyl carbamate and/or vinyl carbamate epoxide in mice and rats after oral, dermal, subcutaneous, intramuscular and/or intraperitoneal administration.

Oral administration of ethyl carbamate or *N*-hydroxyethyl carbamate, followed by topical application of croton oil, induced skin and lung tumours in male and female mice; ethyl carbamate was significantly more potent than *N*-hydroxyethyl carbamate.

Topical application of ethyl carbamate or vinyl carbamate, followed by promotion with croton oil, induced skin and lung tumours in female mice; vinyl carbamate was significantly more active than ethyl carbamate. Topical application of vinyl carbamate or vinyl carbamate epoxide, with or without promotion by 12-*O*-tetradecanoylphorbol-13-acetate, induced skin papillomas in female mice; vinyl carbamate epoxide was significantly more active than vinyl carbamate.

Subcubcutaneous injection of ethyl carbamate or *N*-hydroxyethyl carbamate induced lung adenomas in two strains of mice; ethyl carbamate demonstrated greater activity.

Intramuscular injection of vinyl carbamate or vinyl carbamate epoxide into female rats caused sarcomas at the injection site; vinyl carbamate epoxide was more potent. Intraperitoneal injection of ethyl carbamate or *N*-hydroxyethyl carbamate into three different strains of mice, with or without promotion by topical application of croton oil, induced skin and/or lung tumours; ethyl carbamate had similar or greater activity than *N*-hydroxyethyl carbamate.

Intraperitoneal injection of ethyl carbamate or vinyl carbamate, with or without promotion by topical application of croton oil, induced skin papillomas, lung adenomas and/or carcinomas, liver tumours (hepatomas), thymic lymphomas and/or Harderian gland tumours in CD-1, A/J, B6C3F_1, C3H, C57BL, B6CF_1, CB6F_1-Tg *HRas2*, B6D2F_1 and/or B6CF_1 mice; vinyl carbamate was typically more potent.

Intraperitoneal injection of vinyl carbamate or vinyl carbamate epoxide induced lung adenomas in female A/J mice and liver tumours (hepatomas) in male B6C3F_1 mice; vinyl carbamate epoxide was more active than vinyl carbamate. Intraperitoneal injection of ethyl carbamate or 2-hydroxyethyl carbamate induced lung adenomas in male strain A mice; ethyl carbamate was more potent than 2-hydroxyethyl carbamate.

Intraperitoneal injection of ethyl carbamate or vinyl carbamate into male and female rats induced liver and ear-duct carcinomas and neurofibrosarcomas of the ear lobe; vinyl carbamate showed more activity than ethyl carbamate.

These data indicate that, although *N*-hydroxyethyl carbamate and 2-hydroxyethyl-carbamate are carcinogenic, they probably do not make a significant contribution to the carcinogenicity of ethyl carbamate. The data are also consistent with a metabolic activation pathway in which ethyl carbamate is oxidized to vinyl carbamate, which is subsequently oxidized to vinyl carbamate epoxide.

5.4 Mechanistic and other relevant data

Ethyl carbamate is metabolized predominantly by CYP2E1, which generates metabolites (vinyl carbamate and vinyl carbamate epoxide) that are probably proximate carcinogens. The pathways for the metabolism of ethyl carbamate are similar in rodents and humans. Interactions between ethanol and ethyl carbamate are complex.

The data are too scant to make a comprehensive evaluation of the toxic effects of ethyl carbamate in humans.

At high doses, ethyl carbamate exhibits toxic effects on the central nervous system, the gastrointestinal tract, the spleen and the thymus in experimental animals. Lower doses lead to long-term effects on the spleen and the thymus.

There is strong evidence in experimental animals for the teratogenicity of ethyl carbamate when administered during gestation. The teratogenic effects are evident in the offspring when either male or female rodents are exposed before mating or pregnancy.

The effects of ethyl carbamate on the reproductive system in mice and rats are minimal and occur only at high doses.

Ethyl carbamate is genotoxic, mutagenic and clastogenic, especially in the presence of metabolic activation.

Possible mechanisms for the carcinogenicity of ethyl carbamate are induction of DNA damage by its metabolites and an increase in cell proliferation in target tissues.

6. Evaluation and Rationale

6.1 Carcinogenicity in humans

There is *inadequate evidence* in humans for the carcinogenicity of ethyl carbamate.

6.2 Carcinogenicity in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethyl carbamate.

There is *sufficient evidence* in experimental animals for the carcinogenicity of vinyl carbamate.

There is *sufficient evidence* in experimental animals for the carcinogenicity of vinyl carbamate epoxide.

Overall evaluation

Ethyl carbamate is *probably carcinogenic to humans (Group 2A).*

Rationale

The Working Group noted that (i) experimental evidence suggests great similarities in the metabolic pathways of the activation of ethyl carbamate in rodents and humans; and (ii) the formation of proximate carcinogens that are DNA-reactive and are thought to play a major role in ethyl carbamate-induced carcinogenesis in rodents probably also occurs in human cells.

GLOSSARY

Additive: Any substance not normally consumed as a food by itself and not normally used as a typical ingredient of the food, whether or not it has nutritive value, the intentional addition of which to food for a technological (including organoleptic) purpose in the manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food results, or may be reasonably expected to result (directly or indirectly), in it or its by-products becoming a component of or otherwise affecting the characteristics of such foods (FAO/WHO, 2008).

Alcopop: 'Ready-to-drink' or 'flavoured alcoholic beverage'; tends to be sweet, to be served in small bottles (typically 200–275 mL) and to contain between 5 and 7% vol alcohol

Binge drinking: Heavy episodic drinking, risky single-occasion drinking

Blush wine or rosé wine: Pinkish table wine from red grapes, the skins of which were removed after the start of fermentation

Contaminant: Substance not intentionally added to food which is present in such food as a result of the production, manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food, or as a result of environmental contamination (FAO/WHO, 2008).

Denatured alcohol: Bittered or methylated alcohol

Energy drink with alcohol: Alcopops; contains substances such as caffeine, taurine, gluconolactone.

Fortified wine: Wine with added spirits (e.g. sherry, port)

Higher alcohols: By-products of fermentation such as 1-propanol, isobutanol and isoamyl alcohol

Home-produced alcoholic beverages: Locally produced, unrecorded alcoholic beverages

Liqueur: Sweet spirit (> 100 g/L sugar)

Moonshine: Illicitly distilled spirits; bootleg

Neutral alcohol: Highly rectified alcohol, i.e. without organoleptic properties of the raw materials, used for the production of spirits (vodka and similar products)

Spirits: Distilled alcoholic beverage, liquor, hard liquor (e.g. whisky, rum, gin, vodka, brandy)

Surrogate: Substitute for alcoholic beverage (e.g. hair spray, aftershave)

LIST OF ABBREVIATIONS

ADH	alcohol dehydrogenase
AEAT	acyl-coenzyme A:ethanol *O*-acyltransferase
ALDH	aldehyde dehydrogenase
ALT	alanine aminotransferase
AST	aspartate aminotransferase, aspartate transaminase
AUC	area under the curve
bw	body weight
C/EBP	CCAAT enhancer-binding protein
CI	confidence interval
CoA	coenzyme A
CYP	cytochrome-P450
Dio-dG	N^2-(2,6-dimethyl-1,3-dioxan-4-yl)-2′-deoxyguanosine
DMBA	7,12-dimethylbenz[*a*]anthracene
DMH	1,2-dimethylhydrazine
DMSO	dimethyl sulfoxide
EDTA	ethylene diamine tetraacetic acid
EPIC	European Prospective Investigation of Nutrition and Cancer
EtdG	N^2-ethyl deoxyguanosine
EtidG	N^2-ethylidene-2′-deoxyguanosine
FAEE	fatty acid ethyl ester
FAEES	fatty acid ethyl ester synthase
FAO	Food and Agricultural Organization
FAS	fetal alcohol syndrome
GC	gas chromatography
GEO	Gene Expression Omnibus
GRAS	generally recognized as safe
GSH	glutathione (reduced form)
GST	glutathione *S*-transferase
γGT	γ-glutamyl transferase
HBV	hepatitis B virus

HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high-density lipoprotein
HNF	hepatocyte nuclear factor
HPV	human papilloma virus
ICD	International Classification of Diseases
Ig	immunoglobulin
IGF	insulin-like growth factor
IL	interleukin
K_m	Michaelis constant
LDC	Lieber-DiCarli
MAPK	mitogen-activated protein kinase
3-MCPD	3-monochloropropane-1,2-diol
MCV	mean corpuscular volume
Me-γ-OH-PdG	α-methyl-γ-hydroxyl-1,N^2-propano-2′-deoxyguanosine
MeDAB	3′-methyl-4-dimethylaminobenzene
MeIQx	2-amino-3,8-dimethylimidazo[4,5-*f*]quinoline
MGMT	O^6-methylguanine methyltransfease
MNNG	*N*-methyl-*N*′-nitro-*N*-nitrosoguanidine
MNU	*N*-methyl-*N*-nitrosourea
MS	mass spectrometry
MTHFR	methylenetetrahydrofolate reductase
MTR	5-methyltetrahydrofolate-homocysteine *S*-methyltransferase, methionine synthase
NAD^+	nicotinamide adenine dinucleotide
NADH	nicotinamide adenine dinucleotide (reduced form)
NADPH	nicotinamide adenine dinucleotide phosphate (reduced form)
NDEA	*N*-nitrosodiethylamine
NDMA	*N*-nitrosodimethylamine
NDPA	*N*-nitrosodi-*n*-propylamine
NF	nuclear factor
NF-Y/CP	nuclear factor-Y/CCAAT protein
NMBzA	*N*-nitrosomethylbenzylamine
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	*N*′-nitrosonornicotine
NPC	nasopharyngeal carcinoma
NPYR	*N*-nitrosopyrrolidine
OGG	8-oxoguanine DNA glycosylase

PAH	polycyclic aromatic hydrocarbon
SCC	squamous-cell carcinoma
SCLC	small-cell lung cancer
SD	standard deviation
SE	standard error
SHBG	sex hormone-binding globulin
SIR	standardized incidence ratio
SITC	Standard International Trade Classification
SKF-525A	2-diaminoethyl-2,2-diphenylpentanoate hydrochloride
SMR	standardized mortality ratio
SREPB	sterol regulatory element-binding protein
TEN	total enteric nutrition
TPA	12-*O*-tetradecanoylphorbol-13 acetate
TS	thymidylate synthase
V_{max}	maximum velocity
% vol	percentage by volume
XP	*xeroderma pigmentosum*
XRCC	X-ray repair cross-complementing

CUMULATIVE CROSS INDEX TO *IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS*

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List of IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*

Volume 1
Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, *N*-Nitroso Compounds, and Natural Products
1972; 184 pages (out-of-print)

Volume 2
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1973; 181 pages (out-of-print)

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Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds
1973; 271 pages (out-of-print)

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Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal
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