IARC HANDBOOKS

REDUCTION OR CESSATION OF ALCOHOLIC BEVERAGE CONSUMPTION

VOLUME 20A

IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

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This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Cancer-Preventive Interventions, which met in Lyon, France, 22–26 May 2023

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IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

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International Agency for Research on Cancer

The International Agency for Research on Cancer (IARC) was established in 1965 by the World Health Assembly, as an independently funded organization within the framework of the World Health Organization. The headquarters of the Agency are in Lyon, France.

The Agency has as its mission to reduce the cancer burden worldwide through promoting international collaboration in research. The Agency addresses this mission through conducting cancer research for cancer prevention in three main areas: describing the occurrence of cancer, identifying the causes of cancer, and evaluating preventive interventions and their implementation. Each of these areas is a vital contribution to the spectrum of cancer prevention.

The publications of the Agency contribute to the dissemination of authoritative information on different aspects of cancer research. Information about IARC publications, and how to order them, is available at https://publications.iarc.who.int/.

IARC Handbooks of Cancer Prevention
Volume 20A: Reduction or Cessation of Alcoholic Beverage Consumption
Lyon, France, 22–26 May 2023

IARC Handbooks of Cancer Prevention

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 monographs of critical reviews and evaluations of individual chemicals.

The *IARC Handbooks of Cancer Prevention* complement the *IARC Monographs*' identifications of carcinogenic hazards. The objective of the programme is to coordinate and publish critical reviews of data on the cancer-preventive effects of primary or secondary interventions, and to evaluate these data in terms of cancer prevention with the help of international working groups of experts in prevention and related fields. The lists of evaluations are regularly updated and are available at https://handbooks.iarc.who.int/.

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NOTE TO THE READER

The *IARC Handbooks of Cancer Prevention* series was launched in 1995 to complement the *IARC Monographs*' evaluations of carcinogenic hazards. The *IARC Handbooks of Cancer Prevention* evaluate the published scientific evidence of cancer-preventive interventions.

Inclusion of an intervention in the *Handbooks* does not imply that it is cancer-preventive, only that the published data have been examined. Equally, the fact that an intervention has not yet been evaluated in a *Handbook* does not mean that it may not prevent cancer. Similarly, identification of organ sites with *sufficient evidence* or *limited evidence* that the intervention has a cancer-preventive activity in humans should not be viewed as precluding the possibility that an intervention may prevent cancer at other sites.

The evaluations of cancer-preventive interventions 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 cancer-preventive interventions is encouraged to make this information available to the *IARC Handbooks* programme, International Agency for Research on Cancer, 25 avenue Tony Garnier, CS 90627, 69366 Lyon CEDEX 07, France, or by email to ihb@iarc.who.int, in order that these data may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the *Handbooks* as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the *IARC Handbooks* programme at ihb@iarc.who.int. Corrigenda are published online on the relevant webpage for the volume concerned (IARC Publications: https://publications.iarc.who.int/).

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PREAMBLE – PRIMARY PREVENTION

The Preamble to the *IARC Handbooks of Cancer Prevention* describes the objectives and scope of the programme, general principles and procedures, and scientific review and evaluations. The *IARC Handbooks* embody the principles of scientific rigour, impartial evaluation, transparency, and consistency. The Preamble should be consulted when reading an *IARC Handbook* or a summary of an *IARC Handbook*'s evaluations. Separate Instructions for Authors describe the operational procedures for the preparation and publication of a volume of the *IARC Handbooks*.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Prevention of cancer is the mission of the International Agency for Research on Cancer (IARC). Cancer prevention is needed even more today than when IARC was established, in 1965, because the global burden of cancer is high and continues to increase, as a result of population growth and ageing and increases in cancer-causing exposures and behaviours, especially in low- and middle-income countries (Stewart & Kleihues, 2003; Boyle & Levin, 2008; Stewart & Wild, 2014).

Broadly defined, prevention is "actions aimed at eradicating, eliminating, or minimizing the impact of disease and disability, or if none of these is feasible, retarding the progress of disease and disability" (Porta, 2014). Cancer prevention encompasses primary, secondary, and tertiary prevention. Primary prevention consists of actions that can be taken to lower the risk of developing cancer. Secondary prevention entails methods that can find and ameliorate precancerous conditions or find cancers in the early stages, when they can be treated more successfully. Tertiary prevention is the application of measures aimed at reducing the impact of long-term disease and disability caused by cancer or its treatment.

The *IARC Handbooks of Cancer Prevention* provide critical reviews and evaluations of the scientific evidence on the preventive effects of primary or secondary cancer prevention measures. The evaluations of the *IARC Handbooks* are used by national and international health agencies to develop evidence-based interventions or recommendations for reducing cancer risk.

The *IARC Handbooks of Cancer Prevention* series was launched in 1995 by Dr Paul Kleihues, then Director of IARC, in recognition of the need for a series of publications that would critically review and evaluate the evidence on a wide range of cancer-preventive interventions. The first volume of the *IARC Handbooks* (IARC, 1997) reviewed the evidence on cancer-preventive

effects of non-steroidal anti-inflammatory drugs, specifically aspirin, sulindac, piroxicam, and indomethacin. *Handbooks* Volume 6 (IARC, 2002a) was the first that evaluated behavioural interventions (weight control and physical activity), and *Handbooks* Volume 7 (IARC, 2002b) was the first that evaluated cancer screening (breast cancer screening). *Handbooks* Volumes 11–14 (IARC, 2007, 2008, 2009, 2011) focused on tobacco control. After a 3-year hiatus, the *IARC Handbooks* series was relaunched in 2014 with the preparation of *Handbooks* Volume 15 (IARC, 2016), which re-evaluated breast cancer screening.

IARC's process for developing *Handbooks* engages international, expert scientific Working Groups in a transparent synthesis of different streams of evidence, which is then translated into an overall evaluation according to criteria that IARC has developed and refined (see Part A, Section 6). Scientific advances are periodically incorporated into the evaluation methodology, which must be sufficiently robust to encompass a wide variety of interventions, ranging from broad societal measures to individual behaviour and to chemoprevention.

This Preamble, first prepared as the *Handbooks* Working Procedures in 1995 and later adapted to the topics of cancer screening and tobacco control, is primarily a statement of the general principles and procedures used in developing a *Handbook*, to promote transparency and consistency across *Handbooks* evaluations. In addition, IARC provides Instructions for Authors to specify more detailed operating procedures.

2. Objectives, scope, and definitions

2.1 Objectives and scope

The scope of the *IARC Handbooks of Cancer Prevention* series is to contribute to reducing the incidence of or mortality from cancer worldwide. To this end, the *IARC Handbooks* programme prepares and publishes, in the form of volumes of *Handbooks*, critical scientific reviews and evaluations of the available evidence on the efficacy, effectiveness, and harms of a wide range of cancer-preventive interventions. The primary target audiences for the *Handbooks* are national and international agencies with responsibility for, or advocating for, public health. The *IARC Handbooks* are an important part of the body of information on which public health decisions for cancer prevention may be based. However, public health options to prevent cancer vary from one setting to another and from country to country, and relate to many factors, including socioeconomic conditions and national priorities. Therefore, no recommendations are given in the *Handbooks* with regard to regulations or legislation, which are the responsibility of individual governments or other international authorities. However, the *IARC Handbooks* may aid national and international authorities in devising programmes of health promotion and cancer prevention, understanding important benefits and harms, and considering cost–effectiveness evaluations.

The *IARC Handbooks* programme also does not make formal research recommendations. However, because *Handbooks* synthesize and integrate streams of evidence on cancer prevention, critical gaps in knowledge that merit research may be identified.

2.2 Definition of interventions for primary prevention

The current *IARC Handbook* addresses a specific intervention or class of interventions for **primary prevention**. Primary prevention "aims to reduce the incidence of disease by personal and communal efforts" (Porta, 2014). The term "intervention" in this *Handbook* refers to any action aimed at reducing the incidence of cancer in humans. Primary prevention interventions include increasing human exposure to known cancer-preventive agents, reducing human exposure to known cancer hazards, providing means to reduce the effects of exposure to cancer hazards, or otherwise intervening on human pathological states that cause cancer. In broad terms, such interventions include, for example, regulating exposure to carcinogens, administering chemopreventive pharmaceuticals or other agents, vaccinating against cancer-causing infections, modifying the environment (e.g. planting trees or constructing shade structures in areas of high ambient levels of solar ultraviolet radiation), or promoting personal or societal action to increase the prevalence of healthy lifestyles or behaviours or decrease the prevalence of unhealthy lifestyles or behaviours.

Primary preventive interventions can be applied across a continuum of:

(i) the general population (often circumscribed by age and sex);

(ii) subgroups with particular predisposing host characteristics, such as genetic susceptibility, precursor lesions, or particular diseases other than cancer, or with high exposure to environmental, occupational, or behavioural risk factors; and

(iii) people with a history of cancer who are at high risk of a further primary cancer.

Although the intent of the *IARC Handbooks* is to evaluate interventions, i.e. a dynamic comparison, there will be circumstances under which an evaluation of the association between exposure to an agent and cancer incidence, i.e. a static comparison, is appropriate. In principle, the approaches to scientific review of the relevant studies in this section will not differ between those entailing dynamic interventions and those entailing static exposures. Therefore, in this Preamble the term "intervention" applies to studies of both types, unless specifically stated otherwise.

2.3 Definitions of efficacy, effectiveness, and harms

Efficacy and effectiveness are two fundamental concepts underlying the evaluation of preventive interventions (Cochrane, 1972). Efficacy was defined by Porta (2008) as "the extent to which a specific intervention, procedure, regimen or service produces a beneficial result under ideal conditions … Ideally, the determination of efficacy is based on the results of a randomized controlled trial". Effectiveness was defined by Porta (2008) as "a measure of the extent to which a specific intervention, procedure, regimen or service, when deployed in the field in routine circumstances, does what it is intended to do for a specific population".

The distinction between efficacy and effectiveness of an intervention at the population level is an important one to make when evaluating preventive interventions. Efficacy is a necessary, but not sufficient, basis for recommending an intervention. Whereas efficacy of an intervention can be inferred if effectiveness is established, efficacy does not guarantee effectiveness because of the number of implementation steps, each with uncertainty, required to deliver an efficacious prevention intervention as an effective programme in a target population. Ideally, efficacy is established before a preventive intervention is implemented in a whole community or population, so as to determine whether a case for population-wide implementation can be made

on the basis of the balance of the benefits and harms and the financial costs of the intervention. However, it has not been unusual for preventive interventions to be implemented in the absence of evidence of efficacy. Should that occur, evaluation of effectiveness may be the only way to determine whether the case for the intervention is strong enough to justify its continuation or implementation elsewhere.

In addition to being shown to be efficacious or effective, preventive interventions must satisfy other requirements if they are to be considered for implementation in practice, including an acceptable balance of benefits and harms. In the present context, harm is defined as any impairment or increase in risk of impairment as a result of exposure to or participation in a preventive intervention. Harms include physical, psychological, social, and economic consequences of a preventive intervention. Adverse events in health care are a subset of harms. Evaluation of these potential harms is an important component of the summary of the evidence.

Other issues to be considered include the cost, cost–effectiveness, affordability, economic efficiency, health equity impact, feasibility, acceptability, relative value, and human rights impact of the intervention. Depending on the specific intervention, some of these issues may be of sufficiently high interest to be reviewed in the *IARC Handbook*.

3. Identification and selection of interventions and outcomes for review

3.1 Development of an analytical framework

As one of the first steps in the review and evaluation process of the *IARC Handbooks*, the IARC Secretariat, with the support of the Working Group, drafts an analytical framework. Such a framework depicts the relationships among the study population, intervention, comparator, and intermediate outcomes or changes in health status as relevant. The analytical framework includes both benefits and harms, and key contextual issues related to participation and implementation of the intervention and its impact on population health. The framework defines the intervention in its broadest context and specifies the aspects for which the *Handbook* will review and evaluate the evidence.

In this framework, IARC defines the intervention and the outcome to be evaluated, according to one of two scenarios:

Scenario 1: evaluation of the effect of a specified *intervention*, that is, an action that results in a change in a potentially preventive exposure, in producing a specified change in *cancer incidence*.

Scenario 2: a two-step evaluative framework from which, for scientific reasons, the level of evidence that an intervention prevents cancer is established by way of an intermediate outcome.

- In Step 1, the effect of a specified intervention on an intermediate outcome, such as exposure to a particular risk factor or preventive factor for cancer in humans, is evaluated (Jonas et al., 2018). Step 1 alone might be taken if it **has been established in authoritative sources** (e.g. the *IARC Monographs* programme) that a change in the intermediate outcome (decreasing exposure to a risk factor or increasing exposure to a preventive factor) reduces the risk of cancer in humans.
- In Step 2, the effect of the change in the intermediate outcome (decrease in exposure to the risk factor or increase in exposure to the preventive factor) on cancer incidence in humans is evaluated. Evaluation of data streams to support Step 2 alone might be done in preparation for a subsequent evaluation of data to support Step 1 if it **has not yet been established in authoritative sources** that a

change in the intermediate outcome reduces the risk of cancer in humans.

The analytical framework determines whether evidence is reviewed for Step 1 only, Step 2 only, or both Steps 1 and 2. A *Handbook* might, for example, include both Steps 1 and 2 when a systematic review and evaluation of Step 2 is necessary (e.g. is not yet available from other authoritative sources) and the number of studies to be reviewed for Steps 1 and 2 is manageable. Taking Steps 1 and 2 together is equivalent to Scenario 1 with inclusion of one or more intermediate outcomes in the evaluation scheme. The sections below provide additional details on the selection of the interventions and outcomes for review.

3.2 Selection of the interventions

For each new volume of the *Handbooks*, IARC selects one or more interventions for review by considering the availability of pertinent research studies, the need to evaluate an important development in cancer prevention, or the need to re-evaluate a previously evaluated intervention. IARC will also consider current public health priorities in specific geographical regions, for example the concerns of countries or regions with a high risk of specific cancer types (see Part A, Section 6, Step 1). IARC will also pay attention to topics that extend beyond those covered by other agencies.

Interventions not previously evaluated in the *IARC Handbooks* series are selected for evaluation, where the body of evidence is large enough to warrant evaluation, on the basis of one or both of the following criteria:

- The intervention is of putative preventive value, but its effects have not been established formally;
- The available evidence suggests that the intervention has the potential to significantly reduce the incidence of cancer, or to have a significant impact on an intermediate outcome or outcomes known or highly suspected to be linked to cancer (see Section 3.1; see also Part A, Section 6, Step 2).

In addition, an intervention previously evaluated in a *Handbook* may be re-evaluated if important new data become available about its effects or if its technology or implementation has changed enough for there to be substantial changes in its effects. Occasionally, a re-evaluation may be limited to one or several specific cancer sites or to specific aspects of the preventive intervention (e.g. reduction in excess body fatness) to which the new evidence predominantly relates. For re-evaluations, the full body of evidence relevant to the intervention of interest is considered, either by de novo review of all evidence or by accepting as accurate the evidence review of the previously published *Handbook* and undertaking a de novo review of evidence published since the previous review. Both approaches lead to an evaluation based on all relevant evidence (see Part A, Section 6, Steps 4 and 5). The choice of the approach is subject to the judgement of the Working Group.

3.3 Selection of the outcomes

In primary prevention of cancer, the outcome targeted by the preventive intervention or interventions is reduction in the incidence of cancer (Scenario 1; see Part A, Section 3.1).

As described above, an intermediate outcome may be chosen as the evaluation outcome for a *Handbook* when there is evidence that a change in the intermediate outcome (decreasing exposure to the risk factor or increasing exposure to the preventive factor) can lead to a reduction in the incidence of one or more types of cancer. An example of such a target is an increase in the smoking cessation rate, which is a commonly used outcome for studies designed to determine the preventive effects of new methods of reducing the incidence of tobacco-caused cancer

Table 1 Roles of participants at *IARC Handbooks* meetings

Category of participant	Role			
	Prepare text, tables, and analyses	Participate in discussions	Participate in evaluations	Eligible to serve as Meeting Chair or Subgroup Chair
Working Group members	✓	✓	✓	✓
Invited Specialists	✓[a]	✓		
Representatives of health agencies		✓[b]		
Observers		✓[b]		
IARC Secretariat	✓[c]	✓	✓[d]	

[a] Only for sections not directly relevant to the evaluation
[b] Only at times designated by the Meeting Chair and/or Subgroup Chair
[c] Only when needed or requested by the Meeting Chair and/or Subgroup Chair
[d] Only for supporting Working Group members and for clarifying or interpreting the Preamble

by way of reducing the prevalence of tobacco smoking. Other examples of changes in intermediate outcomes include a decrease in excess body fatness, a decrease in the levels of diesel engine emissions in urban environments, and an increase in the population coverage of human papillomavirus (HPV) vaccination.

Alternatively, a *Handbook* could, as a first step, evaluate the evidence that changing the intermediate outcome can lead to a reduction in the incidence of one or more types of cancer if such evidence is not already available from authoritative sources, followed by an evaluation of the effect of an intervention on the intermediate outcome (Scenario 2, Step 2 followed by Step 1; see Part A, Section 3.1). An example of such a scenario is evaluation of the evidence that reducing consumption of alcoholic beverages reduces incidence of alcohol-related cancer or precancer, followed by evaluation of the efficacy or effectiveness of a specific intervention in reducing the consumption of alcoholic beverages.

4. The Working Group and other meeting participants

Five categories of participants can be present at *IARC Handbooks* meetings (Table 1):

(i) *Working Group* members have ultimate responsibility for determining the final list of studies that contribute evidence to the evaluation, performing the scientific review of the evidence, and making the final, formal evaluation of the strength of evidence for the capacity of the screening interventions to reduce cancer incidence or cancer mortality. The Working Group is multidisciplinary and is organized into Subgroups of experts in the fields that the *Handbook* covers.

IARC selects the Working Group members on the basis of relevant expertise and an assessment of declared interests (see Part A, Section 5). Consideration is also given to diversity in scientific approaches, in stated positions on the strength of the evidence supporting the intervention, and in demographic characteristics. Working Group members generally have published research related to the interventions being reviewed or to the cancer types or intermediate outcomes that the interventions being reviewed are thought to prevent or affect; IARC uses literature searches to identify most experts. IARC also encourages public nominations through its Call for Experts. IARC's reliance on Working Group members with expertise on the subject matter or relevant methodologies is supported

by decades of experience documenting that there is value in specialized expertise and that the overwhelming majority of Working Group members are committed to the objective evaluation of scientific evidence and not to the narrow advancement of their own research results or a predetermined outcome (Wild & Cogliano, 2011). Working Group members are expected to serve the public health mission of IARC and to refrain from using inside information from the meeting or meeting drafts for financial gain until the full volume of the *Handbooks* is published (see also Part A, Section 7).

IARC selects, from among the Working Group members, individuals to serve as Meeting Chair and Subgroup Chairs. Subgroup Chairs have preferably served in previous Handbooks meetings as Working Group members or in similar review processes. At the opening of the meeting, the Working Group is asked to endorse the Meeting Chair selected by IARC or to propose an alternative. The Meeting Chair and Subgroup Chairs take a leading role at all stages of the review process (see Part A, Section 7) to promote open scientific discussions that involve all Working Group members in accordance with committee procedures and to ensure adherence to the processes described in this Preamble.

(ii) *Invited Specialists* are experts with critical knowledge and experience on the interventions being reviewed, the cancer types that the interventions being reviewed are thought to prevent, or relevant methodologies, but who have a declared conflict of interest that warrants exclusion from developing or influencing the evaluations. The Invited Specialists do not draft any section of the *Handbook* that pertains to the description or interpretation of the data on which the evaluation is based, or participate in the evaluations. Invited Specialists are invited in limited numbers, when necessary, to assist the Working Group by contributing their unique knowledge and experience to the discussions.

(iii) *Representatives of national and international health agencies* may attend because their agencies are interested in the subject of the *Handbook*. The Representatives of national and international health agencies do not draft any section of the *Handbook* or participate in the evaluations. Representatives can participate in discussions at times designated by the Meeting Chair or a Subgroup Chair. Relevant World Health Organization (WHO) staff members attend as members of the *IARC Secretariat* (see below).

(iv) *Observers* with relevant scientific credentials are admitted in limited numbers. Attention is given to the balance of Observers from entities with differing perspectives on the interventions under review. Observers are invited only to observe the meeting, do not draft any section of the *Handbook* or participate in the evaluations, must agree to respect the Guidelines for Observers at *IARC Handbooks* meetings (IARC, 2018), and must not attempt to influence the outcomes of the meeting. Observers may speak at Working Group or Subgroup sessions at the discretion of the Chair.

(v) The *IARC Secretariat* consists of scientists who are designated by IARC or WHO and who have relevant expertise. The IARC Secretariat coordinates and facilitates all aspects of the review and evaluation process and ensures adherence to the processes described in this Preamble throughout the development of the scientific reviews and evaluations (see Part A, Sections 5 and 6). The IARC Secretariat announces and organizes the meeting, identifies and invites the Working Group members, and assesses the declared interests of all meeting participants

in accordance with WHO requirements (see Part A, Section 5). The IARC Secretariat supports the activities of the Working Group (see Part A, Section 7) by performing systematic literature searches, performing title and abstract screening, organizing conference calls to coordinate the development of drafts and to discuss cross-cutting issues, and reviewing drafts before and during the meeting. Members of the IARC Secretariat serve as meeting rapporteurs, assist the Meeting Chair and Subgroup Chairs in facilitating all discussions, and may draft text or tables or assist a Subgroup in the conduct of additional analyses when designated by the Meeting Chair or a Subgroup Chair. After the meeting, the IARC Secretariat reviews the drafts for factual accuracy of research results cited. The participation of the IARC Secretariat in the evaluations is restricted to clarifying or interpreting the Preamble.

All meeting participants are listed, with their principal affiliations, in the front matter of the published volume of the *Handbooks*. Pertinent interests, if any, are listed in a footnote to the participant's name. Working Group members and Invited Specialists serve as individual scientists and not as representatives of any organization, government, or industry (Cogliano et al., 2004).

The roles of the participants are summarized in Table 1.

5. Development of a volume of the *IARC Handbooks*

Each volume of the *Handbooks* is developed by an ad hoc, specifically convened Working Group of international experts. Approximately 1 year before the meeting of a Working Group, a preliminary list of interventions to be reviewed (see Part A, Section 3), together with a Call for Data and a Call for Experts, is announced on the *Handbooks* programme website (https://handbooks.iarc.who.int/).

The IARC Secretariat selects potential Working Group members based on the criteria described in Part A, Section 4. Before a meeting invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests form to report financial interests, employment and consulting (including remuneration for serving as an expert witness), individual and institutional research support, and non-financial interests, such as public statements and positions related to the subject of the meeting. IARC assesses the declared interests to determine whether there is a conflict that warrants any limitation on participation (see Table 1).

Approximately 2 months before a meeting, IARC publishes on the *Handbooks* programme website the names and principal affiliations of all participants and discloses any pertinent and significant conflicts of interest, for transparency and to provide an opportunity for undeclared conflicts of interest to be brought to IARC's attention. 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).

The Working Group meets at IARC to discuss and finalize the scientific review and to develop summaries and evaluations. At the opening of the meeting, all meeting participants update their Declarations of Interests forms, which are then reviewed for conflicts of interest by IARC. Declared interests related to the subject of the meeting are disclosed to the meeting participants during the meeting and in the published volume of the *Handbooks* (Cogliano et al., 2004).

The objectives of the meeting are twofold: peer review of the drafts and consensus on the evaluations. During the first part of the meeting, Working Group members work in Subgroups to

Table 2 Public engagement during the development of a volume of the *IARC Handbooks*

Approximate time frame	Milestones
~1 year before a *Handbooks* meeting	IARC posts on the *Handbooks* programme website: Preliminary List of Interventions to be reviewed Call for Data and Call for Experts open Requests for Observer Status open WHO Declarations of Interests form
~8 months before a *Handbooks* meeting	Call for Experts closes
~4 months before a *Handbooks* meeting	Requests for Observer Status close
~2 months before a *Handbooks* meeting	IARC publishes the names, principal affiliations, and declared conflicts of interest of all meeting participants, and a statement discouraging contact of Working Group members by outside parties
~1 month before a *Handbooks* meeting	Call for Data closes
***Handbooks* meeting**	
~2–4 months after a *Handbooks* meeting	IARC publishes a summary of evaluations and key supporting evidence as a scientific article in a high-impact journal or on the *Handbooks* programme website
~9–12 months after a *Handbooks* meeting	IARC Secretariat publishes the verified and edited master copy of the plenary drafts as a *Handbooks* volume

review the pre-meeting drafts, develop a joint Subgroup draft, and draft Subgroup summaries. During the last part of the meeting, the Working Group meets in plenary sessions to review the Subgroup drafts and summaries and to develop the consensus evaluations. As a result, the entire volume is the joint product of the Working Group and there are no individually authored sections. After the meeting, the master copy is verified by the IARC Secretariat (see Part A, Section 4(v)), edited, and prepared for publication. The aim is to publish the volume of the *Handbooks* within approximately 12 months of the Working Group meeting. The IARC Secretariat prepares a summary of the outcome for publication in a scientific journal or on the *Handbooks* programme website soon after the meeting.

The time frame and milestones for public engagement during the development of a volume of the *IARC Handbooks* are summarized in Table 2.

6. Overview of the scientific review and evaluation process

Principles of systematic review are applied to the identification, screening, synthesis, and evaluation of the evidence (as described in Part B, Sections 2–6 and detailed in the Instructions for Authors). For each volume of the *Handbooks*, the information on the conduct of the literature searches, including search terms and the inclusion and exclusion criteria that were used for each relevant stream of evidence, is recorded.

The Working Group considers all relevant studies, including pertinent reports and reviews on: use of the intervention targeted directly to cancer or to a relevant intermediate outcome or outcomes; all experimental and observational studies in humans (including systematic reviews and meta-analyses) of the putative effect of the intervention or interventions on cancer incidence or a relevant intermediate outcome, and any related harms; all relevant experimental studies in animals; and all relevant mechanistic studies.

In general, only studies that have been published or accepted for publication in the openly available scientific literature are reviewed. Materials that are publicly available and whose content is final may be reviewed if there is sufficient information to enable peer evaluation of the quality of the methods and results of the studies (see Step 1, below). Such material may include reports from government agencies, dissertations for higher degrees, and other apparently reputable scientific sources. Systematic Internet searches for potentially relevant "grey literature" are not usually done. The reliance on published and publicly available studies promotes transparency and protects against citation of information that, although purportedly final, may change before it is published.

The steps of the review process are as follows:

Step 1. Identification of the review question: After the intervention (or interventions) and outcome (or outcomes) to be reviewed have been specified, the IARC Secretariat, in consultation with the Working Group, drafts the review question (or questions) in PICO form (population, intervention/exposure, comparator, and outcome) as required to determine the inclusion and exclusion criteria for the studies. An analytical framework is developed to assist in identifying and formulating the review questions, and encompasses the inclusion of studies in humans, studies in experimental animals, and mechanistic studies when relevant, with the aim of making as large a contribution as possible to the global prevention of cancer.

Step 2. Comprehensive and transparent identification of the relevant information: The IARC Secretariat specifies search terms for the key PICO components of each question and identifies relevant studies through initial comprehensive literature searches in authoritative biomedical databases (e.g. PubMed). The literature searches are designed in consultation with a librarian and other technical experts. The scope and specifications of the searches may be modified, and the searches rerun, depending on the amount, relevance, and perceived completeness of the articles they identify. The IARC Secretariat may also identify relevant studies from reference lists of past *Handbooks*, retrieved articles, or authoritative reviews, and through the Call for Data (see Table 2). The Working Group provides input and advice to the IARC Secretariat to refine the search strategies, and identifies additional articles through other searches and personal expert knowledge.

For certain types of interventions (e.g. administration of regulated pharmaceuticals), IARC also gives relevant regulatory authorities, and parties regulated by such authorities, an opportunity to make pertinent unpublished studies publicly available by the date specified in the Call for Data. Consideration of such studies by the Working Group is dependent on the public availability of sufficient information to enable an independent peer evaluation of: (i) completeness of reporting of pertinent data; (ii) study quality; and (iii) study results.

Step 3. Screening, selection, and organization of the studies: The IARC Secretariat screens the retrieved articles by reviewing the title and abstract against the inclusion and exclusion criteria agreed upon by the Working Group and technical experts in the review process. Potentially relevant studies are then made available to Working Group members for full-text screening and inclusion in or exclusion from the evidence base using agreed criteria specific to this task.

Step 4. Extraction of information from included studies, including characteristics relevant to study quality: Working Group members, working individually as members of defined Subgroups before the *Handbooks* meeting, review and succinctly describe pertinent characteristics and results of included studies as detailed in Part B, Sections 2–4. Study design and results are tabulated systematically in a standard format. This step may be iterative with Step 5.

Step 5. Assessment of study quality: Also before the *Handbooks* meeting, Working Group members evaluate the quality and informativeness of each study they included based on the considerations (e.g. design, conduct, analysis, and reporting of results) described in Part B, Sections 2–4. Evaluation of study quality can be done either narratively or by use of a risk of bias assessment tool when a relevant one is available and can add value to the process. Interpretations of the results, and the strengths and limitations of each study, are clearly outlined in square brackets as part of the description of that study (see Part B).

Step 6. Peer review: Several months before the meeting, the pre-meeting drafts produced from Steps 4 and 5 are peer-reviewed by other members of the Working Group (usually within the same Subgroup). The IARC Secretariat also reviews the drafts for completeness, consistency between drafts, and adherence to the *Handbooks* Instructions for Authors. The peer-review comments are sent to the Working Group members, who produce a revised pre-meeting draft. The revised drafts are reviewed and revised in Subgroup sessions during the *Handbooks* meeting.

Step 7. Synthesis of results and quality of the studies: The results and quality of the included studies are synthesized by the Working Group to provide a summary of the evidence and its quality for each outcome. This synthesis can be narrative or quantitative (for details, see the Instructions for Authors), and the quality synthesis may include use of an overall quality of evidence assessment tool, such as GRADE (Siemieniuk & Guyatt, 2019).

Meta-analyses of large bodies of evidence may be performed by the Working Group and/or by the IARC Secretariat before the meeting if such meta-analyses would assist in evidence synthesis and evaluation. For more information on the conduct and use of such meta-analyses, see Part B, Section 2.1d.

Step 8. Interpretation of study results and evaluation of strength of evidence: The whole Working Group reviews the study descriptions and the summaries of the body of evidence for each outcome or end-point, discusses the overall strengths and limitations of the evidence in each stream of data, and evaluates the strength of evidence for a preventive effect on cancer or an intermediate outcome in each stream using transparent methods, which may include the use of established specific tools. The preventive effect is described in terms given in Part B, Sections 6a–c for each stream of evidence. The Working Group then integrates the strength-of-evidence conclusions from all streams of evidence (see Part B, Section 6d) and develops the rationale for its overall consensus evaluation of the cancer-preventive effect of the intervention (see Part B, Sections 6d–e).

7. Responsibilities of the Working Group

The Working Group is responsible for the final list of studies included in the evaluation and the review and evaluation of the evidence for a *Handbook*, as described above. The IARC Secretariat supports these activities (see Part A, Section 4). To ensure that the process is rigorous, independent, and free from individual conflicts of interest, Working Group members must accept the following responsibilities:

(i) Before the meeting, Working Group members:

- help in developing the analytical framework;
- ascertain that all appropriate studies have been identified and selected;
- assess the methods and quality of each included study;
- prepare pre-meeting drafts that present an accurate quantitative and/or textual

synthesis of the body of evidence, with key elements of study design and results and notable strengths and limitations;

- participate in conference calls organized by the IARC Secretariat to coordinate the development of pre-meeting drafts and to discuss cross-cutting issues; and
- review and provide comments on pre-meeting drafts prepared by other members of their Subgroup or of the Working Group.

(ii) At the meeting, Working Group members work in Subgroups to:

- critically review, discuss, and revise the pre-meeting drafts and adopt the revised versions as consensus Subgroup drafts; and
- develop and propose an evaluation of the strength of the evidence summarized in the consensus Subgroup drafts (see Part B, Section 5), using the *IARC Handbooks* criteria (see Part B, Section 6a–c).

(iii) At the meeting, Working Group members work in plenary sessions to:

- present their Subgroup drafts for scientific review by and discussion with the other Working Group members, and subsequent revisions, as needed;
- participate in review and discussion of other Subgroup drafts and in their adoption as a consensus Working Group draft;
- participate in review and discussion of the summaries and evaluations of the strength of the evidence developed in Subgroups (see Part B, Sections 6a–c), and contribute to their revision, as needed, and their adoption by consensus of the full Working Group; and
- contribute to the discussion of and adoption by consensus of an overall evaluation proposed by the Meeting Chair using the guidance provided in Part B, Section 6d.

The Working Group strives to achieve consensus evaluations. Consensus reflects broad agreement among the Working Group members, but not necessarily unanimity. If unanimity has not been reached when the interpretations of the evidence by all Working Group members have been expressed and debated, the judgement of the majority of the Working Group members is taken as the consensus. When consensus is reached in this way, the Meeting Chair may poll Working Group members to determine and record the diversity of scientific opinion on the overall evaluation.

Only the final product of the plenary sessions represents the views and expert opinions of the Working Group. The *Handbook* is the joint product of the Working Group and represents an extensive and thorough peer review of the body of evidence (review of individual studies, synthesis, and evaluation) by a multidisciplinary group of experts. Initial pre-meeting drafts and subsequent revisions are temporarily archived but are not released, because they would give an incomplete and possibly misleading impression of the consensus developed by the Working Group over its complete deliberation.

B. SCIENTIFIC REVIEW AND EVALUATION

This part of the Preamble discusses the types of evidence that are considered and summarized in each section of a *Handbook*, followed by the scientific criteria that guide the evaluations. In addition, a section of General Remarks at the front of the volume discusses the reasons the interventions were scheduled for evaluation and any key issues encountered during the meeting.

1. Intervention and outcome characterization

An intervention for primary cancer prevention has been defined in this Preamble to be any action aimed at reducing the incidence of cancer in humans (Part A, Section 2). Given this definition, the efficacy or effectiveness of an intervention would be most directly approached by research that examines whether the delivery of the intervention results in a measurable change in a cancer-related exposure that leads to a reduction in the incidence of cancer. However, such research is often lacking, and therefore the possibility of cancer-preventive effects has often been inferred from static associations of cancer incidence with prevalence of exposure to cancer-causing agents or cancer-preventive agents. For example, all measures that are now taken to minimize environmental exposure to asbestos (e.g. regulation of removal of asbestos from buildings or demolition of buildings known to contain asbestos) are based on the very strong evidence that people who have had identifiable exposure to asbestos have a higher incidence of cancer than people who have not had such exposure. Similarly, the evaluation of *Handbooks* Volume 16 that there "is *sufficient evidence* in humans for a cancer-preventive effect of absence of excess body fatness" is almost exclusively based on the substantial body of evidence that cancer incidence is lower in people without excess body fatness than it is in people with excess body fatness; this is a static comparison, not a dynamic comparison as the term "intervention" implies.

1.1 Intervention characterization

This section provides informative background on the intervention and the factors that mediate it. It also summarizes the prevalence and level of the intervention across geographical areas and across the life-course. Methods used to assess exposure to the intervention in key experimental and observational epidemiological studies are described and evaluated. This section also reports on validated biomarkers of internal exposure, metabolites, or other intermediate outcomes that are routinely used for exposure assessment. Concepts of absorption, distribution, metabolism, and excretion, where relevant, are considered in the section on mechanistic evidence (see Part B, Section 4b).

(a) Identification of the intervention

The intervention being evaluated is unambiguously identified. The information provided will vary widely depending on the type of intervention but should be sufficient to enable the implementation of an intervention in practice with reasonable confidence that its outcomes in populations would be similar to those of the intervention from which the bulk of the evidence evaluated in the *Handbook* originated.

Many interventions are multifaceted and comprise complex sets of actions. Interventions determined by personal behaviour or circumstances may result from, be influenced by, or be correlated with a diverse range of behavioural and environmental factors, such as smoking, alcohol consumption, diet, sleep and physical activity patterns, remoteness of residence, and socioeconomic circumstances. The description of such interventions should include their variability across human populations and environments, and their known relationships with other health-determining factors.

(b) Global occurrence and use

Geographical patterns and time trends in occurrence are summarized. A concise overview of quantitative information about sources, prevalence, and levels of individual and population interventions, whether purposive or incidental, is provided. Representative data from formal environmental or behavioural monitoring or surveillance data, research studies, government reports and websites, online databases, and other

citable, publicly available sources are tabulated. Data from low- and middle-income countries are sought and included to the extent that is feasible; information gaps for key regions are noted.

If available, data are reported by region and by other relevant characteristics, such as sex, age, socioeconomic status, and other variables considered relevant by the Working Group.

(c) Regulations and guidelines

Regulations or guidelines that have been established for the intervention (e.g. permissible levels of fortification in food, national dietary guidelines) are described and may be tabulated if they are informative for the interpretation of current or historical levels of the intervention. Information on applicable populations, the basis for regulation, and the timing of regulation may be noted.

(d) Intervention assessment in key epidemiological studies

Epidemiological studies reviewed in the context of the *IARC Handbooks* programme evaluate cancer prevention interventions (or effects on intermediate outcomes) by comparing outcomes across groups differently exposed to changes in a putative cancer-preventing intervention. Therefore, the type and the quality of intervention assessment methods used are key considerations when interpreting study findings. This section summarizes and critically reviews the intervention assessment methods used in both experimental and observational epidemiological studies that contribute data relevant to the *Handbooks* evaluation.

All interventions have two principal dimensions: (i) dose (sometimes defined as concentration or intensity), and (ii) time considerations, including duration (time from first to last exposure), pattern or frequency (whether continuous or intermittent), and windows of susceptibility. This section considers how each of the key epidemiological studies characterizes these dimensions. Interpretation of information for chemical, biological, or physical interventions may also be informed by consideration of mechanistic evidence on absorption, distribution, metabolism, and excretion (e.g. as described in Part B, Section 4b).

In experimental epidemiological studies, the investigators determine, usually by way of randomization, who will and who will not be assigned to the intervention; however, in practice the assignment is not always adhered to. Therefore, a critical assessment of such studies requires careful evaluation using appropriate guidelines or assessment frameworks (e.g. fidelity to intervention implementation and extent of non-adherence to intervention).

Intervention intensity and timing in observational epidemiological studies can be characterized by using environmental monitoring data, records from workplaces or other sources, and subject or proxy reports collected by way of questionnaires or interviews. Both objective and subjective data sources are used, individually or in combination, to assign levels or values of an intervention metric to members of the study population.

Key epidemiological studies with interventions on cancer or intermediate outcomes are identified, and the intervention assessment approach and its strengths and limitations are summarized in text and tables. The Working Group identifies concerns about intervention assessment methods and their impacts on the overall quality of each study reviewed. The Working Group notes the studies where the information provided to characterize the intervention properly, the adherence to the intended intervention in each arm of experimental studies, or the assessment of the intervention in observational studies is inadequate. The Working Group further discusses the likely direction of bias due to non-adherence or to error in intervention assessment in studies where adequate information is available.

1.2 Outcome characterization

(a) Evaluation of cancer outcomes

The cancers are defined and described in terms of their International Classification of Diseases for Oncology (ICD-O) (IARC, 2019) or International Classification of Diseases (ICD) categories, with other relevant morphological or molecular characteristics where relevant.

Benign neoplasms, pre-neoplastic lesions, malignant precursors, and other end-points closely related to cancer may also be reviewed when they relate to the intervention reviewed and are known to predict the primary cancer outcome. These studies can strengthen evidence from studies of cancer itself. For example, the results of controlled trials of sun protection measures in preventing development of cutaneous melanocytic naevi (which are strong risk factors for development of later cutaneous melanoma) in children provide support for the efficacy of sun protection measures in preventing cutaneous melanoma in adults (Thun et al., 2018).

(b) Evaluation of intermediate outcomes

Potentially relevant intermediate outcomes vary widely across human biology, pathology, and behaviour. (Intermediate outcomes that are biomarkers of early biological effects, which are not topics evaluated in *IARC Handbooks*, are described in Part B, Section 4.) All intermediate outcomes are described as precisely as possible, using an applicable international standard classification (e.g. ICD classification). When, as with some behavioural or physiological risk factors, they can be defined or measured in a range of ways, the definitions that are acceptable for the evaluation are clearly defined and acceptable standards for measurement stated.

When an intermediate outcome is the outcome being evaluated, the evidence base establishing that the intermediate outcome has an established causal or preventive association with cancer incidence is briefly summarized.

In what follows, the term "cancer incidence" refers to the **outcome of a *Handbooks* evaluation**, that is, to the incidence of **cancer** or of an **intermediate outcome**, as defined in the analytical framework.

2. Studies of cancer prevention in humans

This section includes all pertinent experimental and observational studies in humans that include cancer or a specified intermediate outcome (if it is the topic of the *Handbook*) as a study outcome. As noted above, only observational studies in which changes in the exposure (i.e. intervention) in relation to the outcome have been analysed will be considered, unless specifically stated otherwise. Among many others, these studies also encompass studies with biomarkers as intervention metrics (Alexandrov et al., 2016). As mentioned above, studies that assess biomarkers of early biological effects are reviewed in Part B, Section 4.

This section includes specification and assessment of beneficial effects, as well as potential harms.

2.1 Assessment of beneficial effects

(a) Types of studies considered

Several types of epidemiological study designs contribute to the evaluation of cancer prevention in humans (Table 3). These studies include experimental studies and different types of observational studies (i.e. cohort, case–control, and ecological). In addition to these types of studies, innovations in epidemiology enable other designs that may be considered in *Handbooks* evaluations.

Table 3 Types of epidemiological studies that contribute to the evaluation of cancer prevention

Experimental studies	
	• High level of investigator control over assignment to the intervention and non-intervention group • Ideally random assignment, either of individuals or of groups, to the intervention and non-intervention group • Provides evidence for the efficacy or effectiveness of a preventive intervention • Includes a range of quasi-experimental designs in which there is lack of random assignment to the intervention and non-intervention; quasi-experimental studies are often at high risk of bias
Observational (non-experimental) studies	
Cohort	• In a prospective cohort study, information on the intervention and non-intervention is collected from individuals who are then followed up over time to assess subsequent outcomes. Further intervention information may be collected at intervals during follow-up. • In a retrospective cohort study, information on intervention and subsequent outcomes in a defined group of individuals, which was usually recorded for purposes other than research, is accessed after the outcomes have occurred. • Nested within these studies, case–control and case–cohort studies provide efficiency and an opportunity to collect additional intervention information.
Case–control	• In a case–control study, individuals newly diagnosed with the outcome in a defined population and a sample of "control" individuals without the outcome from the same source population and time period are enrolled, and their intervention histories are compared. • Intervention information collected from cases and controls must refer to time before disease onset to reasonably infer a temporal association.
Mendelian randomization	• Mendelian randomization studies are cohort or case–control studies in which an intervention is inferred using appropriate genomic surrogate(s) (Yarmolinsky et al., 2018). • These studies are considered to be less prone to bias than other observational studies because the genomic variants from which intervention is inferred are randomly allocated at conception.
Ecological	• The association between an intervention and an outcome is examined not in individual people but in units of population defined geographically and/or temporally. Uncontrolled confounding is a major issue for ecological studies. • Results from ecological studies can support a hypothesis about an intervention–outcome association or, when taken together with results of case–control and cohort studies, support judgements on causal associations. • Results may be persuasive when population-wide implementation of an intervention leads to changes in cancer incidence or mortality: (a) in several populations, and there is no similar trend in similar populations not, or much less, subject to the intervention (e.g. Hakama, 1983); or (b) in a single population, by use of time series analysis when longitudinal data on both the intervention and the outcome are available (e.g. Bernal et al., 2017).

(b) Identification of eligible studies in humans

Relevant studies in humans are identified using principles of systematic review as described in Part A and further detailed in the Instructions for Authors provided to each Working Group. Eligible studies include all studies in humans of the association of a putative cancer-preventive intervention with the occurrence of cancer, or a specified intermediate outcome if it is a topic of the *Handbook*. Multiple publications on the same study population are identified so that the number of independent studies is accurately represented. Multiple publications may result, for example, from successive follow-ups of a single trial population or cohort, from analyses focused on different aspects of an intervention–outcome association, or from inclusion of overlapping populations. In these situations, the most recent or most informative report is usually reviewed first, with recourse to the other reports if important information (e.g. methodological

detail) is not included in the most recent or most informative report.

(c) Study quality and informativeness

Epidemiological studies are susceptible to several different sources of error. Study quality is assessed as part of the structured expert review process undertaken by the Working Group. A key aspect of quality assessment is consideration of the possible roles of chance and bias in the interpretation of epidemiological studies.

Chance, also called "random variation", can produce misleading study results. This variability in study results is strongly influenced by the sample size: smaller studies are more likely than larger studies to have effect estimates that are imprecise and, therefore, are more likely to be misleading. Confidence intervals around a study's point estimate of effect are routinely used to indicate the range of values of the estimate that could be produced by chance. Both experimental and observational epidemiological studies are prone to effects of chance, and experimental studies are arguably more prone, because of their smaller sample sizes, associated with the greater cost of conducting such studies.

Bias is the effect of factors in study design, conduct, or reporting that lead an association to erroneously appear stronger than, weaker than, or opposite in direction to the association that really exists between an intervention and an outcome. Biases that require consideration are varied and can be broadly categorized as selection bias, information bias, and confounding bias (Rothman et al., 2008). Selection bias in an epidemiological study can occur when the inclusion of participants from the eligible population or their follow-up in the study is influenced by their intervention status or their outcome (usually disease occurrence). Under these conditions, the measure of association found or not found in the study may not accurately reflect the association or lack thereof that might otherwise have been found in the eligible population (Hernán et al., 2004). Information bias results from inaccuracy in intervention or outcome measurement. Both can cause an association between hypothesized cause and effect to appear stronger or weaker than it really is. Confounding arises when a third factor is associated with both the intervention and the outcome and, because of this, influences the apparent association between them (Rothman et al., 2008). An association between the intervention and another factor that is associated with an increase or a decrease in the incidence of or mortality from the disease can lead to a spurious association or the absence of a real association of the intervention with the outcome. When either of these occurs, confounding is present.

In principle, experimental studies are less prone to each of these sources of bias, because selection for intervention or non-intervention is determined by the investigator (usually by random allocation) and not by the study participants or their characteristics. However, bias may still arise as a result of lack of concealment, non-random allocation, lack of blinding, post-randomization exclusions, non-acceptance of or non-adherence by the study participants to the intervention condition of the study arm to which they are randomized, or study loss to follow-up. One potential shortcoming of randomized studies is their potentially limited external validity (relevance) and consequently limited generalizability to non-studied populations.

In assessing the quality of the studies, the Working Group considers the following aspects:

- **Study description:** Clarity in describing the study design, implementation, and conduct, and the completeness of reporting of all other key information about the study and its results.
- **Study population:** Whether the study population was appropriate for evaluating the association between the intervention and the outcome. Whether the study was designed and conducted in a manner that would

minimize selection bias and other forms of bias. The designated outcomes in the study population must have been identified in a way that was independent of the intervention of interest, and the intervention must have been assessed in a way that was not related to outcome status. In these respects, completeness of recruitment into the study from the population of interest (which is less of an issue for experimental efficacy studies than for effectiveness studies and observational studies) and completeness of follow-up for the outcome (see below) are very important.

- **Outcome measurement:** The appropriateness of the outcome measure (incidence of cancer, mortality from cancer, or an intermediate outcome, as defined in Part B, Section 1.2) for the intervention and the cancer type under consideration, the outcome ascertainment methodology, and the extent to which outcome misclassification may have led to bias in the measure or measures of association.
- **Intervention measurement:** This includes: (i) the adequacy (including the validity and the reliability) of the methods used to assess the intervention in observational studies, and adherence to the intervention condition in experimental studies, and (ii) the likelihood (and direction) of bias in the measure or measures of association because of intervention measurement error or misclassification in observational studies and non-adherence to the intervention condition in experimental studies (see Part B, Section 1.1. Of particular relevance is an assessment of the error associated with the measurement of change over time in several study designs, including prospective longitudinal studies (e.g. change in body weight estimated from contemporary recall of past body weight and self-reported or measured current body weight at recruitment into a cohort study).
- **Assessment of potential confounding:** The extent to which the authors took into account in the study design and analysis potentially confounding variables (including co-exposures, as described in Part B, Section 1d) that could influence the occurrence of the outcome and may be related to the intervention of interest. Important sources of potential confounding by such variables should, where possible, have been addressed in the study design, such as by randomization, matching, or restriction, or in the analysis by statistical adjustment. In some instances, where direct information on confounders is unavailable, use of indirect methods to evaluate the potential impact of confounding on intervention–outcome associations is appropriate (e.g. Axelson & Steenland, 1988; Richardson et al., 2014).
- **Other potential sources of bias:** Each epidemiological study is unique in its study population, its design, its data collection, and, consequently, its potential biases. For example, repeated assessments of exposure to the intervention over time can be influenced by the occurrence of the outcome and thus bias the result and sometimes lead to "reverse causation". All possible sources of bias are considered for their possible impact on the results, including the possibility of reporting bias (selective reporting of some results).
- **Statistical methodology:** The studies are evaluated for the adequacy of the statistical analysis methods used and their ability to obtain unbiased estimates of intervention–outcome associations, confidence intervals, and test statistics for the significance of measures of association. Appropriateness of methods used to address confounding, including adjusting for matching when necessary and avoiding treatment of probable mediating variables as confounders, is considered. For example, the use of directed

acyclic graphs can inform about whether confounding and selection biases have been specified correctly (Hernán et al., 2004). Detailed analyses of cancer risks in relation to summary measures of intervention, such as cumulative exposure to the intervention, or temporal variables, such as age at first intervention or time since first intervention, are reviewed and summarized when available.

For the sake of economy and simplicity, this Preamble refers to the **list of possible sources of error** with the phrase "**chance, bias, and confounding**", but it should be recognized that this phrase encompasses a comprehensive set of concerns pertaining to study quality. These elements of study quality do not constitute and should not be used as a formal checklist of indicators of study quality. Rather, the assessment by the Working Group is reported in a narrative way, in the form of comments in square brackets. **The judgement of the experts is critical** in determining **how much weight to assign to different issues** when considering how all these potential sources of error should be integrated and how to rate the potential for error related to each. However, it is important that the process undertaken, including the weight given to various studies, be **replicable** and be described in a way that is **transparent** to readers.

- **Study informativeness:** The informativeness of a study is its ability to show a true preventive effect, if one exists, between the intervention and the outcome in a relevant population, and not to show an effect if one does not exist. Key determinants of informativeness include having a study population of sufficient size to obtain precise estimates of effect, sufficient elapsed time from intervention to measurement of outcome for an effect, if present, to be observable, presence of at least moderate heterogeneity of exposure to the intervention (intensity, frequency, and/or duration) in the study population, and biologically relevant definitions of the intervention.

(d) Meta-analyses and pooled analyses

Independent epidemiological studies of the same intervention with a comparatively weak effect or small sample size may produce inconclusive results that are difficult to summarize. Combined analyses of data from multiple studies may increase the precision of estimates. There are two types of combined analysis: (i) meta-analysis, which involves combining summary statistics, such as relative risks from individual studies; and (ii) pooled analysis, which involves a pooled analysis of the raw data from the individual studies (Greenland & O'Rourke, 2008). There are also "umbrella reviews", systematic reviews of multiple meta-analyses, which may be evaluated by the Working Group.

The strengths of combined analyses are increased precision due to increased sample size and, in the case of pooled studies, the opportunity to better control for potential confounders and to explore interactions and modifying effects that may help to explain heterogeneity between studies. A disadvantage of combined analyses is the possible lack of comparability of results from various studies, because of differences in specification of the intervention or the outcome, population characteristics, subject recruitment, data collection procedures, methods of measurement, and effects of unmeasured covariates, which may differ among studies. These differences in study methods and quality can influence the results of both pooled analyses and meta-analyses.

Meta-analyses considered by the Working Group may include high-quality published meta-analyses, updates of such meta-analyses, and new meta-analyses. When published meta-analyses are considered by the Working Group, they should comply with basic quality standards for meta-analyses and their underlying systematic reviews (e.g. AMSTAR, 2017):

their risk of bias is carefully evaluated, including the completeness of the studies included, the methods used to identify and the criteria used to select eligible studies, and the accuracy of the data extracted from the individual studies.

Subject to the judgement of the IARC Secretariat and in consultation with the Working Group, the updating of meta-analyses or the conduct of ad hoc meta-analyses may be performed by the Working Group and/or by the IARC Secretariat during preparation for a *Handbooks* meeting, when there are sufficient studies of an intervention–outcome association to aid the Working Group's assessment of the association. When results from both experimental and observational studies are available, any combined analyses should be conducted separately for experimental and observational studies, with consideration given to separate combined analyses of cohort and case–control studies, because of their different propensities to bias. The results of such ad hoc meta-analyses, which are specified in the text of the *Handbook* by presentation in square brackets, may come from the addition of the results of more recent studies to those of published meta-analyses or from de novo meta-analyses. Additional details on the conduct of such ad hoc meta-analyses are provided in the Instructions for Authors.

Irrespective of the source of the information for the meta-analyses and pooled analyses, the criteria for information quality applied are the same as those applied to individual studies. The sources of heterogeneity among the studies contributing to them are carefully considered and the possibility of publication bias evaluated.

(e) Considerations in assessing the body of epidemiological evidence

The ability of the body of epidemiological evidence to inform the Working Group about the cancer-preventive effect of an intervention is related to both the quantity and the quality of the evidence. There is no formulaic answer to the question of how many cancer prevention studies in humans are needed from which to draw inferences about preventive effect, although more than a single study in a single population will almost always be needed.

After the quality of individual epidemiological studies of cancer or of an intermediate outcome has been assessed and the informativeness of the various studies on the association between the intervention and cancer or an intermediate outcome has been evaluated, the body of evidence is assessed and a consensus scientific judgement is made about the strength of the evidence that the intervention under review prevents cancer in humans. In making its judgement, the Working Group considers several aspects of the body of evidence (e.g. Hill, 1965; Rothman et al., 2008; Vandenbroucke et al., 2016).

A strong association (e.g. a large relative risk or a relative risk that is well below 1.0) is more likely to be causal than a weak association, because it is harder for confounding or other biases to create a false strong association. However, it is recognized that estimates of effect of small magnitude do not imply lack of causality and may have a substantial impact on public health if the outcome is common or if the intervention is highly feasible. Estimates of effects of small magnitude can also contribute useful information if the magnitude of the effect correlates with the level of intervention in populations that are differently exposed.

Associations that are consistently observed in several studies of the same design, in studies that use different epidemiological approaches, or under different circumstances of intervention are more likely to indicate preventive efficacy or effectiveness than are isolated observations from single studies. If there are inconsistent results among investigations, possible reasons for such inconsistencies are sought – such as differences in time since initiation of the intervention (latency), intervention levels (e.g. dosage), or assessment

methods – and their implications for the overall findings are assessed.

Results of studies that are judged to be of high quality and highly informative are given more weight than those of studies that are judged to be methodologically less sound or less informative.

Temporality of the association is also an essential consideration, that is, the intervention must precede the outcome. The likelihood of reverse causation (i.e. the outcome prompts the intervention) is greater in observational studies of interventions, which often entail self-reported behaviour change, than in studies of static exposures.

An observation that cancer incidence decreases with increasing exposure to a putative preventive intervention is considered to be an indication of a preventive effect, although the absence of a graded response is not necessarily evidence against a causal relationship, and there are several reasons why the shape of the intervention–outcome association may be non-monotonic (e.g. Stayner et al., 2003).

Confidence in a causal interpretation of the evidence from studies in humans is enhanced if it is coherent with physiological and biological knowledge, including information about target organ exposure to the intervention, characteristics of tumour subtypes, and evidence of biological mechanisms by which the intervention could exert a cancer-preventive effect (see Part B, Section 4b).

The Working Group considers whether or not there are subpopulations with increased susceptibility to the cancer-preventive effects of the intervention. For example, studies that identify inter-individual differences in cancer susceptibility to the intervention on the basis of sociodemographic characteristics (e.g. age, sex, race, ethnicity), other behavioural factors (e.g. smoking or alcohol consumption), genetic polymorphisms, or age at first intervention (e.g. childhood interventions) may contribute to the identification of cancer-preventive interventions in humans. Such studies may be particularly informative if genetic polymorphisms are found to be modifiers of the intervention–outcome relationship, because evaluation of polymorphisms may increase the ability to detect an effect in susceptible subpopulations. Identifying susceptible subpopulations can also improve the specificity of targeting interventions.

2.2 Harms of the intervention

Potential harms to individuals that are linked to the intervention under review are also reviewed. Evidence of harm may come from any type of epidemiological study and may also be reported separately from evidence on the potential beneficial effects of the intervention. Although the *IARC Handbooks* do not formally evaluate the harms associated with an intervention in the way that is done for the benefits, the review of the evidence of harms aims to be as complete, rigorous, and informative as it is for the evidence of beneficial effects.

There are three broad categories of possible harms associated with interventions: (i) biological harm (e.g. toxicity of a chemopreventive agent), (ii) physical harm (e.g. injury associated with increased physical activity), and (iii) psychosocial harm (e.g. community-based interventions and social marketing campaigns specifically targeting obesity; Walls et al., 2011). Evidence of occurrence of biological, physical, and psychosocial harm (including emerging harms identified using qualitative methods in intervention studies) is reviewed and described, and the potential impacts of the harm are discussed.

Known financial harms or opportunity costs (Walls et al., 2011), which can apply at the individual level (e.g. higher cost of healthy foods, impacts of increases in tobacco taxes on smokers of lower socioeconomic status, membership of a weight-loss plan) or the community level (e.g. community-based interventions and campaigns), may be noted.

2.3 Balance of benefits and harms

Ideally, the benefits and harms of primary prevention interventions are expressed in similar terms, such as quality-adjusted life years (QALYs) gained (benefits) or lost (harms) per 1000 individuals of the target population. After identification of all published estimates of the balance of benefits and harms based on the same combination or combinations of intervention and outcome, the Working Group selects those based on the highest-quality evaluative studies of the intervention, critically assesses each, and summarizes the results, in narrative or tabular format as appropriate. The results do not contribute to the overall evaluation of each intervention, but they may be highlighted in the rationale after the evaluation and can be used to aid decisions about implementation of and participation in the relevant primary preventive interventions.

2.4 Cost–effectiveness

For a primary preventive intervention that can deliver a beneficial outcome, cost–effectiveness is usually expressed as the estimated financial cost of implementing the intervention per unit of benefit it delivers, which is most often measured in terms of QALYs gained. The ratio of costs to benefits (i.e. level of cost–effectiveness) needed to implement a health service programme varies from country to country, depending principally on the wealth of the country and on who pays (e.g. the government or individual citizens). Although most primary preventive interventions come at a net cost to health services, some can deliver a gain in QALYs and a reduction in health service cost (Vos et al., 2010). Although assessments of cost–effectiveness that account for all costs (e.g. that are not restricted to health service costs) are less frequently done, it is important to note that their perspective may differ markedly from one based on health service costs only.

Taking a similar approach to that taken for the balance of benefits and harms described above, the Working Group identifies published reports of well-conducted cost–effectiveness analyses based on the highest-quality evaluative studies of the primary preventive intervention, critically assesses each, and summarizes the results, in narrative or tabular format as appropriate. The results do not contribute to the overall evaluation of each intervention, but they may be highlighted in the rationale after the evaluation and can be used by governments and health services to aid decisions about implementation of the intervention for which there is sufficient evidence of a preventive effect. In addition, it is important to note that when the intervention is targeted towards a risk factor for cancer that is also a risk factor for other chronic diseases, any estimate of cost–effectiveness that is based solely on cancer is of limited use for policy purposes.

3. Studies of cancer prevention in experimental animals

(a) Types of study considered

Animal models are an important component of research on cancer prevention. Models are available that enable the evaluation of the effects of interventions on the development or progression of cancer in most major organ sites. Animal models for cancer include: (i) carcinogen-induced (e.g. chemical, physical, or infectious/biological); (ii) genetically engineered; (iii) transplantable systems (e.g. xenograft, organoid); and (iv) spontaneously developing tumours. Most cancer-preventive interventions investigated can be categorized at the biological level as those that: (i) prevent molecules from reaching or reacting with critical target sites; (ii) reduce the sensitivity of target tissues to carcinogens; or (iii) interrupt the evolution of the neoplastic process. There is increasing interest in the use of combinations of interventions as a means

of increasing efficacy and minimizing toxicity; animal models are useful in evaluating such combinations. The development of optimal strategies for intervention in humans can be facilitated by the use of animal models that mimic the neoplastic process in humans. The questions posed below (modified from Lewis et al., 2017) may assist in determining the relevance of individual studies in experimental animals to the evaluation of cancer-preventive effects in humans:

- Are the timing, route, level, and frequency of exposure comparable with those in humans, after accounting for relevant species differences?
- Is the cancer that is induced (i.e. by a biological, physical, or chemical agent, or genetic manipulation) relevant to the cancer in humans?
- Is the time at which the outcome is assessed relevant and justified?
- Does the study explore only mechanisms or pathways of cancer development?
- Is the outcome measure cancer incidence or progression rather than surrogate measures of tumour activity, such as tumour size or number of tumours?
- Do the outcome measures mimic those being evaluated in humans? More specifically, does the tumour mimic the human disease in terms of the organs or tissues affected, and at the histopathological or genetic level? Does the progression of the disease mimic the cancer in humans?

Relevant studies of cancer in experimental animals are identified using principles of systematic review as described in Part A and further detailed in the Instructions for Authors provided to each Working Group. Consideration is given to all available long-term (i.e. lifetime or near-lifetime) studies of cancer in experimental animals with the intervention under review and, when appropriate, related interventions (see Part A, Section 7). After a thorough evaluation of the pertinent study features (see Part B, Section 3b), studies judged to be irrelevant or inadequate according to the criteria determined in consultation with the Working Group may be excluded. Guidelines for conducting and reporting studies in experimental animals have been published (e.g. OECD, 2018; Percie du Sert et al., 2018).

(b) Study evaluation

Important considerations for assessing study quality include: (i) whether the intervention under review was clearly characterized; (ii) whether the intervention exposure or dose was characterized and monitored adequately; (iii) whether the control animals, exposure doses, duration of dosing, timing and frequency of dosing, duration of observation, and route of exposure to the intervention were appropriate; (iv) whether appropriate experimental animal species and strains were evaluated, including appropriate sex and age; (v) whether there were adequate numbers of animals per group; (vi) whether animals were allocated randomly to groups; (vii) whether all experimental conditions, with the exception of the tested intervention, were identical between the groups; (viii) whether the histopathology review was adequate; and (ix) whether the data were analysed correctly and reported according to well-accepted standards (e.g. Percie du Sert et al., 2018).

Specific factors to be considered in interpreting the results of cancer prevention experiments include: (i) the timing of the intervention over the course of the animals' lifespan; (ii) the timing and duration of administration of the intervention in relation to any carcinogen administration; (iii) dose–response effects; (iv) the site specificity of the anticipated cancer-preventive outcome; (v) the spectrum and relevance of the preventive outcome, from pre-neoplastic lesions to invasive cancers; (vi) the incidence, latency, and magnitude of the outcome, and the multiplicity

of the relevant neoplasms and/or other lesions; and (vii) the number and structural diversity of experimental or environmental exposures, and carcinogenic mechanisms underpinning the animals' baseline risk of the cancer to which the intervention was targeted. In addition, because administration of an intervention may result in prevention of tumours at one site but unintended consequences at other sites, it is important that multiple organs are examined in animal experiments.

Because certain factors, including diet, food or water consumption, infection, and stress, may modulate cancer risk, consideration should be given to the potential for interaction between these factors and the intervention being studied.

(c) Statistical considerations

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). An appropriate unit of analysis should be used (e.g. cage or individual animal in feed studies). The statistical methods should reflect the outcomes of the study (e.g. tumour incidence or multiplicity, or overall survival of the animals). For outcomes other than survival, the potential influence of different overall survival time between exposed and unexposed animals should be considered.

4. Mechanistic evidence and other relevant biological data

For a rational implementation of cancer-preventive measures, it is important not only to assess preventive end-points but also to understand the mechanisms by which the intervention exerts its cancer-preventive action. Mechanistic studies derived from human research and complemented by experimental models support cancer prevention research in humans by providing critical insight into the biological processes that can mediate the relationship between an intervention and a cancer outcome. Studies of mechanisms provide evidence for biological plausibility, inform causality, and can identify biomarkers relevant to the carcinogenic process. The study of mechanistic biomarkers can provide insights into human heterogeneity in response to carcinogens according to age, sex, genetic background, and other variables that are important to the application of cancer-preventive interventions in human populations. This array of possible contributions by mechanistic studies means that outcomes and end-points will vary widely depending on the types of intervention and the specific types of cancer examined in each *Handbook*.

Mechanistic studies and data are identified, screened, and evaluated for quality and human relevance using principles of systematic review, as described in Part A and further elaborated in the Instructions for Authors provided to each Working Group, and as detailed below.

(a) Types of studies considered

This section focuses primarily on studies in humans, including intervention trials and longitudinal studies with cancer-relevant biomarkers that may serve as exposure or intermediate end-points. Data from relevant experimental models may also be incorporated, especially when data from studies in humans are limited or are not practical to obtain.

(b) Evidence of cancer prevention

Possible mechanisms of action of interventions aiming at cancer prevention may include, but are not limited to: (i) altering the absorption, distribution, metabolism, and excretion of a known cancer-promoting or cancer-preventive agent; (ii) reducing endogenous DNA damage (e.g. by decreasing the oxidative stress and DNA–protein cross-links) or activating DNA repair or modulating epigenetic mechanisms;

(iii) altering host physiology, such as the endocrine environment (e.g. by modulation of exogenous ligands, including hormones) or the microbiome; (iv) affecting cell biology to reduce a cell's susceptibility to transformation, initiation, and progression of tumorigenesis (e.g. by regulating cell differentiation, proliferation, migration, invasion, and cell death through apoptosis and senescence); and (v) modifying the tumour microenvironment, including the inflammatory and immune responses. Inter-individual variations in these responses or outcomes associated with host factors such as age, sex, race/ethnicity, and genetic heterogeneity (e.g. metabolic polymorphisms) are also considered.

In the case of potentially chemopreventive agents, studies of absorption, distribution, metabolism, and excretion in humans and other mammalian species are summarized. The metabolic fate of the intervention agent is described, noting the metabolites that have been identified and their reactivity. A metabolic schema may indicate the relevant metabolic pathways and products, and whether supporting evidence is derived from studies in humans, in experimental animal systems, or in in vitro models. When available, physiologically based pharmacokinetic models and their parameter values are included.

(c) Harms of the preventive intervention

Any intervention that has putative beneficial effects must be assessed for potential harms. Toxic and other potentially harmful effects of a cancer-preventive intervention that are observed in studies in humans or studies in experimental animals and that might predict harmful effects in humans are reviewed, and the relevant evidence about them is summarized.

(d) Study quality and evidence synthesis

The Working Group summarizes the studies, with an emphasis on characterizing consistencies or differences in results within and across studies of varying experimental designs and model systems. Based on considerations of the quality of the studies (e.g. design, methods and reporting of results, as described in Part B, Section 3b) and relevance to humans, the Working Group may give greater weight to some included studies.

Evaluation of the results of studies in humans includes consideration of study quality, as discussed in Part B, Section 2. For observational and other studies of mechanisms of cancer prevention in humans, the quality of the study design, the intervention exposure assessment, and the accuracy (validity and precision) of the biomarker measurement are considered, as are other important factors, including those described for the evaluation of studies of cancer prevention in humans (Vermeulen et al., 2018). Specific guidelines to assess the quality of molecular biomarker and genetic studies are given in STROBE-ME (Gallo et al., 2011) and STREGA (Little et al., 2009), respectively.

In addition to studies in humans, mechanistic insights may be complemented by studies in experimental systems, including animal models (Le Magnen et al., 2016) and in vitro studies. Important considerations for in vitro studies include the ability of the system to recapitulate the carcinogenic process that occurs in humans and to model the exposure of the intervention as would be experienced in vivo (Lewis et al., 2017; Gordon et al., 2018).

The synthesis is focused on the evidence that is most informative for the overall evaluation. Evidence from several streams of mechanistic data, especially those from studies in humans, can strengthen mechanistic conclusions.

5. Summary of data reported

(a) Intervention characterization

The nature of the intervention and its characteristics, common use, and implementation in different settings, including geographical patterns and time trends, are summarized as

appropriate depending on the intervention under review. Intervention assessment methods used in key epidemiological studies reviewed by the Working Group, their strengths, and their limitations are also summarized.

(b) Cancer prevention in humans

Results of epidemiological studies pertinent to an evaluation of the cancer-preventive effects of the interventions and their harms in humans are summarized. The overall strengths and limitations of the epidemiological evidence are highlighted to indicate how the evaluation was reached. The target organ(s) or tissue(s) in which a decrease in cancer occurrence was observed are identified. Intervention–outcome associations and other quantitative data may be summarized when available. When the available epidemiological studies pertain to a mixed intervention (e.g. fruits and vegetables), the Working Group may seek to identify the specific agent or group of agents most likely to be responsible for any cancer-preventive effect. The evaluation is focused as narrowly as is appropriate or as the available data permit. Summaries of the evidence on the balance of benefits and harms and on cost–effectiveness are also provided.

(c) Cancer prevention in experimental animals

Results pertinent to an evaluation of a cancer-preventive effect in animals are summarized to indicate how the evaluation was reached. For each animal species and study design, it is stated whether or not changes in overall survival or tumour incidence, latency, severity, or multiplicity were observed, and the tumour sites are indicated. Dose–response patterns are also summarized. Possible harms of the intervention are noted.

(d) Mechanistic and other relevant data

Results pertinent to mechanisms of cancer prevention are summarized. The summary encompasses the informative studies on cancer-preventive mechanisms with adequate evidence for evaluation, and on any other aspects of sufficient importance to affect the overall evaluation. High-quality studies in humans, when available, are prioritized. In addition, supporting findings from experimental animal models or in vitro systems are summarized, especially when data from studies in humans are limited.

6. Evaluation and rationale

Evaluation of the evidence is guided by an analytical framework that depicts the relationships among the population, intervention, comparator, and outcomes (including both benefits and harms), and key contextual issues related to adherence to and implementation of the intervention and its impact on population health. The analytical framework may articulate both direct pathways (the intervention has a direct effect on cancer outcomes) and indirect pathways (the intervention has an effect on an intermediate outcome that has an established causal or preventive association with cancer incidence).

Consensus evaluations of the strength of the evidence of cancer-preventive effects of the intervention in humans, in experimental animals, and in mechanistic studies are made using transparent criteria and defined descriptive terms (see below). The Working Group then develops a consensus overall evaluation of the strength of the evidence that the intervention under review prevents cancer and assigns the intervention to one of four categories (see below).

When the Working Group has reviewed multiple, closely related interventions (e.g. different forms of an intervention on the same presumed cause of cancer), they may be grouped together for the purpose of a unified evaluation

of the strength of the evidence that they prevent cancer.

The framework for these evaluations, described below, may not encompass all factors relevant to a particular evaluation of preventive effect. After considering all relevant scientific findings, the Working Group may, exceptionally, assign the intervention to a different category from the one that a strict application of the framework would indicate, while providing a clear rationale for the overall evaluation reached.

When there are substantial differences of scientific interpretation among the Working Group members, the overall evaluation will be based on the consensus of the Working Group. A summary of the alternative interpretations may be provided, together with their scientific rationale and an indication of the degree of support for each.

The evaluation categories refer to the strength of the evidence that an intervention can prevent cancer in humans. Consideration may be given to how strongly or weakly the intervention can prevent cancer. In addition, actual and potential harms of the proposed intervention are addressed qualitatively and quantitatively, as the evidence base permits.

In what follows, the term "cancer prevention" refers to the **outcome of a *Handbooks* evaluation**, that is, to a **cancer outcome** or an **intermediate outcome**, as defined in the analytical framework. Thus, the wording of these evaluations is the same when an intermediate outcome, not cancer itself, is the outcome studied. As noted above, evaluation of an intermediate outcome is performed only when the intermediate outcome has an established causal or preventive association with cancer incidence.

(a) Cancer prevention in humans

Cancer-preventive effects in humans are evaluated on the basis of the principles outlined in Part B, Section 2. The evidence relevant to cancer prevention in humans is classified into one of the following categories:

Sufficient evidence of cancer prevention in humans: A causal preventive association between the intervention and cancer in humans has been established. That is, a cancer-preventive association has been observed consistently in the body of evidence (including several high-quality studies) and chance, bias, and confounding as causes of this association were ruled out with reasonable confidence.

Limited evidence of cancer prevention in humans: A causal preventive association between the intervention and cancer in humans is plausible. That is, a cancer-preventive association has been observed in the body of evidence, but chance, bias, or confounding as causes of this association could not be ruled out with reasonable confidence.

Inadequate evidence of cancer prevention in humans: The current body of evidence does not enable a conclusion to be drawn about the presence or absence of a preventive association between the intervention and cancer in humans. Common situations that lead to a determination of *inadequate evidence of cancer prevention in humans* include: (a) no data are available in humans; (b) there are studies available in humans, but of poor quality or informativeness; and (c) there are studies available in humans of sufficient quality, but their results are inconsistent or otherwise do not enable a conclusion to be drawn.

Evidence suggesting lack of cancer prevention in humans: There are several high-quality studies covering, through direct or indirect pathways, the full range of levels of the intervention that humans are known to encounter that are mutually consistent in not showing a preventive association between the intervention and the studied cancers at any observed level of intervention. The results from these studies alone or in combination had narrow confidence intervals with their upper bounds above or close to the

null value (e.g. a relative risk of 1.0). Similarly, bias and confounding as possible causes of this null result were ruled out with reasonable confidence, and the studies were considered informative. A conclusion of *evidence suggesting lack of cancer prevention in humans* is limited to the cancer sites, populations, life stages, conditions and levels of intervention, and length of observation covered by the pertinent studies. The target organ(s) or tissue(s) where evidence suggesting of lack of cancer prevention was observed in humans are identified.

(b) Cancer prevention in experimental animals

Cancer-preventive effects in experimental animals are evaluated on the basis of the principles outlined in Part B, Section 3. The evidence relevant to cancer prevention in experimental animals is classified into one of the following categories:

Sufficient evidence of cancer prevention in experimental animals: A preventive association has been established between the intervention and increased cancer-related survival, decreased incidence, increased latency, and/or decreased multiplicity of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in several independent, high-quality studies and model systems.

Limited evidence of cancer prevention in experimental animals: The data suggest a preventive association between the intervention and cancer in experimental animals. That is, an association has been observed but the data are limited for making a definitive evaluation because: (a) the evidence of a cancer-preventive association is based on only a few high-quality studies; (b) the intervention decreases incidence, increases latency, and/or decreases multiplicity only of benign neoplasms; or (c) there are unresolved questions about the adequacy of the design, conduct, or interpretation of the available studies.

Inadequate evidence of cancer prevention in experimental animals: The studies cannot be interpreted as showing the presence or absence of a preventive association between the intervention and cancer in experimental animals because of major qualitative or quantitative limitations of the data available, or no data are available on cancer in experimental animals.

Evidence suggesting lack of cancer prevention in experimental animals: Evidence from high-quality studies in several experimental models shows that, within the limits of the tests used (e.g. tumour site, age at intervention, conditions and levels of intervention tested), the intervention has no preventive association with cancer in experimental animals.

(c) Mechanistic evidence

Mechanistic studies are evaluated on the basis of the principles outlined in Part B, Section 4. The mechanistic evidence is classified into one of the following categories:

Strong mechanistic evidence: There are a substantial number of high-quality studies in humans that consistently link the intervention to a mechanistic pathway by which it could prevent cancer.

Limited mechanistic evidence: The evidence from mechanistic data in humans is suggestive of a cancer-preventive effect of the intervention, but (a) there are a limited number of high-quality studies, or (b) the studies cover a narrow range of experiments or relevant end-points, or (c) there are some inconsistencies in studies of similar design, or (d) there is unexplained incoherence across studies of different end-points, or (e) the available data are limited to studies in experimental model systems.

Inadequate mechanistic evidence: The evidence from mechanistic data in both humans and experimental model systems is lacking, or the data are inconsistent in linking the intervention to any mechanistic pathway by which it could prevent cancer.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole. Overall evaluation of the intervention is a matter of scientific judgement that reflects the strength of the evidence derived from the studies reviewed. The levels of evidence from studies in humans, mechanistic data, and studies in experimental animals are weighed into the overall evaluation, and statements are made about cancer prevention in humans with the wording of one of the standard categories as described below.

One of the two overall evaluation scenarios (see Part A, Section 3.1) will apply, depending on the nature of the evidence that has been reviewed (Table 4; see also Part A). If, for logistic reasons, evidence for Step 1 and Step 2 of Scenario 2 has been reviewed at two separate *Handbooks* meetings, no overall evaluation will be made for Step 2 alone.

None of these evaluations quantify the fraction of the burden of a particular cancer that a specific intervention would prevent; thus, some interventions may prevent a small fraction of the cancer, some may prevent a larger fraction, and these fractions may vary across populations, for example as a function of the prevalence of the relevant risk factors.

Overall evaluation categories

(i) The intervention *is established to prevent cancer in humans* (Group A)

This category is used for interventions for which there is *sufficient evidence* of cancer prevention in humans, either directly (Scenario 1) or in two steps (Scenario 2): from the intervention to the intermediate outcome (Step 1) and from the intermediate outcome to cancer (Step 2).

The organ sites on which the evidence in humans is based are stated here. A statement is also made of what the Working Group considers to be the magnitudes of the benefits and the harms of the intervention, in as nearly comparable terms as possible, for people adhering to the intervention as commonly implemented in practice, and whether or not the benefits outweigh the harms.

(ii) The intervention *probably prevents cancer in humans* (Group B1)

In Scenario 1, this category is used for interventions for which there is *limited evidence* of cancer prevention in humans and either *strong mechanistic evidence* in humans or *sufficient evidence* in experimental animals with all the criteria for the relevance to humans being met (see Part B, Section 3a).

In Scenario 2, this category is used for interventions for which there is *sufficient evidence* in humans that the intervention has a cancer-preventive effect on the intermediate outcome (Step 1), *limited evidence* that the intermediate outcome has a cancer-preventive effect in humans (Step 2), and either *sufficient evidence* in experimental animals with all the criteria for the relevance to humans being met or *strong mechanistic evidence* in humans (see Part B, Section 3a). Alternatively, this category is used when there is *limited evidence* in humans that the intervention has a cancer-preventive effect in the intermediate outcome (Step 1) and *sufficient evidence* that the intermediate outcome has a cancer-preventive effect in humans (Step 2).

(iii) The intervention *possibly prevents cancer in humans* (Group B2)

In Scenario 1, this category is used for interventions for which there is *limited evidence* of cancer prevention in humans, *less than strong evidence* from mechanistic data, and *less than sufficient evidence* of cancer prevention in experimental animals.

In Scenario 2, this category is used when (i) there is *sufficient evidence* in humans that the intervention has a cancer-preventive effect on the intermediate outcome (Step 1), and *limited evidence* in humans and *less than sufficient evidence* in experimental animals or *less than strong evidence* from mechanistic data that the intermediate outcome has a cancer-preventive

Table 4 Summary of the strength of the evidence in each evidence stream contributing to the overall evaluation

<table>
<tr><th colspan="4">Scenario 1: Direct evidence that the intervention prevents cancer</th></tr>
<tr><th>Strength of the evidence that the intervention prevents cancer in humans</th><th>Strength of the evidence from mechanistic studies that the intervention prevents cancer</th><th>Strength of the evidence that the intervention prevents cancer in experimental animals</th><th>Overall evaluation</th></tr>
<tr><td>Sufficient</td><td>–</td><td>–</td><td>Group A</td></tr>
<tr><td>Limited</td><td>Strong</td><td>–</td><td>Group B1</td></tr>
<tr><td>Limited</td><td>–</td><td>Sufficient</td><td>Group B1</td></tr>
<tr><td>Limited</td><td>Less than strong</td><td>Less than sufficient</td><td>Group B2</td></tr>
<tr><td>Inadequate</td><td>–</td><td>–</td><td>Group C</td></tr>
<tr><td>Evidence suggesting lack of cancer prevention</td><td>–</td><td>Evidence suggesting lack of cancer prevention</td><td>Group D</td></tr>
<tr><th colspan="4">Scenario 2: Evidence that the intervention prevents cancer by way of an intermediate outcome
(risk factor or preventive factor)</th></tr>
<tr><th>Step 1</th><th colspan="2">Step 2[a]</th><th rowspan="2">Overall evaluation[a]</th></tr>
<tr><th>Strength of the evidence that the intervention decreases exposure to the risk factor or increases exposure to the preventive factor in humans</th><th>Strength of the evidence that decreasing exposure to the risk factor or increasing exposure to the preventive factor prevents cancer in humans</th><th>Strength of the evidence that decreasing exposure to the risk factor or increasing exposure to the preventive factor prevents cancer in experimental animals or mechanistic studies[b]</th></tr>
<tr><td>Sufficient</td><td>Sufficient[c]</td><td>–</td><td>Group A</td></tr>
<tr><td>Sufficient</td><td>Limited</td><td>Sufficient</td><td>Group B1</td></tr>
<tr><td>Sufficient</td><td>Limited</td><td>Less than sufficient</td><td>Group B2</td></tr>
<tr><td>Limited</td><td>Sufficient</td><td>–</td><td>Group B1</td></tr>
<tr><td>Limited</td><td>Limited</td><td>–</td><td>Group B2</td></tr>
<tr><td>Inadequate</td><td>–</td><td>–</td><td>Group C</td></tr>
<tr><td>–</td><td>Evidence suggesting lack of cancer prevention</td><td>Evidence suggesting lack of cancer prevention</td><td>Group D</td></tr>
<tr><td>Evidence suggesting lack of cancer prevention</td><td>–</td><td>–</td><td>Group D</td></tr>
</table>

[a] This overall evaluation applies only when evidence from both Step 1 and Step 2 is available. When a *Handbook* evaluates only Step 2, no overall evaluation is made.
[b] Evidence in experimental animals and mechanistic data is considered to be *sufficient* when there is *strong evidence* from mechanistic data (mechanistic studies in humans) or *sufficient evidence* in experimental animals.
[c] The evidence in this category may be considered to be *sufficient* when it is based on observational studies of change in cancer incidence associated with self-reported or observed (by way of time-separated repeated measures) change in the level of a risk factor or preventive factor (e.g. smoking cessation; increase in consumption of fruits and vegetables), OR, exceptionally, studies of variation in cancer incidence with the level of a risk factor or preventive factor measured at one time point.

effect; OR (ii) there is *limited evidence* in humans that the intervention has a cancer-preventive effect on the intermediate outcome (Step 1), and *limited evidence* in humans that the intermediate outcome has a cancer-preventive effect, and any evidence category in experimental animals and mechanistic data.

When the evidence is classified in Group B1 or Group B2, the evaluation is followed by a description of harms, actual and potential.

(iv) The intervention *is not classifiable as to its capacity to prevent cancer in humans* (Group C)

In both Scenario 1 and Scenario 2, this category is used for interventions for which there is *inadequate evidence* in humans, irrespective of the level of evidence from mechanistic data and studies in experimental animals. Interventions that do not fall into any other category are also placed in this category.

***(v)* The intervention *probably does not prevent cancer in humans* (Group D)**

In Scenario 1, this category is used for interventions for which there is *evidence suggesting lack of cancer prevention* both in humans and in experimental animals. In Scenario 2, this category is used when there is *evidence suggesting lack of cancer prevention* both in humans and in experimental animals for the intermediate outcome to cancer, irrespective of the level of evidence for the intervention to the intermediate outcome; or there is *evidence suggesting lack of cancer prevention* for the intervention to the intermediate outcome, irrespective of the level of evidence for the intermediate outcome to cancer.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is summarized so that the basis for the evaluation offered is transparent. It includes concise statements of the principal line or lines of argument that emerged in the deliberations of the Working Group, the conclusions of the Working Group on the strength of the evidence for each stream, an indication of the body of evidence that was pivotal to these conclusions, and an explanation of the reasoning of the Working Group in making evaluations.

In the rationale, the Working Group may draw attention to the fact that actions on the evaluations should be taken in the light of country- or setting-specific circumstances that influence the public health priority, feasibility, and acceptability of programmes based on the interventions evaluated.

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GENERAL REMARKS

In 1987, the *IARC Monographs* programme first classified alcoholic beverages as carcinogenic to humans (Group 1), on the basis of *sufficient evidence* of causality for cancers of the oral cavity, pharynx, larynx, oesophagus, and liver in humans (IARC, 1988). Subsequent reviews and evaluations of the evidence for *IARC Monographs* Volumes 96 and 100E (IARC, 2010, 2012) and for the World Cancer Research Fund/American Institute for Cancer Research Continuous Update Project (WCRF, 2023) reaffirmed that alcohol consumption causes the above-mentioned five types of cancer – specifying that the evidence was *sufficient* for squamous cell carcinoma of the oesophagus and hepatocellular carcinoma of the liver – and extended the list to include cancers of the colorectum and of the female breast.

The causal effects of alcoholic beverage consumption on cancer risk do not differ by beverage type (IARC 2010, 2012; WCRF, 2023). Also, for cancers of the oral cavity, pharynx, larynx, oesophagus, and breast, risk increases for any amount of consumption (WCRF, 2023).

The World Health Organization (WHO) reports that alcohol consumption contributes to more than 200 diseases, injuries, and other health conditions, and estimates that about 3 million deaths annually (5.3% of all deaths worldwide) are attributable to harmful use of alcohol (WHO, 2022). Regarding cancer, it was estimated that in 2020, 4.1% of all new cancer cases globally were attributable to alcohol consumption (Rumgay et al., 2021).

Rationale for *IARC Handbooks* Volumes 20A and 20B on alcohol control

Promoting reduction or cessation of alcoholic beverage consumption could have a substantial impact on reducing alcohol-related morbidity and mortality. In 2010, the Sixty-third World Health Assembly endorsed the Global Strategy to Reduce the Harmful Use of Alcohol (Resolution WHA63.13) (WHO, 2010). This strategy includes 10 recommended target areas for population-level policies and individual-level interventions.

Alcohol control policies or other interventions to reduce alcohol-related cancer risk have not been evaluated before by the *IARC Handbooks* programme. Following a request by and in collaboration with the WHO Regional Office for Europe, the *IARC Handbooks* programme undertook to prepare two volumes on alcohol control to address this knowledge gap. The analytical framework for the review and evaluation of the evidence that alcohol control policies reduce cancer incidence or mortality follows Scenario 2, as described in the Preamble to the

IARC Handbooks for Primary Prevention (IARC, 2019). Scenario 2 involves a two-step process. In Step 1, the effect of a specified intervention on an intermediate outcome (e.g. exposure to a risk factor) is evaluated. In Step 2, the effect of the change in the intermediate outcome (e.g. decrease in exposure to the risk factor) on cancer incidence in humans is evaluated (Fig. 1A). The Preamble further stipulates that if Step 2 has not yet been established from authoritative sources, then Step 2 should be conducted first.

Accordingly, *IARC Handbooks* Volume 20A provides the review and evaluation of the epidemiological and mechanistic evidence that reduction or cessation of alcoholic beverage consumption reduces the risk of each of the seven alcohol-related cancer types (Step 2) (Fig. 1B). *IARC Handbooks* Volume 20B will provide the review and evaluation of the available evidence that selected population-level alcohol control policies lead to a reduction or cessation of alcoholic beverage consumption.

Considerations on *IARC Handbooks* Volume 20A

The primary goal of *IARC Handbooks* Volume 20A is to provide a critical appraisal of the human epidemiological and mechanistic evidence on reduction or cessation of alcoholic beverage consumption in relation to the risk of the seven alcohol-related cancer types.

In reviewing the literature, the Working Group noted that the terms used to characterize drinking status (e.g. lifetime abstinence, recent abstinence, current drinking), the amount of consumption (e.g. light, moderate, heavy), and the amount of pure alcohol (i.e. ethanol) in a single alcoholic drink have been defined differently among different studies, in different settings, and between men and women, and have changed over time. In a recent WHO report, drinking status was categorized as abstinence over the lifetime, abstinence in the previous 12 months (i.e. former drinking), and current consumption. The amount of alcohol consumed was categorized as moderate (≤ 2 drinks per day), risky (3–6 drinks per day), and heavy (> 6 drinks per day), where a single drink contains 10 g of pure alcohol (WHO, 2020). However, because of the variability among studies reviewed, these terms are specifically defined in each section and, when appropriate, for each study.

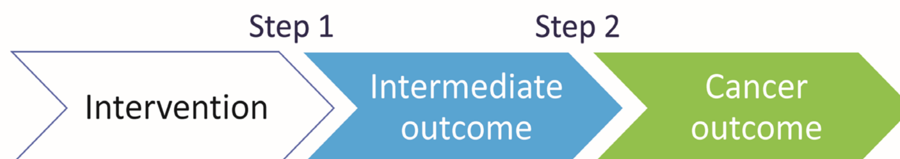
Similarly, when reviewing the epidemiological evidence, the Working Group identified numerous methodological concerns. These concerns were carefully considered and are described and discussed in detail in Section 2.1. Section 3 provides, for the first time, a review and evaluation of the available evidence on biological mechanisms of cessation of alcoholic beverage consumption. This evidence comes largely from studies conducted among individuals with alcohol use disorders who are in treatment and have become abstinent. Although the biological effects of alcohol cessation in this group may differ from the effects of cessation among individuals who drink lower amounts, these studies inform our understanding of the effects of alcohol cessation on alcohol-related carcinogenesis.

The Working Group did not quantify the extent of risk reduction due to reduction or cessation of alcoholic beverage consumption, overall or for any strata of amount of alcohol originally consumed. Nor did the Working Group quantify the time course of cessation necessary to observe a reduction in cancer risk.

Fig. 1 (A) The *IARC Handbooks* analytical framework for review of the evidence for primary prevention; (B) *IARC Handbooks* Volumes 20A and 20B.

A

Scenario 2: A two-step evaluative framework from which, for scientific reasons, the level of evidence that an intervention prevents cancer is established by way of an intermediate outcome.

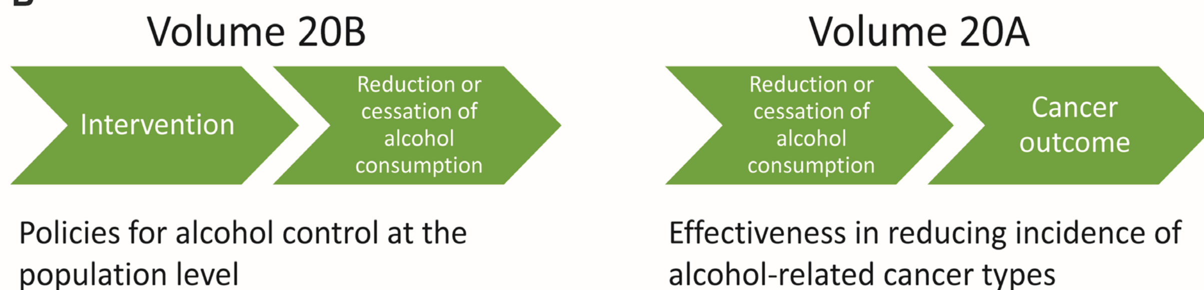


Intermediate outcome = decreased exposure to a risk factor or increased exposure to a preventive factor

Step 1: The effect of a specified intervention on an intermediate outcome, such as exposure to a particular risk factor or preventive factor for cancer in humans, is evaluated.

Step 2: The effect of the change in the intermediate outcome (decrease in exposure to the risk factor or increase in exposure to the preventive factor) on cancer incidence in humans is evaluated.

B



Alcoholic beverage consumption guidelines for cancer prevention

Current alcohol consumption guidelines and recommendations from public health agencies have relied on evidence from studies that assessed alcohol consumption in relation to disease risk. Some guidelines and recommendations are specific for cancer prevention. For example, the European Code Against Cancer states "If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention" (Schüz et al., 2015), the World Cancer Research Fund guideline for the United Kingdom states "To reduce your cancer risk as much as possible, we recommend not drinking alcohol at all. If you do choose to drink alcohol, follow national guidelines. In the UK, the guideline is to drink no more than 14 units a week, spread over at least three days for both men and women" (WCRF, 2024), and the American Cancer Society's guideline for diet and physical activity for cancer prevention states "It is best not to drink alcohol. People who choose to drink alcohol should limit their intake

to not more than 2 drinks per day for men and 1 drink per day for women" (Rock et al., 2020). To reduce all alcohol-related harm, the WHO position, issued in 2023, is that no amount of alcohol consumption is safe, even low intakes (Anderson et al., 2023; WHO, 2023).

Public awareness that consumption of alcoholic beverages causes cancer

Public awareness that alcohol consumption is an established cause of cancer is limited, although the extent of such awareness varies globally. In some countries, less than 50% of the population report alcohol consumption as a risk factor for cancer (Scheideler and Klein, 2018). In one survey of people in the USA, only one third reported believing that alcohol was a risk factor for cancer (Kiviniemi et al., 2021).

Overall, *IARC Handbooks* Volume 20A is an important contribution to the understanding of the impact of reduction and cessation of alcohol consumption on reducing cancer risk. It extends the existing evidence base for alcohol consumption guidelines for cancer prevention by establishing that reduction or cessation of alcohol consumption plays a role in cancer prevention. In addition, it has the potential to influence public health organizations' communication strategies focused on increasing awareness of the link between alcohol consumption and cancer risk by highlighting the benefits of alcohol reduction and cessation in reversing alcohol-related cancer risk.

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LIST OF ABBREVIATIONS

^{51}Cr-EDTA	^{51}Cr-labelled ethylenediaminetetraacetic acid
ACTH	adrenocorticotropic hormone
ADH	alcohol dehydrogenase
ALD	alcohol-related liver disease
ALDH	aldehyde dehydrogenase
APC	alcohol per capita consumption
ARH	alcohol-related hepatitis
AUD	alcohol use disorder
BMI	body mass index
CAP	controlled attenuation parameter
CCL2	C–C motif chemokine ligand 2
CI	confidence interval
CLD	chronic liver disease
CRP	C-reactive protein
CYP2E1	cytochrome P450 2E1
DSM	Diagnostic and Statistical Manual of Mental Disorders
ER	estrogen receptor
FDR	false discovery rate
GPx	glutathione peroxidase
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HED	heavy episodic drinking
HLI	healthy lifestyle index
HOMA	homeostatic model assessment
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
I-FABP	intestinal fatty acid binding protein
IFN-γ	interferon γ
IgG	immunoglobulin G
IL-17	interleukin 17
INHANCE	International Head and Neck Cancer Epidemiology

IP-10	interferon γ-induced protein 10
IRR	incidence rate ratio
JACC	Japan Collaborative Cohort Study for Evaluation of Cancer Risk
K_M	Michaelis constant
KORA	Cooperative Health Research in the Augsburg Region
LBP	lipopolysaccharide binding protein
LHD	less heavy drinking
LPS	lipopolysaccharide
MAIT	mucosal-associated invariant T
MCCS	Melbourne Collaborative Cohort Study
mRNA	messenger RNA
NADH	nicotinamide adenine dinucleotide, reduced form
NK	natural killer
OR	odds ratio
PAF	population attributable fraction
PCR	polymerase chain reaction
PR	progesterone receptor
PTH	parathyroid hormone
rDNA	ribosomal DNA
RR	relative risk
SCC	squamous cell carcinoma
sCD14	soluble CD14
SD	standard deviation
SHBG	sex hormone-binding globulin
TNF-α	tumour necrosis factor α
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone
VHD	very heavy drinking
WHO	World Health Organization

GLOSSARY

Alcohol use disorder	A medical condition characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences. It encompasses the conditions that some people refer to as alcohol abuse, alcohol dependence, alcohol addiction, and the colloquial term alcoholism. According to World Health Organization (WHO) nomenclature, alcohol use disorders include two diagnostic categories of the 11th revision of the International Classification of Diseases (ICD-11): alcohol dependence and harmful pattern of alcohol use.
Cirrhosis	A consequence of chronic liver inflammation that is followed by diffuse hepatic fibrosis, in which the normal hepatic architecture is replaced by regenerative hepatic nodules, which eventually leads to liver failure.
Dysbiosis	A microbial imbalance on or inside the body, commonly observed within the digestive tract, where it has been associated with illness.
Endotoxaemia	The presence of endotoxins in the blood; endotoxins are toxic substances bound to the cell wall of certain bacteria.
Genomic polymorphism	The presence of two or more genomic variant forms of a specific DNA sequence that occur among different individuals or populations. The most common type of polymorphism involves variation at a single nucleotide (also called a single-nucleotide polymorphism, or SNP). Other genomic polymorphisms can involve longer stretches of DNA.
Heavy episodic drinking	Consuming 60 grams or more of pure alcohol on at least one occasion in the past 30 days. A consumption of 60 grams of pure alcohol corresponds approximately to 6 standard alcoholic drinks in many countries. Definitions by other organizations may differ in the level of consumption or the amount of pure alcohol per drink, and may be sex-specific.
Heterozygote	A diploid individual with different alleles at one or more genetic loci.
Homozygote	A diploid individual with identical alleles at one or more genetic loci.
Low- and middle-income countries	Countries with a gross national income (GNI) per capita of up to US$ 13 845 in 2022.
Michaelis constant (K_M)	The concentration of the substrate at which the reaction velocity is 50% of the maximum velocity (V_{max}).
Microbiome	The microbiome contains the microbiota (community of microorganisms) and their theatre of activity (structural elements, metabolites/signal molecules, and the surrounding environmental conditions).
Population attributable fraction	The proportion of an outcome that would be avoided in a population over a given period of time by decreasing the population's exposure to a risk factor to a theoretical-minimum-risk level.
Population preventable fraction	The proportion of an outcome that would be avoided in a population over a given period of time by decreasing the population's exposure to a risk factor to an attainable level.

Pyroptosis	An inflammatory form of cell death that not only protects multicellular organisms from invasion by pathogenic bacteria and microbial infections but can also lead to sepsis and lethal septic shock if overactivated.
Recorded alcohol	Alcoholic beverages consumed according to the official statistics at the country level based on production, import, export, and sales or taxation data and intended for consumption.
Secosteroid hormone	A molecule that is very similar structurally to steroids but in which one of the four carbon rings is broken and the B-ring carbon atoms are not joined. An example is vitamin D.
Sociodemographic index	A summary measure of overall development based on educational attainment, fertility, and income per capita within a location.
Surrogate alcohol	Non-beverage alcohol that is not officially intended for human consumption.
Total adult alcohol per capita consumption (APC)	The total amount of alcohol consumed per person (individuals aged ≥ 15 years) over a calendar year, in litres of pure alcohol. The estimate is the sum of the 3-year average of the per capita (≥ 15 years) recorded alcohol consumption and of the per capita (≥ 15 years) unrecorded alcohol consumption for a calendar year, adjusted for tourist consumption.
Tourist consumption	Tourist consumption takes into account consumption by tourists visiting the country and consumption by inhabitants visiting other countries. Positive figures denote alcohol consumption of outbound tourists being greater than alcohol consumption by inbound tourists, and negative numbers the opposite. Tourist consumption is based on United Nations tourist statistics.
Unrecorded alcohol	Alcohol products that are not taxed and are outside the official system of government control, such as home or informally produced (legal or illegal) alcohol, smuggled alcohol, surrogate alcohol, or alcohol products obtained through cross-border shopping (i.e. recorded in a different jurisdiction).
WHO African Region	Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cabo Verde, Cameroon, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Eswatini, Ethiopia, Gabon, The Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, South Africa, South Sudan, Togo, Uganda, United Republic of Tanzania, Zambia, Zimbabwe.
WHO Eastern Mediterranean Region	Afghanistan, Bahrain, Djibouti, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates, West Bank and Gaza Strip, Yemen.
WHO European Region	Albania, Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Monaco, Montenegro, The Netherlands, North Macedonia, Norway, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, Türkiye, Turkmenistan, Ukraine, United Kingdom, Uzbekistan.
WHO Region of the Americas	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia (Plurinational State of), Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, USA, Venezuela (Bolivarian Republic of).
WHO South-East Asia Region	Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste.
WHO Western Pacific Region	Australia, Brunei Darussalam, Cambodia, China, Cook Islands, Fiji, Hong Kong Special Administrative Region, Japan, Kiribati, Lao People's Democratic Republic, Macao Special Administrative Region, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, New Zealand, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Singapore, Solomon Islands, Taiwan (China), Tonga, Tuvalu, Vanuatu, Viet Nam.

1. ALCOHOLIC BEVERAGES

1.1 Definitions and types of products

1.1.1 Types of products containing alcohol for human consumption

There are two main categories of products containing alcohol: (i) alcoholic beverages, which are liquids containing ethanol (or ethyl alcohol: C_2H_5OH) that are intended for consumption (WHO, 2018), and (ii) surrogate alcohol, which is non-beverage alcohol that is not officially intended for human consumption (WHO, 2021). Alcohol products for consumption can also be categorized as either (i) recorded alcohol, which refers to alcoholic beverages consumed according to the official statistics at the country level based on production, import, export, and sales or taxation data and intended for consumption, or (ii) unrecorded alcohol, which refers to alcohol products that are not taxed and are outside the official system of government control, such as home or informally produced (legal or illegal) alcohol, smuggled alcohol, surrogate alcohol, or alcohol products obtained through cross-border shopping (i.e. recorded in a different jurisdiction) (UNSTAT, 2020). In 2019, about 21% of global alcohol consumption was unrecorded (WHO, 2024).

Alcoholic beverages are typically produced through yeast fermentation of carbohydrate-rich staple foods such as cereals, grapes, fruits, vegetables, or potatoes, with or without subsequent distillation (Peterson, 2013). The main categories of alcoholic beverages are beer, wine, and spirits (WHO, 2010). Because ethanol is the main type of alcohol found in alcoholic beverages, the term “alcohol” is usually used as a synonym for ethanol and, by extension, for alcoholic beverages (European Commission, 2022). Most countries that have a legal definition for “alcoholic beverages” set ethanol content thresholds, which range from 0.8% volume in the World Health Organization (WHO) Region of the Americas to 1.3% volume in the WHO European Region (WHO, 2010, 2014, 2018). The ethanol content varies by the major type of beverage and also by country, because of local customs or regulations. Beer generally contains 4–5% volume of alcohol, but the content can range from < 2% to > 10% volume (alcohol content is lower in alcoholic beverages produced at home or locally, such as sorghum beer); wine is about 12% volume, with a range of 8–15% volume, and spirits range from 15–20% volume for liqueurs and aperitifs to > 40% volume for vodka and whiskey (IARC, 2010). Chinese strong spirits may contain ≥ 50% volume (Zheng and Han, 2016). Alcopops, hard seltzer, or other types of flavoured alcoholic drinks or pre-mixed packaged beverages typically contain 4–7% volume of alcohol (IARC, 2010). In recent decades, beverages with a

reduced or lower volume of alcohol and non-alcoholic variants of alcoholic beverages have been developed (Anderson et al., 2021; Okaru and Lachenmeier, 2022). Table 1.1 provides an overview of the ethanol content of various alcoholic beverages.

Alcohol-containing commodities sold on regional and international markets include beer made from barley, wine made from grapes, and several types of distilled spirits. However, in many low- and middle-income countries, home-made, artisanal, or locally produced alcoholic beverages, such as sorghum beer, palm wine, and sugarcane spirits, are the main types of alcoholic beverages available (WHO, 2004; IARC, 2010).

1.1.2 Toxicants in alcohol products

The *IARC Monographs* programme has classified alcoholic beverages (Volumes 44, 96, and 100E), ethanol in alcoholic beverages (Volumes 96 and 100E), and acetaldehyde associated with consumption of alcoholic beverages (Volume 100E) as carcinogenic to humans (Group 1) (IARC, 1988, 2010, 2012a).

In addition to ethanol and acetaldehyde, alcoholic beverages may contain several toxicants that are derived from the raw materials used or that may arise during the production process (IARC, 2010; Fuller et al., 2011b). Some of these agents are carcinogenic (IARC, 2010) (Table 1.2).

Occasionally, toxic compounds that are not approved for use in commercial production are deliberately added to alcohol products, most often in unrecorded alcohol. Of these toxic compounds, methanol is the one associated with the greatest burden of morbidity, including blindness, and mortality (Fuller et al., 2011b). Methanol poisonings of individuals and groups of people associated with consumption of unrecorded alcohol have been regularly reported worldwide in recent decades (Lachenmeier et al., 2021).

1.1.3 Nutritional aspects of alcohol consumption

The primary components of most alcoholic beverages are alcohol and water; some sweet liqueurs may contain more sugar than ethanol (IARC, 2010).

Alcoholic beverages may also contain other macronutrients, such as carbohydrates, nitrogen (proteins and amino acids), and lipids (fats). Carbohydrates are present in significant amounts in fermented alcoholic beverages such as wine and beer, whereas nitrogen and lipids are present in relatively small amounts. All three macronutrients are typically absent from distilled spirits (Peterson, 2013). Alcohol provides 7 kcal/g [29 kJ/g] of energy, which is more than for carbohydrates or proteins and almost as much as for pure fat (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2013; European Commission, 2022; WHO, 2022a). Alcoholic beverages can contribute significantly to total energy intake, and their calories have no nutritional value (Fuller et al., 2011a, b; WHO, 2022a). Alcohol consumption without a concomitant reduction in energy intake from carbohydrates, fats, and proteins can lead to an excess in energy intake (Fuller et al., 2011b). Evidence suggests that energy intake from alcohol is more likely to contribute to weight gain in people who have a high fat intake and a low level of physical activity, who are overweight, and who have a family history of obesity (WHO, 2022a).

1.2 Surveillance, prevalence, trends, and determinants of consumption

1.2.1 Monitoring of consumption at the population level

Alcohol consumption is monitored in many countries, and globally by WHO (Poznyak et al., 2013). The monitoring systems can be broadly

Table 1.1 Variety and strength of selected commercially and non-commercially produced alcoholic beverages worldwide

Product name	Country or region	Ethanol content (% volume)[a]
1. Fermented alcoholic beverages		
(a) Commercially produced		
Beer	USA	2.9–8.5
	Germany	3.2–7.8
	Bangladesh	4–8
Table wine	USA	6.0–20.0
Toddy	Bangladesh	5–10
(b) Local/homebrewed/unrecorded		
Tella (brewed from various grains)	Ethiopia	3.8–6.5
Tej (honey wine)	Ethiopia	8.9–13.2
Fruit wine	Poland	9.5–12.2
Unrecorded wine and fortified wine	Europe	9.6–23.5
2. Distilled alcoholic beverages		
(a) Commercially produced		
Bourbon	USA	32.3–50.7
Brandy	USA	28.0–40.0
Cognac	USA	38.7–40.7
Fruit spirits	Germany	31.2–49.1
Vodka	Ukraine	39.3–39.9
(b) Local/homemade/unrecorded		
Areki (distilled grain fermentation)	Ethiopia	34.0–39.9
Bai jiu	China	40.8–72.1
Samohon	Ukraine	32.5–52.2
Unrecorded spirits	Poland	18.8–85.3
Chang'aa	Kenya	42.8–85.8
Ogogoro	Nigeria	32.2–42.6
Unrecorded spirits	Europe	20.8–88.8
Ekchuani (rice spirits)	Bangladesh	30–40
3. Other types		
Alcopops	International	5–8
Low alcohol	International	0.5–1.2[b]
No alcohol or alcohol-free	International	< 0.5[b]

[a] Decimals as reported in the original article.
[b] Conventions for ethanol or alcohol content (% volume) in no and low (NoLo) alcohol products vary widely among countries (range for low alcohol, 0.05–2.8; range for no alcohol, ≤ 0.05–≤ 2.8) (Okaru and Lachenmeier, 2022).
Compiled by the Working Group (Lachenmeier and Musshoff, 2004; Ejim et al., 2007; Lachenmeier et al., 2009, 2010, 2011; Guelinckx et al., 2011; DiLoreto et al., 2012; Yohannes et al., 2013; Dewan and Chowdhury, 2015; Okaru et al., 2017; Newman et al., 2018; Okaru and Lachenmeier, 2022).

Table 1.2 IARC evaluations of agents that may be present in alcoholic beverages

Agent	Occurrence in alcoholic beverages[a]	IARC evaluation (Group)[b]
Acetaldehyde associated with consumption of alcoholic beverages[c]	All types	1
Acetaldehyde	All types	2B
Acrolein	All types	2A
Acrylamide	Beer	2A
Aflatoxins	Beer and unrecorded fermented products	1
Alcoholic beverages	–	1
Aniline	Historical use: wine adulterant	2A
Arsenic	All types	1
Benzene	Contaminated beer	1
Cadmium	All types	1
Crotonaldehyde	Beer and spirits	2B
Ethanol in alcoholic beverages	(1.5–80% volume)	1
Ethyl carbamate (urethane)	All types, with major occurrence in stone-fruit spirits	2A
Formaldehyde	All types	1
Furan	Beer	2B
Furfuryl alcohol	Wine and beer	2B
Glyphosate	Beer	2A
Lead compounds, inorganic	All types	2A
3-Monochloro-1,2-propanediol	Beer	2B
4-Methylimidazole	Some coloured products	2B
β-Myrcene	Beer and some flavoured products	2B
N-Nitrosodimethylamine	Beer	2A
Ochratoxin A	Wine and beer	2B
Pentachlorophenol	Oak-barrel aged beverages	1
Pulegone	Some flavoured products	2B
Safrole	Some spirits	2B
2,4,6-Trichlorophenol	Oak-barrel aged beverages	2B

IARC, International Agency for Research on Cancer.
[a] The concentrations of most compounds vary, depending on the origin of a beverage, differing production technologies, and the level of contamination, which typically is trace level. Most jurisdictions provide guidelines or regulations to mitigate contamination of beverages containing alcohol.
[b] Agents classified by the *IARC Monographs* programme. Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; Group 3, not classifiable as to its carcinogenicity to humans. https://monographs.iarc.who.int/agents-classified-by-the-iarc/
[c] Refers to the acetaldehyde that forms in the body after ingestion of alcohol.
Compiled by the Working Group (Lachenmeier et al., 2012; Pflaum et al., 2016; Okaru and Lachenmeier, 2021; IARC, 1976, 1978, 1980, 1982a, 1982b, 1985, 1987a, 1987b, 1988, 1991, 1993a, 1993b, 1995a, 1995b, 1999, 2002, 2006a, 2006b, 2010, 2012a, 2012b, 2012c, 2013, 2015, 2017, 2018, 2019a, 2019b, 2021a, 2021b, 2022).

divided into two categories: monitoring based on routine government statistics, such as taxation, production, and imports and exports in a country (Rehm et al., 2007), and monitoring by national surveys (Nugawela et al., 2016).

Recorded alcohol consumption data for almost every country are based on routine statistics (Rehm et al., 2007; Poznyak et al., 2013). Unrecorded alcohol consumption data are based on surveys (such as the WHO STEPS survey) (WHO, 2005), derived from expert judgements (Rehm and Poznyak, 2015), or estimated statistically on the basis of economic data, levels of poverty and malnutrition, prohibition of alcohol, and region (Probst et al., 2019). Tourist consumption data are based on United Nations tourist statistics and take into account consumption by tourists visiting the country and consumption by inhabitants visiting other countries (UNSTAT, 2020). Total adult alcohol per capita consumption (APC) is defined as the total (sum of recorded and unrecorded alcohol) amount of alcohol consumed per person (individuals aged ≥ 15 years) over a calendar year, in litres of pure alcohol, adjusted for tourist consumption (UNSTAT, 2020). APC is the indicator of United Nations Sustainable Development Goal 3.5: Strengthen the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol, for 2030 (UNSTAT, 2017).

Although APC is considered the best indicator of alcohol consumption at the country level (Gmel and Rehm, 2004), it is only indicative of the overall level of consumption. To differentiate the level of alcohol consumption among different groups, data from surveys about variables such as sex, age, or sociodemographic status are needed. Because surveys tend to underestimate total APC, often by > 50% (Midanik, 1982; Rehm et al., 2010), they cannot be used to measure overall alcohol consumption.

Surveys enable estimation of the prevalence of abstinence (both lifetime abstention and current abstention among individuals who formerly consumed alcohol) and, through triangulation with APC, estimation of specific indicators such as APC per drinker or by sex, which serve as additional indicators globally (WHO, 2018). Triangulation of APC and surveys is also essential for estimating the alcohol-attributable burden of disease for comparative risk assessments (Rehm et al., 2010), which are important when setting priorities for disease prevention and alcohol control policies.

The third indicator of alcohol consumption available globally is for heavy episodic drinking (HED), which is also referred to as binge drinking.

1.2.2 Prevalence of and trends in alcohol consumption by WHO region

The countries included in each WHO region are listed in the Glossary.

(a) Prevalence and level of alcohol consumption in 2019

Alcohol is the most widely used psychoactive substance in the world (GBD 2019 Risk Factors Collaborators, 2020). Information about the indicators of alcohol consumption is provided for 2019 (Table 1.3; Fig. 1.1, 1.2, 1.3), because changes in alcohol consumption behaviours during the COVID-19 pandemic are not fully understood (Schmidt et al., 2021; Kilian et al., 2022; Sohi et al., 2022).

In 2019, 57% of adults abstained from alcohol consumption (WHO, 2024); 47% of adults had abstained throughout their lives, and 10% formerly consumed alcohol but were abstinent in the previous 12 months (WHO, 2024) (Table 1.3). However, the prevalence of alcohol abstention and consumption differs considerably by country and region.

In 2019, the highest APC overall was reported in the WHO European Region, followed by the WHO Region of the Americas and the WHO

Table 1.3 Characteristics of alcohol consumption behaviours in WHO regions in 2019

Alcohol consumption indicator[a]	WHO African Region	WHO Region of the Americas	WHO Eastern Mediterranean Region	WHO European Region	WHO South-East Asia Region	WHO Western Pacific Region	World
Overall							
APC (3-year moving average, L of pure alcohol)	4.52	7.51	0.31	9.20	3.84	6.06	5.45
Lifetime abstention (%)	61.3	18.2	92.4	26.3	64.0	34.0	46.6
Former alcohol consumption (%)	9.5	21.8	3.5	11.3	8.4	5.6	9.6
Current alcohol consumption (%)	29.2	60.0	4.1	62.4	27.6	60.4	43.8
HED (%)	15.2	26.0	0.8	26.1	10.4	19.1	16.7
APC per drinker (L)	15.50	12.53	7.44	14.74	14.01	9.85	12.35
Current alcohol consumption among individuals aged 15–19 years (%)	13.4	42.1	1.1	44.3	11.4	35.9	21.8
HED among individuals aged 15–19 years (%)	8.5	21.5	0.2	21.5	5.4	14.7	10.6
Women							
Lifetime abstention (%)	69.8	23.9	95.1	32.6	73.5	44.9	54.5
Former alcohol consumption (%)	9.2	24.2	2.7	12.5	7.8	6.2	10.1
Current alcohol consumption (%)	21.0	51.9	2.2	54.9	18.7	49.0	35.4
HED (%)	8.7	15.8	0.3	16.1	5.1	10.8	9.7
APC per drinker (L)	7.67	6.31	3.02	7.27	6.71	4.89	6.10
Current alcohol consumption among individuals aged 15–19 years (%)	12.2	40.0	1.0	42.3	10.2	33.3	20.3
HED among individuals aged 15–19 years (%)	7.4	18.4	0.2	18.0	4.5	12.5	9.0

Table 1.3 (continued)

Alcohol consumption indicator[a]	WHO African Region	WHO Region of the Americas	WHO Eastern Mediterranean Region	WHO European Region	WHO South-East Asia Region	WHO Western Pacific Region	World
Men							
Lifetime abstention (%)	52.6	12.3	89.8	19.5	54.7	23.2	38.7
Former alcohol consumption (%)	9.8	19.2	4.3	9.9	9.0	5.0	9.1
Current alcohol consumption (%)	37.6	68.5	5.9	70.7	36.3	71.8	52.2
HED (%)	22.2	35.9	1.4	36.1	15.7	26.6	23.5
APC per drinker (L)	19.98	17.45	8.96	21.05	17.66	13.24	16.63
Current alcohol consumption among individuals aged 15–19 years (%)	14.6	44.2	1.2	46.1	12.4	38.2	23.3
HED among individuals aged 15–19 years (%)	9.5	24.0	0.3	24.2	6.2	16.3	11.8

APC, alcohol per capita consumption; HED, heavy episodic drinking (≥ 60 g of ethanol [pure alcohol] at least once per month); WHO, World Health Organization.

[a] All proportions are based on the general population aged ≥ 15 years, except for current alcohol consumption among individuals aged 15–19 years and HED among individuals aged 15–19 years.

[b] 0 denotes proportions < 0.5%.

Modelled by the Working Group based on survey data collected for WHO (2022b). For modelling details, see Manthey et al. (2019); data are partially reported in WHO (2024).

Fig. 1.1 Prevalence of current alcohol consumption (previous 12 months) in 2019

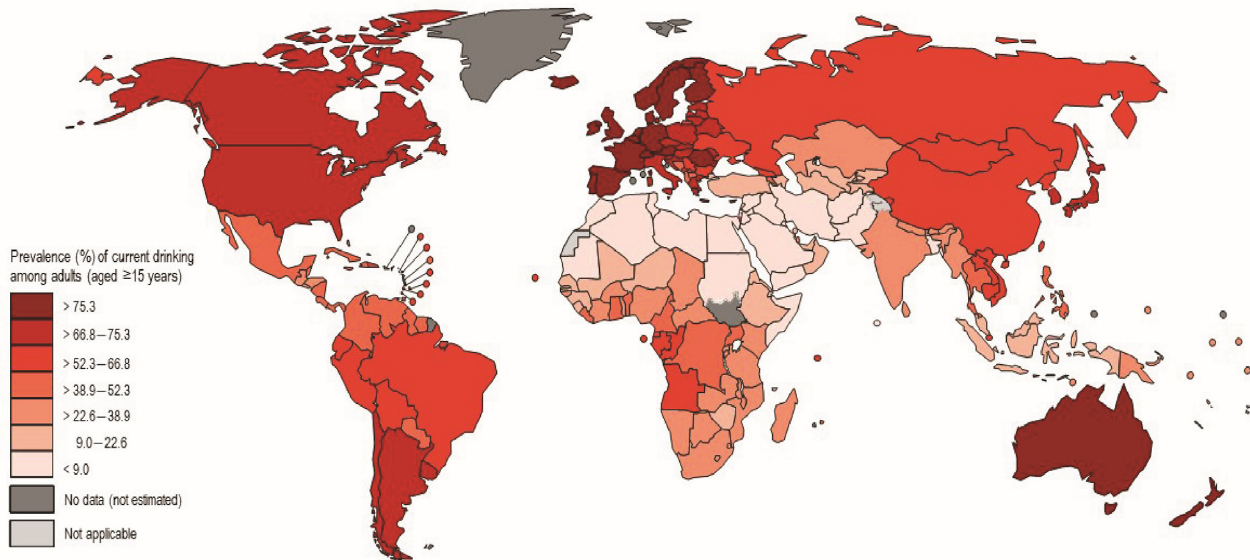


Figure modelled by the Working Group based on survey data collected for WHO (2022b); for modelling details, see Manthey et al. (2019).

Fig. 1.2 Prevalence of heavy episodic drinking in 2019

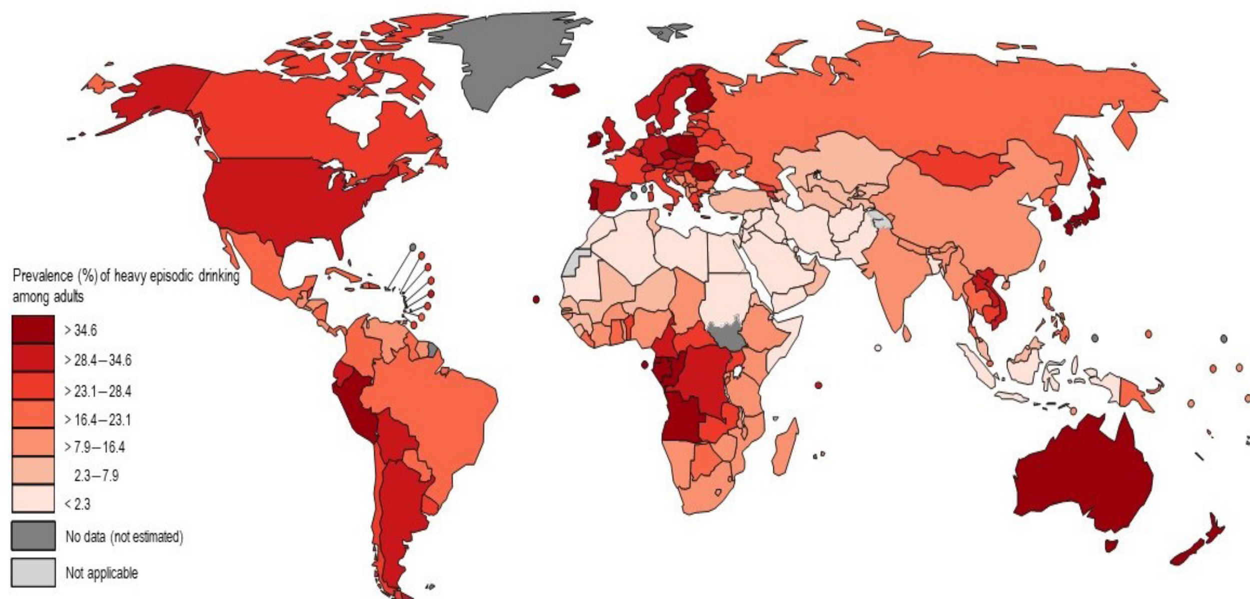


Figure modelled by the Working Group based on survey data collected for WHO (2022b); for modelling details, see Manthey et al. (2019).

Fig. 1.3 Adult alcohol per capita consumption among individuals who drink in 2019, in litres of pure ethanol

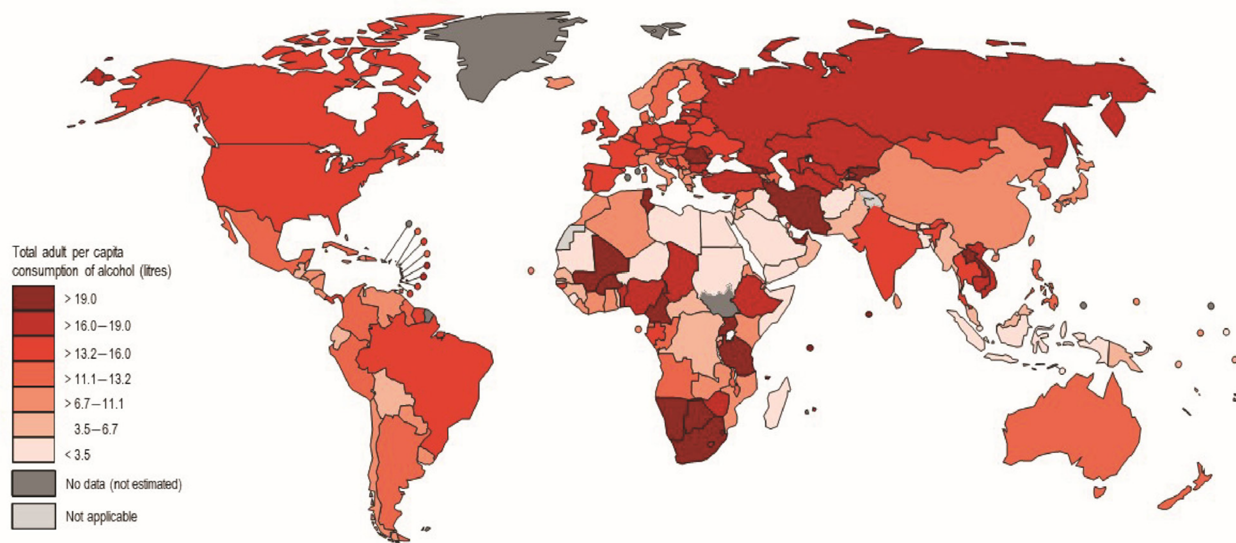


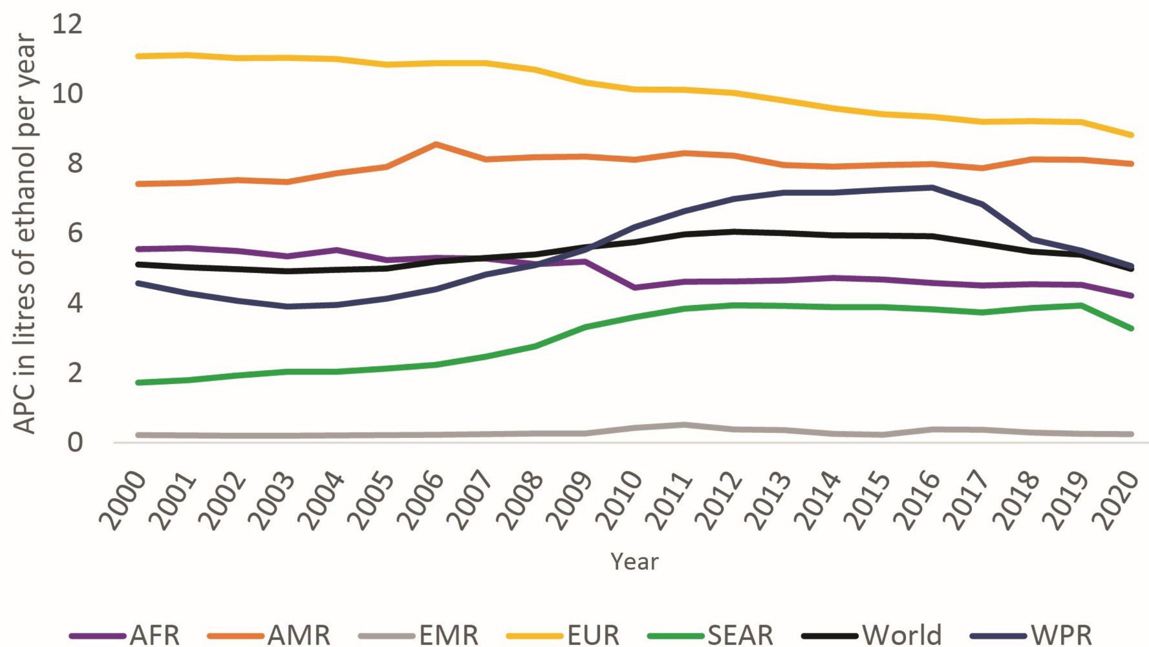
Figure modelled by the Working Group based on alcohol per capita consumption (APC) data and survey data collected for WHO (2022b); for modelling details, see Manthey et al. (2019).

Western Pacific Region (Table 1.3). The APCs in other regions were below the global average, and the WHO Eastern Mediterranean Region had the lowest APC. The level of consumption is also correlated with the prevalence of current alcohol consumption (any alcohol consumed in the previous 12 months; WHO, 2018) and has the same rank order as the APC. At the country level, the prevalence of alcohol consumption was highest in high-income countries in Europe and Australasia, where more than three quarters of adults consumed alcohol, and lowest in a belt of Muslim-majority countries that stretches from northern Africa across the Near and Middle East to Indonesia (Fig. 1.1).

Another indicator considers the amount of alcohol consumed by individuals who drink, i.e. adult APC per drinker (Fig. 1.3). The APC per drinker in 2019 was relatively stable, with some regional differences, i.e. highest in the WHO African Region and lowest in the WHO Eastern Mediterranean Region and the WHO Western Pacific Region (Table 1.3). Notably, some countries with low or relatively low APC have high adult APC per drinker, whereas countries with the highest overall APC also show a high prevalence of alcohol consumption. In some Muslim-majority countries, the prevalence of alcohol consumption is underestimated because of social norms; thus, the APC per drinker is overestimated.

HED does not have the same rank order as APC (Table 1.3), because it is an independent, but correlated, dimension that cannot be derived from the level of alcohol consumption alone (Rehm and Gmel, 2000; Rehm et al., 2004). Thus, with the same overall level of alcohol consumption, an individual could consume 10 g of alcohol (one standard drink in many countries) daily on weekdays or consume 70 g on the weekend and abstain on all weekdays. Whereas regional averages give an overview of HED, the prevalence of HED in 2019 shown in Fig. 1.2 reveals important between-country differences within regions.

Fig. 1.4 Trends in adult alcohol per capita consumption since 2000



AFR, WHO African Region; AMR, WHO Region of the Americas; APC, alcohol per capita consumption; EMR, WHO Eastern Mediterranean Region; EUR, WHO European Region; SEAR, WHO South-East Asia Region; WHO, World Health Organization; WPR, WHO Western Pacific Region.
Data source: WHO (2024).

Also, the prevalence of HED is only a rough indicator of HED because the average number of heavy drinking occasions may vary considerably, depending on the culture in a particular country (Gmel et al., 2003).

According to all alcohol indicators, men have more detrimental patterns of alcohol consumption than women do. Compared with women, men have a higher prevalence of consumption, have a higher APC (Manthey et al., 2019), and are more likely to engage in HED (Table 1.3; for details, see Section 1.2.3).

(b) Trends in alcohol consumption

Fig. 1.4 provides an overview of trends in the levels of alcohol consumption as measured in adult APC over the past two decades. Globally, the level of alcohol consumption was relatively stable, with an increase starting in 2000 and a decrease after 2016.

The WHO European Region reported reduced adult APC over the past two decades, which was driven mainly by decreased alcohol consumption in the eastern part of the region (Rehm et al., 2019) attributable largely to the implementation of strong alcohol control policies, particularly increased taxation (Berdzuli et al., 2020). The APC in the WHO Region of the Americas was stable overall (see also Monteiro et al., 2021).

The WHO Western Pacific Region had the greatest variability in alcohol consumption levels in recent decades, which was driven mainly by the largest country in the region, China. The increases until 2016 can be attributed largely to economic growth (Rehm et al., 2021). The sharp decrease after 2016 has often been attributed to “anti-corruption” regulations introduced in 2012, which prohibited alcohol consumption at military functions and serving alcohol as part of invitations for business events or public

administration meetings and events, as well as to the implementation of other alcohol control policies (Shu and Cai, 2017; Guo and Huang, 2015; Hu et al., 2022).

In the WHO African Region, there was a relatively stable level of consumption (Morojele et al., 2021). In the WHO South-East Asia Region, in which India is the largest country, until the COVID-19 pandemic began, alcohol consumption had increased steadily due to economic growth (Rehm et al., 2021), coupled with a fractured response to control policies (Gururaj et al., 2021).

Finally, in Muslim-majority countries, where alcohol is often prohibited, a very low level of alcohol consumption in general has persisted over the past two decades, despite some loosening of alcohol control policies (Al-Ansari et al., 2016).

The trends in the prevalence of current alcohol consumption globally are much less pronounced than the trends in APC. Overall, the prevalence of current alcohol consumption has fluctuated between 43% and 45% over the past two decades, with a COVID-19-associated decrease of 1% in 2020 (WHO, 2024). Similarly, the prevalence of current alcohol consumption in different WHO regions has remained relatively stable. Again, there may be some subregional variations that are not fully reflected in the trends from the WHO regions. The most remarkable trend in recent years was the increase in alcohol consumption in countries in the WHO South-East Asia Region (Manthey et al., 2019; Sornpaisarn et al., 2020).

1.2.3 Determinants of consumption

(a) Sex and gender

Globally, 52% of males and 35% of females currently consume alcohol (WHO, 2024). Among individuals who consume alcohol, males also generally consume greater quantities than females do (reported daily mean of 36 g of pure ethyl alcohol for males vs 13 g for females) (WHO, 2024). Less of a difference has been observed between males and females in the prevalence and quantity of alcohol consumption in geographical areas with a high sociodemographic index (i.e. comparatively advantaged) than in areas with a lower sociodemographic index (GBD 2016 Alcohol Collaborators, 2018) and in the prevalence of HED in higher-income countries than in low- and middle-income countries (Grittner et al., 2020). Alcohol use disorders are more common among males than among females (Glantz et al., 2020).

Although sex-related differences in the prevalence of alcohol consumption persist, a meta-regression of 50 studies (primarily in North America and Europe) shows convergence over time, with a male-to-female ratio of 2.2 for individuals born in 1891–1910 compared with 1.1 for those born in 1991–2000, driven primarily by an increase in alcohol consumption among women (Slade et al., 2016). However, a review of published data for the prevalence of alcohol consumption in the USA (collected at various time points between 1975 and 2017, with all included studies reporting on data up to at least 2008) showed differences in alcohol consumption patterns by age group. Compared with previous generations, middle-aged and older females consumed more alcohol, whereas males consumed about the same amount of alcohol. In general, adolescents and younger adults have been found to consume less alcohol than previous generations, and consumption is decreasing more among males than among females (Keyes et al., 2019).

The sex-related differences in the prevalence and patterns of alcohol consumption are also related to gender influences (i.e. socially constructed roles and norms) (Hughes et al., 2016), which contribute to the generally narrower gap between males and females in some countries and cultures than in others (Sudhinaraset et al., 2016). Furthermore, when considering sex-related differences in alcohol consumption, it is important to acknowledge that evidence is

lacking about the prevalence of alcohol consumption and cessation in intersex and transgender subpopulations (Gilbert et al., 2018).

(b) Age and life-course

Globally, consumption of alcohol often begins in adolescence or in the early 20s, and there is a clear increase in the prevalence of current alcohol consumption and HED between individuals aged 15–19 years and individuals aged 20–24 years in all regions of the world and among both males and females. The prevalence of current consumption then remains relatively stable from the late 20s to the 50s and decreases at older ages (WHO, 2024) (Table 1.4).

The age at which alcohol consumption peaks varies by location. A synthesis of nine cohort studies in the United Kingdom (using data collected in 1979–2013, with the age at data collection ranging from 15 years to > 90 years) showed a steep increase in the quantity of alcohol consumption in adolescence, with a peak in the mid-20s, followed by a decrease and plateau in middle age and a further decrease in the 60s and 70s (Britton et al., 2015). In contrast, in the USA, a slightly earlier peak in various alcohol consumption-related outcomes (in the early 20s) has been observed, with a subsequent decrease for the remainder of the lifespan (Lee and Sher, 2018).

Although most individuals reduce their alcohol consumption as they age relative to their own earlier consumption, it is important to contextualize this observation in relation to general population trends, which point toward overall increased levels of consumption among older people compared with earlier cohorts, particularly in higher-income countries (Han et al., 2017; Bye and Moan, 2020), and a slower rate of decrease in alcohol consumption among recent cohorts of older people compared with earlier cohorts (Moore et al., 2005).

(c) Race, ethnicity, and cultural and religious factors

Globally, the prevalence, pattern, and nature of alcohol consumption are highly variable between, and sometimes within, cultural groups, and therefore cannot easily be summarized. In considering alcohol consumption by race, ethnicity, culture, and religion, it is important to acknowledge that these concepts overlap and are socially constructed, multidimensional, and subject to change, particularly in the context of migration and globalization (Savic et al., 2016; Hunt et al., 2018; Aresi and Bloomfield, 2021). In general, there is also more evidence about ethnicity-related alcohol consumption patterns in high-income countries that have well-established data collection systems, such as the USA, the United Kingdom, and European countries, than from other geographical areas. Also, some genetic polymorphisms in some racial and ethnic groups are known to affect alcohol metabolism, making such individuals less likely to consume alcohol, or likely to consume less (see Section 3.1.1). The concomitant role of environmental factors in influencing consumption has also been studied (Wall et al., 2016). Furthermore, in some countries, colonization and ensuing intergenerational trauma have had a profound effect on patterns of alcohol consumption among some Indigenous groups, which is not representative of traditional culture (King et al., 2009). Despite these caveats, examining alcohol consumption by race, ethnicity, culture, and religion can offer some insights into potential disparities, as illustrated by the deliberately diverse examples presented here.

A 2014 survey in Yunnan Province in China examined the alcohol consumption of people aged 12–35 years from Han (Chinese ethnic majority), Lisu, and Yi backgrounds using a variety of measures (He et al., 2016). Compared with people in the other two groups, the individuals with a Lisu background consumed

Table 1.4 Prevalence of current alcohol consumption and heavy episodic drinking by age group, sex, and WHO region

Alcohol consumption indicator by region	Age group (years)																	
	Males						Females						Overall					
	15–19	20–24	25–34	35–49	50–64	≥ 65	15–19	20–24	25–34	35–49	50–64	≥ 65	15–19	20–24	25–34	35–49	50–64	≥ 65
Prevalence of current alcohol consumption (%)																		
World	23.3	47.2	56.3	58.5	58.5	52.3	20.3	34.7	37.5	40.5	38.5	30.4	21.8	41.1	47.1	49.6	48.4	40.1
WHO African Region	14.6	38.4	46.8	46.0	40.0	28.0	12.2	24.7	25.0	24.6	19.1	10.4	13.4	31.5	35.8	35.2	29.0	18.2
WHO Region of the Americas	44.2	71.1	76.0	74.6	70.9	58.0	40.0	58.1	57.3	57.8	52.2	38.5	42.1	64.7	66.7	66.2	61.3	47.2
WHO Eastern Mediterranean Region	1.2	5.0	7.7	7.7	6.0	3.7	1.0	2.5	2.7	2.7	2.0	1.0	1.1	3.7	5.3	5.3	4.0	2.2
WHO European Region	46.1	67.0	72.8	75.0	74.4	68.8	42.3	57.0	57.9	61.1	57.6	46.1	44.3	62.2	65.4	68.0	65.6	55.4
WHO South-East Asia Region	12.4	34.8	43.5	43.3	38.6	28.2	10.2	21.6	22.2	22.2	17.9	10.2	11.4	28.4	33.1	33.0	28.3	18.5
WHO Western Pacific Region	38.2	70.3	78.0	78.4	74.7	64.4	33.3	54.7	55.8	56.6	48.8	33.7	35.9	62.9	67.3	67.8	61.7	47.5
Prevalence of HED (%)																		
World	11.8	24.2	27.8	27.5	24.0	12.6	9.0	13.1	10.8	9.9	7.1	3.5	10.4	18.8	19.5	18.8	15.4	7.6
WHO African Region	9.5	24.2	28.6	26.9	21.4	9.8	7.4	13.0	11.1	9.7	6.4	2.4	8.5	18.6	19.8	18.2	13.5	5.7
WHO Region of the Americas	24.0	40.6	43.4	41.0	35.0	16.5	18.4	23.4	18.6	16.1	11.2	4.8	21.2	32.1	31.1	28.4	22.7	10.0
WHO Eastern Mediterranean Region	0.3	1.4	2.1	1.9	1.3	0.4	0.2	0.5	0.4	0.3	0.2	0.0	0.2	0.9	1.3	1.2	0.7	0.2
WHO European Region	24.2	38.2	40.8	40.6	35.9	18.8	18.0	22.3	17.8	16.4	11.3	5.0	21.2	30.5	29.5	28.4	23.1	10.7
WHO South-East Asia Region	6.2	17.1	20.7	19.5	15.3	6.3	4.5	8.0	6.6	5.6	3.5	1.2	5.4	12.8	13.8	12.7	9.4	3.5
WHO Western Pacific Region	16.3	29.9	32.2	31.1	25.1	12.9	12.5	16.2	12.2	10.8	7.3	3.8	14.5	23.4	22.6	21.2	16.1	7.9

Table 1.4 (continued)

Alcohol consumption indicator by region	Age group (years)																	
	Males						Females						Overall					
	15–19	20–24	25–34	35–49	50–64	≥ 65	15–19	20–24	25–34	35–49	50–64	≥ 65	15–19	20–24	25–34	35–49	50–64	≥ 65
Prevalence of HED among individuals who currently consume alcohol (%)																		
World	50.6	51.3	49.4	47.0	41.0	24.1	44.2	37.6	28.8	24.5	18.5	11.6	47.7	45.7	41.4	37.9	31.9	18.8
WHO African Region	64.9	63.2	61.2	58.5	53.6	35.1	60.6	52.8	44.3	39.4	33.4	22.9	62.9	59.1	55.3	51.8	46.6	31.2
WHO Region of the Americas	54.2	57.2	57.2	54.9	49.3	28.5	46.0	40.2	32.4	27.8	21.4	12.5	50.4	49.7	46.6	43.0	37.0	21.3
WHO Eastern Mediterranean Region	23.9	27.5	26.6	24.8	20.9	10.0	20.1	18.7	14.4	12.2	8.7	4.2	22.2	24.7	23.7	21.8	18.0	8.7
WHO European Region	52.4	57.0	56.1	54.1	48.3	27.4	42.5	39.1	30.8	26.8	19.7	10.8	47.8	49.0	45.1	41.8	35.2	19.3
WHO South-East Asia Region	49.7	49.2	47.6	45.0	39.7	22.3	44.4	37.3	29.6	25.3	19.8	11.6	47.4	44.9	41.8	38.5	33.4	19.1
WHO Western Pacific Region	42.7	42.5	41.3	39.7	33.6	20.0	37.6	29.7	21.9	19.2	14.9	11.4	40.5	37.2	33.6	31.3	26.1	16.6

HED, heavy episodic drinking (≥ 60 g of ethanol [pure alcohol] at least once per month); WHO, World Health Organization.
Calculated by the Working Group.

significantly more alcohol (daily and annually), and proportionately more of them reporting binge drinking. In contrast, a significantly larger proportion of the participants with a Han background reported experiencing intoxication.

The potential impact of globalization on patterns of alcohol consumption in China was evident from a survey of university students from northern, central, and southwestern China. The students who had a "Western cultural orientation" (as assessed with the Chinese Cultural Orientation Questionnaire) were > 3 times as likely to have consumed alcohol within the previous 30 days as those who did not have such a cultural orientation (Wang et al., 2016).

Another study examined alcohol consumption patterns among Ghanaians who lived in rural and urban areas of Ghana and in three European cities (London, Berlin, and Amsterdam). The prevalence of consumption was generally highest among Ghanaians living in Europe (except for males living in London, of whom fewer consumed alcohol compared with their counterparts in rural Ghana). The number of years since migration was positively associated with the prevalence of alcohol consumption (Addo et al., 2018).

A meta-analysis of 41 studies of alcohol consumption patterns among Australian Aboriginal and Torres Strait Islander (Indigenous) people found that 59% of almost 60 000 individuals currently consumed alcohol (Conigrave et al., 2020). About one third of the individuals consumed four or more standard drinks on a single occasion (i.e. were at single-occasion risk), and about one fifth averaged more than two drinks per day (i.e. were at lifetime risk). However, there was substantial variation within and between samples, and factors such as geography, local alcohol policy context, study design, and diversity among Indigenous communities must be considered.

(d) Smoking

Smoking tobacco and consuming alcohol are recognized as overlapping behaviours, with a higher likelihood of concomitancy (Shiffman and Balabanis, 1996; Room, 2004; Anand and Roy, 2016; Francisco et al., 2019). The extent to which the two behaviours overlap varies between populations (Noble et al., 2015; Meader et al., 2016; Wu et al., 2023). A recent review and meta-analysis estimated that smoking is associated with an almost 3-fold risk of HED, although the magnitude of this effect varies by sex and nationality (Molaeipour et al., 2023), and a study in Brazil found that individuals who smoked were more likely to consume alcohol than those who did not smoke (Francisco et al., 2019). Smoking tobacco and consuming alcohol concurrently increases the risk of developing cancer in a multiplicative manner (Ho et al., 2021).

(e) Socioeconomic status

In general, people with higher socioeconomic status consume alcohol more often and in larger quantities compared with individuals with lower socioeconomic status, although individuals from disadvantaged groups are at a greater risk of alcohol-related harm per litre of alcohol consumed (Collins, 2016; Probst et al., 2021; Xu et al., 2022; Room and Rehm, 2023).

However, there are some exceptions to the generally linear association between alcohol consumption and socioeconomic status. A 2018 review of 23 studies in 10 countries in South-East Asia and Africa found that alcohol consumption was more prevalent among individuals with low income and no formal education in South-East Asia, especially men (Allen et al., 2018). In upper-middle-income countries, HED was found to be more likely among people with low socioeconomic status, whereas the opposite was observed in low-income countries (Xu et al., 2022).

Unrecorded alcohol accounts for a larger proportion of the total alcohol consumed in low- and lower-middle-income countries than in higher-income countries (Probst et al., 2018; Probst et al., 2019). Furthermore, evidence indicates that in some countries, consumption of counterfeit and surrogate alcohol is associated with socioeconomic measures such as lower per capita income and unemployment (Neufeld et al., 2016; Kotelnikova, 2017).

(f) Social role transition

Among young adults, the transition to full-time work has been associated with HED and negative outcomes from alcohol consumption (Lee et al., 2018).

Separation and divorce have been associated with increased alcohol consumption, especially among men (Kretsch and Harden, 2014; Salvatore et al., 2020).

The transition to retirement has been associated with an increase in alcohol consumption (or no change or a decrease among a minority of individuals), and the differences in these outcomes have been attributed to context and personal characteristics (e.g. job satisfaction and stress before retirement, social roles and networks, involuntary retirement, gender, and previous alcohol consumption), rather than to retirement itself (Kuerbis and Sacco, 2012; Halonen et al., 2017; Holdsworth et al., 2017; Holton et al., 2019). Britton and Bell (2015) found that changes in roles and social connections among older individuals can be a risk factor for alcohol consumption, with self-reported increases in alcohol consumption among people older than 60 years being attributed to participating in more social events and having fewer responsibilities.

1.2.4 Determinants of reduction or cessation

In this section, a distinction is made between a factor experienced by an individual that contributes to a reduction or cessation of alcohol consumption and any *interventions* that may have contributed to it. For example, the affordability of alcohol, which may influence an individual's decision about whether to consume alcohol, is discussed here. However, alcohol pricing policies, which may as a precursor have influenced affordability, are not discussed.

(a) Age

Multiple reports have shown a decrease in alcohol consumption since the early 2000s among adolescents and young adults (Ng Fat et al., 2018; Pape et al., 2018; De Looze et al., 2019; Holmes et al., 2022). A recent analysis of survey data published between 1995 and 2017 explored the relative timing and magnitude of this trend among adolescents in 39 of 80 high-income countries (Vashishtha et al., 2021). A decrease in the prevalence of alcohol consumption in the previous month was first observed in the late 1990s in North America, followed by decreases in northern Europe, western Europe, and Australasia, with the largest decrease noted in northern Europe and the British Isles. Similarly, between 2000 and 2016, the reported prevalence of HED decreased among young people in many regions, with the largest decrease noted in the WHO European Region (10.5% among individuals aged 15–19 years and 12.1% among individuals aged 20–24 years) and a smaller decrease in the WHO Region of the Americas, the WHO African Region, and the WHO Eastern Mediterranean Region (WHO, 2018). It remains to be seen whether the reported decreases in alcohol consumption among young people will continue as these cohorts age and/or will persist into future generations.

The tendency for alcohol consumption to decrease at older ages has been widely observed. An international study of alcohol consumption in later life combined longitudinal survey data collected in 1998–2016 for adults aged > 50 years in 21 countries. Overall, there was a decreasing trajectory in alcohol consumption

with age, although those who were younger (aged 50–64 years) consumed more alcohol but less frequently than those who were older (aged ≥ 65 years) (Calvo et al., 2020). Biological changes that affect alcohol metabolism that occur as people age may partly explain this phenomenon and include decreased ability to metabolize alcohol because of reduced enzymatic activity, increased liver size, changes in body water volume, and increased susceptibility to the unpleasant effects of alcohol consumption (Meier and Seitz, 2008). The potential for interactions with medication and an increased risk of falls may also contribute to reduced alcohol consumption by some people at older ages (65–103 years) (Pringle et al., 2006).

(b) Health

Health-related reasons for reducing alcohol consumption generally fall into two broad categories: preserving or improving health, and being ill (sick quitters) (Shaper et al., 1988; Dawson et al., 2013). Numerous studies that have elicited self-reports from individuals about their reasons for reducing alcohol consumption or abstaining have identified physical health-related and mental health-related factors as predominant contributors, among both the general population and people who engage in HED: a systematic review of studies on cessation (Rosansky and Rosenberg, 2020), studies on reduction and possibly cessation (Britton and Bell, 2015; Beard et al., 2017), and studies on both cessation and reduction (Pennay et al., 2019). The specific health reasons measured vary across studies but commonly include the following: as a health precaution, for weight loss, concern about kilojoules/effects on body weight, psychological health, medical advice, or current health problems. For example, 40% of participants in the Whitehall II Cohort Study, who were aged 60–85 years when they completed the 2012–2013 follow-up questionnaire, reported reducing their alcohol consumption in the previous decade. Of these individuals, 41.6% indicated that they did so as a health precaution, 21.0% reduced their alcohol consumption due to illness or because of a medication they were taking, and 2.0% gave past problems with alcohol consumption as the reason (Britton and Bell, 2015).

Several cohort studies have tracked measures of alcohol consumption and health over time, and evidence suggests that moving from consumption to abstinence (Wannamethee and Shaper, 1988; Dawson et al., 2013; Park et al., 2017), or to abstinence or consumption only on special occasions (Ng Fat et al., 2015), may be associated with various measures of poor health.

Emerging health conditions may also lead to abstinence. For example, Sarich et al. (2019) found that the emergence of three cardiovascular disease-related conditions (heart disease, stroke, and blood clot) predicted abstinence, whereas Park et al. (2017) found no relationship between the emergence of cardiovascular disease and abstinence.

(c) Smoking

A survey of households in the USA found that among adults who consume alcohol regularly, the likelihood of ceasing alcohol consumption was higher if they did not smoke than if they did smoke, and that smoking cessation was associated with a greater likelihood of ceasing alcohol consumption (Dawson et al., 2013). This contrasts with a prospective cohort study conducted in the United Kingdom, the USA, Australia, and Canada, which found that people who ceased smoking for ≥ 6 months were not more likely to change their alcohol consumption compared with people who continued to smoke (Kahler et al., 2010).

Studies have also shown that tobacco control policies have some effect on alcohol consumption. At the population level, Krauss et al. (2014) found that smoke-free air policies and higher tobacco taxes were associated with decreases in APC. At the individual level, Kasza et al. (2012)

found that smoke-free bars were associated with minor decreases in the amount of alcohol typically consumed in hazardous alcohol consumption (i.e. consumption of > 14 drinks per week by men and > 7 drinks per week by women).

In a review of studies of people being treated for alcohol use disorders, not smoking or reducing smoking was significantly associated with reduced alcohol consumption and/or a higher likelihood of maintaining abstinence from alcohol consumption in about half of the included studies. However, participating in a smoking cessation intervention while being treated for alcohol use disorders did not improve alcohol consumption outcomes in most studies (van Amsterdam and van den Brink, 2022). Furthermore, one study found that whereas smoking increased the overall likelihood of relapse to alcohol consumption, the number of cigarettes smoked may have an independent effect on outcomes (i.e. the higher the number of cigarettes smoked per day, the lower the likelihood of relapse to alcohol consumption) (Hufnagel et al., 2017).

A review of natural and intervention studies found that alcohol consumption was associated with a lapse or relapse to smoking and a shorter duration of smoking cessation in most of the included studies (van Amsterdam and van den Brink, 2023). Smoking cessation intervention studies have found that a reduction in smoking is associated with reduced alcohol consumption overall and reduced HED, and that the greater the reduction in smoking, the greater the reduction in alcohol consumption (Philibert et al., 2021; Yonek et al., 2021).

(d) Social role transition

A large body of cross-sectional and longitudinal evidence links social roles and transitions between roles (e.g. establishing a romantic partnership or marriage, parenthood, and retirement) with reductions in alcohol consumption.

Multiple studies have found that, among both men and women, the transition to marriage or cohabitation is predictive of reduced alcohol consumption (e.g. Hajema and Knibbe, 1998; Kretsch and Harden, 2014; Staff et al., 2014; Evans-Polce et al., 2020; Leggat et al., 2020; Salvatore et al., 2020).

Pregnancy and the transition to motherhood have been identified as protective against alcohol consumption for most women (Pryor et al., 2017; Borschmann et al., 2019; Voutilainen et al., 2022). However, the strength of the protective effect of motherhood may vary based on an individual's sociodemographic characteristics. For example, older mothers are more likely to consume alcohol, and women with more children are less likely to consume alcohol (Vicario et al., 2023), but these effects may diminish over time (Borschmann et al., 2019; Leggat et al., 2021). The impact of pregnancy on alcohol consumption by a male partner has been associated with both reduced (Högberg et al., 2016) and unchanged (Borschmann et al., 2019) alcohol consumption relative to the period before the pregnancy. Similarly, the gap in HED between parents and non-parents was lower for men than for women, particularly among individuals in their mid-20s to mid-30s (Evans-Polce et al., 2020).

The transition to retirement has been associated with a decrease in alcohol consumption among a minority of individuals, and an increase or no change in alcohol consumption in other people (see Section 1.2.3). These findings have been attributed to context and personal characteristics (e.g. job satisfaction and stress before retirement, social roles and networks, involuntary retirement, gender, and previous alcohol consumption), rather than to retirement itself (Kuerbis and Sacco, 2012; Halonen et al., 2017; Holdsworth et al., 2017; Holton et al., 2019). Britton and Bell (2015) found that changes in roles and social connections among older individuals can also be protective against alcohol consumption by older individuals, with self-

reported reductions in alcohol consumption attributed to participation in fewer social events.

(e) Social networks

The understanding of how alcohol consumption patterns shift within a population has long been informed by Skog's theory of collectivity of "drinking cultures", which postulates that as the population average of alcohol consumption increases or decreases, so does the distribution of alcohol consumption across the population (Skog, 1985). The proposed mechanism of this effect is the "direct and indirect influences between drinkers in a social network" (Skog, 1985), which may shape alcohol consumption across an entire population. This notion of collectivity has been influential in public health responses to reduce alcohol consumption and harms, and empirical evidence has tended to support the theory (Raninen and Livingston, 2020). However, more recently, studies have identified patterns of reduction in alcohol consumption within populations that are less pronounced in some groups than in others (i.e. "soft collectivity") or that indicate polarization between groups, suggesting that there may be barriers to social transmission of behaviour across some groups (e.g. by age) (Oldham et al., 2020; Raninen and Livingston, 2020; Mojica-Perez et al., 2022). Even if collectivity does not hold true across an entire population, there is evidence that interactions within an individual's immediate social network, including their social media contacts, may influence when they begin consuming alcohol and whether they maintain, increase, or reduce their alcohol consumption (Studer et al., 2014; Reid et al., 2015; Knox et al., 2019; Pennay et al., 2019; Morris et al., 2020; Lau-Barraco et al., 2022). This influence may occur through shared behaviour or informal social control (Skog, 1985). For example, in a sample of people with "high-risk" alcohol consumption – defined as scoring ≥ 8 on the Alcohol Use Disorders Identification Test (AUDIT) or ≥ 5 on questions 1–3 of the AUDIT – who were currently trying to reduce their consumption, 6% indicated that something that their family, friends, or children had said contributed to their decision (Beard et al., 2017).

(f) Religion

Although religions differ in their beliefs and values regarding alcohol consumption, religiosity generally has been shown to be a protective factor against initiation of alcohol consumption and a high level of alcohol consumption, and it is associated with abstinence (Porche et al., 2015; Lin et al., 2020). For example, in a two-wave study in the USA, individuals who reported former alcohol consumption in both waves were more likely to have attended religious services at least twice a week and to regard their religious beliefs as "very important" than those who started consuming alcohol again between the study waves; this suggests that both public and intrinsic aspects of religiosity may support continued alcohol cessation (Lin et al., 2020). However, a cross-sectional study among young people in Australia found that, compared with individuals who did not identify as being part of a religious group, those who did were less likely to decrease their alcohol consumption or cease alcohol consumption (Raggatt et al., 2019). Periods of religious significance or fasting, such as Islamic Ramadan, Buddhist Lent, and Orthodox Christian Lent, have also been linked to temporary periods of reduced alcohol consumption or abstinence in the countries where they are observed (Çelen, 2015; Jirarattanasopha et al., 2019; Necula and Mann, 2020).

(g) Affordability and availability

Alcohol affordability is a function of both income and price and has been associated with population levels of alcohol consumption, such that consumption is higher when alcohol is more affordable and lower when it is less affordable (Rabinovich et al., 2009; Wall and Casswell, 2013). There is strong evidence from several

countries that budgetary constraints associated with periods of economic downturn (i.e. potentially lower affordability) are connected to less spending on alcohol, and hence lower consumption (i.e. a pro-cyclical effect) (de Goeij et al., 2015). This effect is exemplified through the relationship between alcohol sales (which correlate with total population alcohol consumption) and gross domestic product in Sweden from 1861 to 2000, between alcohol consumption and regional gross domestic product in Finland from 1982 to 2001, and between alcohol consumption and unemployment rates in the USA from 1987 to 1999 (Ruhm and Black, 2002; Johansson et al., 2006; Krüger and Svensson, 2010). Unfavourable economic conditions have been associated with a shift from heavier to lighter consumption of alcohol, rather than to increased abstention (Ruhm and Black, 2002; Johansson et al., 2006). However, the pro-cyclical effect linked to affordability described previously may not hold true for all individuals, because there is also evidence that some people, particularly men, respond to the stress of reduced income from unemployment, or the threat of this, by consuming more alcohol than they previously did (Dee, 2001; de Goeij et al., 2015). That is, there may be a counter-cyclical effect of economic downturn, even when the overall population effect may be pro-cyclical.

Survey-based studies provide further evidence that affordability (indirectly measured through reasons such as "to save money" and because alcohol is "too expensive") is a contributing factor in the decision to reduce alcohol consumption or abstain for a minority of people, for example 9.9% of older people who had already reduced their alcohol consumption (Britton and Bell, 2015) and 7.6% of individuals who were trying to cut down their "high-risk" consumption (defined previously) (Beard et al., 2017). However, affordability does not appear to be the most salient factor in this decision. In a review of studies of reasons for abstinence among individuals who had abstained all their lives, were currently abstinent, and had a history of "problematic drinking" but no longer consumed alcohol, "financial reasons" were rarely among the top three reasons for abstinence (Rosansky and Rosenberg, 2020).

During the COVID-19 pandemic, there was an overall reduction in alcohol consumption, and probably a lower 12-month prevalence of consumption due to the lower availability of alcohol, partly because of limitations on gatherings, especially in low- and middle-income countries. Globally, APC decreased by about 8% during the first year of the pandemic (WHO, 2024).

1.3 Population attributable fraction

1.3.1 Definitions and general considerations

Population attributable fraction (PAF) in the context of alcohol consumption and cancer includes abstinence as the theoretical-minimum-risk exposure (Shield et al., 2020; Rumgay et al., 2021a). However, the proportion of alcohol-attributable cancer cases that could be prevented is likely to be smaller than PAFs because public health interventions are unlikely to completely eliminate alcohol consumption in the entire population. Several studies have estimated that the population preventable fraction represents the level that can be attained by interventions, although the attainable level may vary across studies (Mons et al., 2018; Young et al., 2018; Grevers et al., 2019). Because contemporary estimates for population preventable fraction are lacking worldwide, this section highlights global and regional PAF estimates for 2020, as reported by IARC (Rumgay et al., 2021b).

The calculation of PAF for cancers generally requires information about the prevalence of exposure levels, relative risks for the association between the exposure and the cancer of interest, and cancer counts or rates. Researchers

frequently use risk-factor exposure data from representative surveys, which often are adjusted for underestimation by self-report (see below), cancer data from cancer registries or vital statistics databases, and relative risks from a single study or pooled analyses or meta-analyses (preferably of prospective cohort studies). Most studies take into consideration lag time between exposure and cancer occurrence (usually 10 years) (Rehm et al., 2010; Shield et al., 2020; Rumgay et al., 2021a).

There are several considerations when interpreting PAF estimates for alcohol consumption and cancer (Greenland, 2015). First, because data about alcohol consumption and cancer may not be available for some countries or populations, researchers may impute this information by modelling subnational, regional, or other available data (Shield et al., 2020; GBD 2019 Cancer Risk Factors Collaborators, 2022). Second, some studies may not include former alcohol consumption when estimating PAFs, which may result in underestimation of PAFs (Wilson et al., 2018; Chen et al., 2019; Goding Sauer et al., 2021), largely because of the sparsity of reliable data about former alcohol consumption or associated relative risks. Some other studies may impute data on former alcohol consumption by using modelling of other available data about such consumption (Shield et al., 2020). Third, because alcohol consumption is generally highly underreported in surveys, researchers may adjust data about consumption based on production, sales, or taxation statistics using different methods (Islami et al., 2018; Esser et al., 2022). However, these statistics generally are not stratified by age, sex, or other demographic characteristics, whereas the extent of underreporting may differ across population groups. Fourth, studies have generally used the same cancer-specific relative risks for all evaluated populations; therefore, variations in PAFs across populations reflect differences in alcohol consumption and distribution of cases by cancer site. However, the burden of a cancer associated with alcohol in a population may be substantially high due to other risk factors, which may result in overestimation of the number of alcohol-attributable cases for that cancer site and, consequently, overestimation of the total number and proportion of alcohol-attributable cases (all cancers combined) in that population. Fifth, previous studies generally have not taken into account possible interactions between alcohol consumption and genetic or potentially modifiable risk factors (e.g. cigarette smoking, viral hepatitis), which may result in misestimation of PAFs. Finally, PAF estimates may vary across studies because of differences in the list of cancer sites included in the analyses.

1.3.2 Cancer cases attributable to alcohol consumption

Whereas the APC reported in the previous section was reported by WHO region, this section describes regional patterns using the United Nations geographical regions (UNSTAT, 2024).

(a) All cancers combined

(i) Global patterns

In 2020, an estimated 741 300 new cancer cases, or 4.1% of all new cancer cases globally, were attributable to current alcohol consumption (Rumgay et al., 2021b) (Table 1.5). About three quarters of those cancers occurred among males (568 700 cases among males, and 127 600 cases among females), resulting in a larger proportion of alcohol-attributable new cancer cases among males (6.1%) than among females (2.0%). Although consuming > 60 g of alcohol per day contributed the most alcohol-attributable new cancer cases (346 400 cases; 46.7%), followed by consuming 20–60 g of alcohol per day (291 800 cases; 39.4%), consuming a moderate amount of alcohol (< 20 g per day) also contributed a considerable number of cases (103 100 cases; 13.9%) (Rumgay et al., 2021a).

Table 1.5 Number and proportion of new cancer cases in 2020 attributable to alcohol consumption by cancer site, sex, and region, all ages combined

Cancer site (ICD-10 codes) by region	Overall		Males		Females	
	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]
All sites excluding non-melanoma skin cancer (C00–C97 excluding C44)						
Global	4.1 (3.1–5.3)	741 300 (558 500–951 200)	6.1 (4.6–7.9)	568 700 (422 500–731 100)	2.0 (1.6–2.5)	172 600 (135 900–220 100)
Africa						
Eastern Africa	2.6 (1.8–3.4)	8300 (5800–11 100)	4.9 (3.4–6.4)	6000 (4200–7900)	1.1 (0.8–1.6)	2300 (1700–3100)
Middle Africa	2.5 (1.7–3.5)	2600 (1700–3700)	4.3 (2.8–5.8)	1900 (1200–2600)	1.2 (0.8–1.7)	740 (510–1000)
Northern Africa	0.3 (0.1–3.3)	990 (420–9800)	0.6 (0.2–6.5)	820 (350–9500)	0.1 (0.0–0.2)	180 (80–370)
Southern Africa	3.9 (2.7–5.0)	4200 (2900–5400)	5.7 (4.2–7.0)	2800 (2100–3500)	2.3 (1.4–3.3)	1400 (830–1900)
Western Africa	2.9 (1.8–4.2)	7000 (4300–10 100)	4.5 (2.6–6.5)	4400 (2500–6300)	1.8 (1.3–2.6)	2700 (1900–3700)
Asia						
Eastern Asia	5.7 (3.6–7.9)	332 100 (208 800–460 200)	8.6 (5.4–11.8)	275 900 (172 600–378 400)	2.1 (1.4–3.1)	56 300 (36 200–81 900)
South-central Asia	3.5 (2.0–6.9)	68 100 (37 900–133 800)	6.2 (3.5–12.0)	59 200 (33 200–114 800)	0.9 (0.5–1.9)	8900 (4800–19 000)
South-eastern Asia	2.6 (1.6–3.7)	27 700 (17 500–39 700)	4.4 (2.7–6.4)	23 000 (14 100–33 400)	0.8 (0.6–1.1)	4700 (3300–6400)
Western Asia	0.7 (0.5–1.2)	3000 (2000–5200)	1.0 (0.7–1.7)	2300 (1500–3900)	0.4 (0.2–0.6)	750 (480–1300)
Europe						
Central and eastern Europe	5.6 (4.6–6.6)	71 400 (57 800–84 200)	7.8 (6.5–9.0)	49 900 (41 100–57 300)	3.4 (2.6–4.3)	21 500 (16 700–26 900)
Northern Europe	3.9 (3.0–4.8)	24 800 (19 200–30 300)	4.7 (3.8–5.5)	15 600 (12 600–18 300)	3.0 (2.2–4.0)	9200 (6600–12 100)
Southern Europe	3.6 (2.8–4.4)	32 400 (25 200–39 400)	4.8 (3.8–5.7)	23 100 (18 300–27 400)	2.3 (1.7–3.0)	9300 (6900–12 000)
Western Europe	4.2 (3.3–5.1)	52 800 (41 300–63 500)	5.1 (4.1–6.0)	34 400 (27 500–40 300)	3.2 (2.4–4.1)	18 400 (13 800–23 200)
Americas						
Latin America and the Caribbean	2.8 (2.1–3.5)	39 300 (29 600–49 400)	3.9 (3.0–4.7)	26 800 (20 600–32 300)	1.8 (1.3–2.4)	12 600 (9100–17 100)
North America	3.0 (2.1–4.0)	59 600 (40 600–77 800)	3.8 (2.7–4.8)	38 500 (27 000–48 400)	2.2 (1.4–3.0)	21 200 (13 500–29 400)
Oceania						
Australia and New Zealand	4.1 (3.0–5.1)	6800 (5000–8600)	4.8 (3.7–5.8)	4200 (3200–5100)	3.3 (2.2–4.4)	2600 (1700–3500)
Melanesia, Micronesia (Federated States of), and Polynesia	1.2 (0.2–2.2)	190 (40–370)	2.1 (0.4–4.1)	160 (30–310)	0.4 (0.1–0.7)	30 (10–60)

Table 1.5 (continued)

Cancer site (ICD-10 codes) by region	Overall		Males		Females	
	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]
Lip and oral cavity (C00–C06)						
Global	20.2 (12.1–32.3)	74 900 (44 600–119 600)	25.9 (15.6–40.9)	66 700 (40 000–105 300)	7.3 (4.1–12.7)	8200 (4600–14 300)
Africa						
Eastern Africa	13.5 (7.2–21.1)	630 (340–980)	20.1 (10.8–30.9)	540 (290–830)	4.5 (2.4–7.7)	90 (50–150)
Middle Africa	19.7 (11.1–29.2)	280 (160–420)	27.4 (15.5–40.0)	240 (140–350)	7.5 (4.0–12.1)	40 (20–70)
Northern Africa	2.3 (1.0–15.8)	70 (30–510)	4.0 (1.7–28.5)	70 (30–490)	0.4 (0.1–1.2)	6 (< 5–20)
Southern Africa	27.3 (14.4–40.9)	580 (310–870)	37.3 (20.1–53.8)	490 (260–700)	11.5 (5.4–20.4)	100 (40–170)
Western Africa	18.4 (10.8–27.8)	520 (310–790)	27.3 (16.4–40.2)	430 (260–630)	7.5 (3.9–12.7)	100 (50–160)
Asia						
Eastern Asia	22.4 (11.7–33.9)	9700 (5100–14 800)	31.1 (16.2–46.3)	8300 (4400–12 400)	8.4 (4.5–14.0)	1400 (750–2300)
South-central Asia	14.5 (6.3–30.2)	25 300 (11 100–52 700)	18.2 (8.1–36.4)	23 800 (10 500–47 500)	3.3 (1.3–11.9)	1400 (550–5200)
South-eastern Asia	12.7 (6.9–19.8)	2300 (1300–3600)	18.0 (9.8–27.9)	2000 (1100–3100)	4.2 (2.4–6.9)	300 (170–490)
Western Asia	7.2 (3.7–15.4)	320 (160–670)	10.7 (5.5–23.0)	290 (150–620)	1.6 (0.7–2.9)	30 (10–50)
Europe						
Central and eastern Europe	38.6 (22.5–53.6)	10 100 (5900–14 000)	45.3 (26.5–62.0)	9000 (5300–12 300)	17.0 (9.4–26.6)	1100 (580–1700)
Northern Europe	31.4 (18.3–45.4)	2800 (1700–4100)	41.7 (24.7–58.8)	2300 (1400–3300)	14.8 (8.0–23.8)	510 (280–820)
Southern Europe	27.3 (15.6–39.4)	3400 (1900–4900)	36.7 (21.1–52.1)	2900 (1700–4100)	10.6 (5.9–16.9)	470 (260–750)
Western Europe	32.2 (18.9–45.6)	5700 (3400–8100)	42.2 (24.8–58.9)	4700 (2800–6500)	15.3 (8.9–23.5)	1000 (590–1600)
Americas						
Latin America and the Caribbean	24.3 (13.5–35.7)	4300 (2400–6400)	32.9 (18.3–47.5)	3800 (2100–5600)	8.1 (4.4–13.3)	500 (270–820)
North America	28.0 (15.3–41.4)	7700 (4200–11 400)	36.0 (19.8–52.8)	6700 (3700–9800)	11.3 (6.0–17.8)	1000 (540–1600)
Oceania						
Australia and New Zealand	33.2 (19.1–47.6)	1000 (590–1500)	41.9 (24.4–58.9)	870 (510–1200)	15.6 (8.4–24.9)	160 (90–260)
Melanesia, Micronesia (Federated States of), and Polynesia	6.3 (0.6–14.3)	80 (8–190)	9.1 (0.9–21.0)	70 (7–170)	1.7 (0.2–3.7)	8 (< 5–20)

Table 1.5 (continued)

Cancer site (ICD-10 codes) by region	Overall		Males		Females	
	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]
Pharynx (C09–C10, C12–C13)						
Global	22.0 (9.0–37.8)	39 400 (16 100–67 800)	25.3 (10.4–43.4)	37 000 (15 200–63 400)	7.4 (2.8–13.4)	2500 (940–4400)
Africa						
Eastern Africa	16.1 (5.9–27.5)	250 (90–430)	19.1 (7.0–32.4)	230 (90–400)	5.5 (2.0–10.5)	20 (7–40)
Middle Africa	23.6 (9.32–38.0)	180 (70–300)	26.5 (10.4–42.4)	170 (70–280)	7.5 (2.8–13.7)	9 (< 5–20)
Northern Africa	1.9 (0.6–16.5)	20 (6–170)	3.1 (1.0–28.2)	20 (6–170)	0.4 (0.1–1.1)	< 5 (< 5–5)
Southern Africa	27.0 (10.3–45.0)	200 (80–330)	32.2 (12.4–52.8)	180 (70–300)	10.2 (3.3–20.0)	20 (6–30)
Western Africa	15.9 (6.2–27.1)	140 (50–230)	22.7 (9.1–37.5)	110 (40–180)	7.3 (2.4–13.7)	30 (9–50)
Asia						
Eastern Asia	24.5 (9.3–39.9)	4900 (1900–8000)	27.1 (10.2–44.0)	4700 (1800–7700)	7.5 (3.0–12.9)	200 (80–340)
South-central Asia	12.3 (4.1–33.1)	8100 (2700–21 900)	14.5 (4.9–39.0)	7700 (2600–20 800)	2.9 (0.7–8.6)	370 (90–1100)
South-eastern Asia	15.2 (5.7–26.7)	1500 (560–2600)	17.9 (6.7–31.4)	1400 (530–2500)	3.4 (1.3–6.3)	60 (20–120)
Western Asia	8.5 (3.2–17.0)	90 (30–170)	12.4 (4.7–24.7)	80 (30–160)	1.4 (0.4–3.0)	< 5 (< 5–10)
Europe						
Central and eastern Europe	37.1 (15.5–56.0)	7500 (3100–11 300)	40.3 (16.9–60.2)	7100 (3000–10 600)	15.9 (6.0–27.2)	420 (160–710)
Northern Europe	31.3 (12.9–48.4)	1800 (740–2800)	36.9 (15.3–56.2)	1600 (660–2400)	13.6 (5.5–23.9)	190 (80–330)
Southern Europe	29.1 (11.7–45.2)	1900 (750–2900)	32.8 (13.3–50.6)	1800 (710–2700)	9.6 (3.6–16.8)	100 (40–170)
Western Europe	31.6 (13.2–48.9)	5000 (2100–7800)	37.5 (15.8–57.1)	4500 (1900–6800)	14.1 (5.3–24.3)	560 (210–970)
Americas						
Latin America and the Caribbean	24.7 (9.6–40.1)	2800 (1100–4500)	28.4 (11.1–45.9)	2600 (1000–4300)	7.4 (2.9–13.3)	150 (60–270)
North America	28.2 (11.1–45.5)	4600 (1800–7500)	32.1 (12.7–51.4)	4300 (1700–6900)	10.4 (3.9–18.5)	310 (120–550)
Oceania						
Australia and New Zealand	33.7 (14.1–52.4)	430 (180–660)	37.4 (15.7–57.8)	400 (170–610)	14.4 (5.7–25.0)	30 (10–50)
Melanesia, Micronesia (Federated States of), and Polynesia	6.8 (0.5–16.6)	10 (< 5–30)	7.5 (0.6–18.1)	10 (< 5–20)	1.6 (0.3–3.8)	< 5 (< 5–< 5)

Table 1.5 (continued)

Cancer site (ICD-10 codes) by region	Overall		Males		Females	
	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]
Larynx (C32)						
Global	15.0 (8.6–23.6)	27 600 (15 700–43 300)	16.6 (9.5–26.1)	26 400 (15 100–41 600)	4.7 (2.5–7.0)	1200 (620–1700)
Africa						
Eastern Africa	11.6 (6.2–17.9)	260 (140–410)	13.4 (7.2–20.7)	250 (130–380)	3.5 (1.9–5.4)	10 (8–20)
Middle Africa	13.7 (7.4–20.2)	90 (50–130)	15.6 (8.4–23.0)	80 (50–120)	3.6 (1.9–5.6)	< 5 (< 5–6)
Northern Africa	1.9 (0.9–26.4)	90 (40–1200)	2.1 (1.0–29.2)	90 (40–1200)	0.2 (< 0.1–0.5)	< 5 (< 5–< 5)
Southern Africa	19.0 (10.1–28.9)	180 (100–280)	21.7 (11.7–32.8)	170 (90–260)	6.5 (3.0–10.7)	10 (5–20)
Western Africa	14.8 (8.3–22.5)	230 (130–350)	17.2 (9.6–26.0)	220 (120–330)	4.8 (2.5–7.8)	10 (7–20)
Asia						
Eastern Asia	17.3 (8.8–26.7)	6200 (3200–9600)	18.8 (9.6–28.9)	6100 (3100–9300)	4.7 (2.3–7.5)	180 (90–290)
South-central Asia	8.5 (3.5–22.0)	4200 (1700–10 800)	9.6 (3.9–25.1)	4100 (1700–10 600)	1.7 (0.6–3.2)	110 (40–220)
South-eastern Asia	9.1 (4.9–14.2)	1000 (560–1600)	9.9 (5.4–15.4)	1000 (550–1600)	2.5 (1.3–3.9)	30 (20–50)
Western Asia	5.5 (2.7–11.2)	380 (190–780)	6.0 (3.0–12.3)	380 (190–770)	1.0 (0.5–1.7)	6 (< 5–10)
Europe						
Central and eastern Europe	26.6 (15.4–38.0)	4800 (2800–6900)	28.2 (16.4–40.1)	4700 (2700–6700)	10.3 (5.5–15.1)	160 (90–230)
Northern Europe	22.8 (12.9–32.5)	870 (490–1200)	25.7 (14.6–36.5)	810 (460–1100)	9.1 (4.8–13.9)	60 (30–90)
Southern Europe	20.1 (11.6–29.4)	1900 (1100–2700)	22.0 (12.7–32.0)	1800 (1000–2600)	6.7 (3.5–9.9)	70 (40–110)
Western Europe	22.8 (13.0–32.8)	2000 (1100–2800)	25.9 (14.9–37.1)	1800 (1000–2600)	9.4 (5.0–14.0)	150 (80–220)
Americas						
Latin America and the Caribbean	16.4 (8.8–24.4)	2600 (1400–3900)	18.6 (10.0–27.5)	2500 (1300–3700)	5.1 (2.7–8.0)	130 (70–210)
North America	18.7 (9.9–27.6)	2500 (1300–3700)	21.7 (11.5–31.9)	2300 (1200–3400)	7.0 (3.5–11.0)	190 (100–300)
Oceania						
Australia and New Zealand	23.7 (13.5–34.4)	160 (90–230)	25.7 (14.7–37.1)	150 (90–220)	9.3 (4.8–14.6)	7 (< 5–10)
Melanesia, Micronesia (Federated States of), and Polynesia	4.4 (0.9–8.4)	7 (< 5–10)	5.3 (1.1–10.2)	7 (< 5–10)	1.1 (0.4–2.1)	< 5 (< 5–< 5)

Table 1.5 (continued)

Cancer site (ICD-10 codes) by region	Overall		Males		Females	
	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]
Oesophagus (C15)						
Global	31.6 (18.4–45.7)	189 700 (110 900–274 600)	39.2 (22.7–55.6)	163 100 (94 200–231 000)	14.3 (9.0–23.5)	26 600 (16 700–43 700)
Africa						
Eastern Africa	25.2 (13.2–37.3)	4100 (2100–6000)	37.3 (19.1–53.8)	3200 (1600–4600)	11.6 (6.6–18.8)	880 (500–1400)
Middle Africa	26.9 (14.7–39.2)	580 (310–840)	35.7 (19.4–51.4)	480 (260–690)	12.1 (6.9–18.5)	100 (50–150)
Northern Africa	2.7 (1.1–11.2)	90 (40–360)	4.2 (1.8–18.9)	70 (30–330)	0.9 (0.3–2.3)	10 (< 5–30)
Southern Africa	35.5 (17.4–53.7)	1300 (630–1900)	47.4 (23.1–67.8)	1000 (490–1400)	18.8 (9.3–33.9)	280 (140–510)
Western Africa	22.2 (12.2–33.4)	530 (290–800)	31.2 (16.9–45.7)	410 (220–600)	11.3 (6.5–18.5)	120 (70–200)
Asia						
Eastern Asia	37.7 (21.2–53.1)	133 800 (75 200–188 700)	46.4 (26.0–64.0)	115 500 (64 700–159 400)	17.2 (9.9–27.6)	18 300 (10 500–29 300)
South-central Asia	17.8 (9.4–40.2)	18 700 (9800–42 200)	24.5 (12.9–52.3)	16 000 (8400–34 100)	6.7 (3.5–20.4)	2700 (1400–8100)
South-eastern Asia	29.7 (16.5–43.2)	4300 (2400–6200)	34.7 (19.2–50.4)	4000 (2200–5800)	9.2 (5.7–13.9)	260 (160–400)
Western Asia	7.5 (3.7–22.6)	320 (160–970)	11.3 (5.6–25.1)	260 (130–580)	3.0 (1.5–19.8)	60 (30–390)
Europe						
Central and eastern Europe	48.5 (28.0–63.9)	7500 (4300–9900)	53.5 (30.8–69.1)	6700 (3900–8700)	27.2 (15.7–41.4)	790 (460–1200)
Northern Europe	15.8 (9.5–21.4)	2000 (1200–2800)	15.6 (9.3–20.3)	1400 (840–1800)	16.4 (10.2–23.9)	640 (400–930)
Southern Europe	34.0 (20.4–45.7)	2100 (1300–2900)	38.7 (23.1–51.5)	1900 (1100–2500)	17.5 (11.0–25.4)	250 (160–360)
Western Europe	28.9 (17.4–38.1)	5300 (3200–7000)	31.4 (18.8–40.9)	4400 (2600–5700)	20.7 (13.0–29.4)	900 (560–1300)
Americas						
Latin America and the Caribbean	30.6 (17.5–43.0)	5800 (3300–8200)	35.7 (20.2–49.9)	5100 (2900–7200)	14.6 (8.9–21.6)	670 (410–990)
North America	14.2 (8.3–19.5)	3000 (1700–4100)	14.4 (8.3–19.5)	2400 (1300–3200)	13.3 (8.2–19.5)	600 (370–880)
Oceania						
Australia and New Zealand	18.9 (11.3–25.6)	360 (220–490)	18.3 (10.8–23.9)	250 (150–330)	20.5 (12.7–30.2)	110 (70–160)
Melanesia, Micronesia (Federated States of), and Polynesia	5.0 (1.0–9.4)	10 (< 5–20)	6.0 (1.3–11.3)	10 (< 5–20)	2.9 (0.6–5.6)	< 5 (< 5–5)

Table 1.5 (continued)

Cancer site (ICD-10 codes) by region	Overall		Males		Females	
	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]
Colorectum (C18–C20)						
Global	8.4 (6.3–10.6)	156 700 (116 800–196 500)	13.0 (9.7–16.2)	134 300 (100 500–167 200)	2.7 (2.0–3.5)	22 400 (16 300–29 400)
Africa						
Eastern Africa	4.9 (3.2–6.5)	790 (520–1100)	8.2 (5.3–10.7)	650 (430–860)	1.7 (1.1–2.4)	140 (90–200)
Middle Africa	5.6 (3.9–7.6)	270 (190–370)	9.2 (6.4–12.3)	240 (160–310)	1.6 (1.0–2.3)	40 (20–50)
Northern Africa	0.7 (0.3–1.2)	140 (50–250)	1.3 (0.5–2.2)	130 (50–220)	0.1 (< 0.1–0.3)	10 (< 5–30)
Southern Africa	9.6 (6.4–12.7)	690 (460–910)	15.1 (10.6–19.4)	560 (390–720)	3.8 (2.0–5.4)	130 (70–190)
Western Africa	8.0 (5.9–10.2)	950 (690–1200)	12.1 (9.1–15.3)	790 (590–990)	3.0 (2.0–4.1)	160 (110–220)
Asia						
Eastern Asia	7.9 (4.8–10.9)	57 600 (35 000–80 200)	12.3 (7.7–16.7)	51 400 (32 000–69 900)	2.0 (0.9–3.3)	6200 (2900–10 300)
South-central Asia	4.1 (1.6–5.9)	3900 (1600–5700)	6.2 (2.5–8.8)	3500 (1400–5000)	0.9 (0.3–1.6)	360 (130–640)
South-eastern Asia	4.0 (2.8–5.5)	4200 (2900–5700)	6.3 (4.4–8.4)	3700 (2600–5000)	1.1 (0.7–1.7)	500 (300–770)
Western Asia	2.1 (1.1–2.9)	860 (470–1200)	3.3 (1.8–4.4)	760 (420–1000)	0.6 (0.3–0.9)	100 (50–160)
Europe						
Central and eastern Europe	13.0 (9.8–16.2)	22 200 (16 700–27 700)	19.8 (15.1–24.3)	17 500 (13 300–21 500)	5.8 (4.1–7.5)	4800 (3400–6200)
Northern Europe	11.5 (8.4–14.7)	9100 (6700–11 700)	17.4 (13.1–21.9)	7600 (5700–9600)	4.2 (2.8–5.9)	1500 (980–2100)
Southern Europe	9.7 (7.1–12.4)	11 800 (8600–15 100)	14.7 (10.8–18.6)	10 300 (7600–13 000)	2.9 (2.0–4.0)	1500 (1000–2000)
Western Europe	11.7 (8.8–14.7)	15 900 (12 000–20 000)	17.7 (13.5–21.8)	13 300 (10 200–16 500)	4.3 (2.9–5.8)	2600 (1800–3500)
Americas						
Latin America and the Caribbean	7.6 (5.5–9.9)	9900 (7100–12 700)	12.7 (9.3–16.1)	8300 (6100–10 500)	2.5 (1.6–3.5)	1600 (1000–2200)
North America	9.4 (6.2–12.7)	16 100 (10 500–21 800)	14.8 (10.1–19.5)	13 700 (9300–18 000)	3.1 (1.6–4.9)	2500 (1300–3900)
Oceania						
Australia and New Zealand	11.7 (8.2–15.5)	2200 (1600–2900)	17.9 (12.9–22.9)	1800 (1300–2300)	4.5 (2.7–6.8)	400 (230–590)
Melanesia, Micronesia (Federated States of), and Polynesia	2.1 (0.5–3.9)	20 (< 5–30)	3.3 (0.9–6.1)	20 (< 5–30)	0.3 (< 0.1–0.7)	< 5 (< 5–5)

Table 1.5 (continued)

Cancer site (ICD-10 codes) by region	Overall		Males		Females	
	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]
Liver (C22)						
Global	17.3 (4.9–31.6)	154 700 (43 700–281 500)	22.7 (6.4–40.9)	141 300 (39 600–255 000)	5.0 (1.5–9.8)	13 400 (4100–26 400)
Africa						
Eastern Africa	11.4 (2.9–21.7)	1400 (360–2700)	16.5 (4.2–31.1)	1200 (300–2200)	4.0 (1.1–8.4)	200 (60–430)
Middle Africa	12.5 (3.3–23.5)	760 (200–1400)	16.4 (4.2–30.6)	690 (180–1300)	3.8 (1.2–7.4)	70 (20–140)
Northern Africa	1.5 (0.1–25.8)	460 (40–8200)	2.1 (0.2–39.7)	440 (30–8100)	0.2 (< 0.1–0.9)	30 (< 5–100)
Southern Africa	19.3 (5.0–35.4)	500 (130–920)	27.0 (6.9–47.9)	440 (110–780)	6.4 (1.7–14.7)	60 (20–140)
Western Africa	15.5 (4.2–28.6)	2700 (730–5000)	20.7 (5.5–37.7)	2400 (640–4400)	5.3 (1.5–11.1)	320 (90–670)
Asia						
Eastern Asia	20.4 (5.6–37.1)	97 400 (26 800–177 600)	25.8 (7.0–46.6)	89 700 (24 500–162 300)	5.9 (1.7–11.7)	7700 (2200–15 300)
South-central Asia	7.8 (1.7–20.6)	4300 (940–11 300)	11.1 (2.4–27.8)	4000 (870–10 100)	1.5 (0.4–6.5)	290 (80–1200)
South-eastern Asia	11.6 (3.1–21.6)	11 500 (3100–21 400)	15.0 (4.0–27.9)	10 800 (2900–19 900)	2.7 (0.8–5.4)	750 (230–1500)
Western Asia	4.7 (1.1–13.5)	530 (130–1500)	7.0 (1.7–20.5)	490 (120–1400)	1.0 (0.3–2.2)	40 (10–90)
Europe						
Central and eastern Europe	24.2 (7.0–40.2)	6000 (1700–10 000)	32.6 (9.5–52.4)	5000 (1400–8000)	10.8 (3.2–21.1)	1000 (300–2000)
Northern Europe	17.5 (5.0–29.6)	2100 (600–3500)	25.3 (7.1–42.0)	1900 (530–3100)	4.5 (1.4–8.9)	200 (60–400)
Southern Europe	19.7 (5.3–33.8)	4900 (1300–8400)	26.2 (6.9–44.5)	4400 (1200–7500)	5.7 (1.9–10.7)	450 (150–840)
Western Europe	23.8 (6.9–39.7)	6200 (1800–10 400)	30.6 (8.9–50.5)	5700 (1600–9400)	7.1 (2.3–13.3)	540 (170–1000)
Americas						
Latin America and the Caribbean	12.8 (3.5–22.9)	5000 (1400–9000)	20.2 (5.5–36.0)	4300 (1200–7700)	3.9 (1.1–7.4)	710 (200–1300)
North America	21.5 (6.0–37.6)	10 000 (2800–17 500)	28.1 (7.8–48.6)	9100 (2500–15 800)	6.5 (2.0–12.2)	920 (280–1700)
Oceania						
Australia and New Zealand	23.8 (6.6–40.1)	800 (220–1300)	30.2 (8.3–50.0)	730 (200–1200)	6.9 (2.3–13.6)	60 (20–120)
Melanesia, Micronesia (Federated States of), and Polynesia	4.3 (0.7–9.7)	40 (8–100)	6.5 (1.1–14.6)	40 (7–90)	0.8 (0.1–1.8)	< 5 (< 5–7)

Table 1.5 (continued)

Cancer site (ICD-10 codes) by region	Overall		Males		Females	
	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]
Breast, female (C50)						
Global	–	–	–	–	4.4 (3.0–5.8)	98 300 (68 200–130 500)
Africa						
Eastern Africa	–	–	–	–	2.1 (1.3–3.0)	940 (570–1400)
Middle Africa	–	–	–	–	2.7 (1.5–4.1)	480 (270–730)
Northern Africa	–	–	–	–	0.2 (< 0.1–0.4)	120 (50–230)
Southern Africa	–	–	–	–	4.6 (2.5–6.9)	750 (420–1100)
Western Africa	–	–	–	–	3.9 (2.4–5.7)	1900 (1200–2800)
Asia						
Eastern Asia	–	–	–	–	4.1 (2.5–6.0)	22 300 (13 200–32 600)
South-central Asia	–	–	–	–	1.5 (0.7–2.5)	3700 (1700–6500)
South-eastern Asia	–	–	–	–	1.8 (1.1–2.5)	2800 (1800–4000)
Western Asia	–	–	–	–	0.8 (0.5–1.3)	520 (310–760)
Europe						
Central and eastern Europe	–	–	–	–	8.3 (5.7–11.2)	13 200 (9000–17 800)
Northern Europe	–	–	–	–	7.3 (4.8–10.0)	6100 (4000–8300)
Southern Europe	–	–	–	–	5.4 (3.6–7.2)	6500 (4400–8700)
Western Europe	–	–	–	–	7.5 (5.1–9.9)	12 700 (8600–16 800)
Americas						
Latin America and the Caribbean	–	–	–	–	4.2 (2.8–6.0)	8800 (5900–12 600)
North America	–	–	–	–	5.6 (3.5–8.0)	15 700 (9800–22 400)
Oceania						
Australia and New Zealand	–	–	–	–	7.7 (5.1–10.9)	1800 (1200–2500)
Melanesia, Micronesia (Federated States of), and Polynesia	–	–	–	–	0.7 (0.3–1.3)	20 (7–30)

Table 1.5 (continued)

Cancer site (ICD-10 codes) by region	Overall		Males		Females	
	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]	PAF (95% CI)	Alcohol-attributable cases (95% CI)[a,b]
All 7 cancer types associated with alcohol consumption combined						
Global	11.7 (8.8–15)	741 300 (558 500–951 200)	21.6 (16–27.7)	568 700 (422 500–731 100)	4.7 (3.7–5.9)	172 600 (135 900–220 100)
Africa						
Eastern Africa	8.4 (5.9–11.2)	8300 (5800–11 100)	20.5 (14.1–26.9)	6000 (4200–7900)	3.3 (2.4–4.5)	2300 (1700–3100)
Middle Africa	7.8 (5.2–10.8)	2600 (1700–3700)	18.7 (12.1–25.6)	1900 (1200–2600)	3.1 (2.1–4.4)	740 (510–1000)
Northern Africa	0.8 (0.3–8.1)	990 (420–9800)	2.1 (0.9–24.5)	820 (350–9500)	0.2 (0.1–0.5)	180 (80–370)
Southern Africa	12.4 (8.6–16)	4200 (2900–5400)	28.1 (20.6–34.6)	2800 (2100–3500)	5.7 (3.5–8.1)	1400 (830–1900)
Western Africa	8.1 (5.0–11.6)	7000 (4300–10 100)	19.2 (11.0–27.9)	4400 (2500–6300)	4.2 (2.9–5.8)	2700 (1900–3700)
Asia						
Eastern Asia	15 (9.5–20.9)	332 100 (208 800–460 200)	25.3 (15.8–34.7)	275 900 (172 600–378 400)	5.0 (3.2–7.3)	56 300 (36 200–81 900)
South-central Asia	8.5 (4.7–16.7)	68 100 (37 900–133 800)	15.4 (8.6–29.8)	59 200 (33 200–114 800)	2.1 (1.2–4.6)	8900 (4800–19 000)
South-eastern Asia	6.6 (4.2–9.5)	27 700 (17 500–39 700)	13.4 (8.2–19.4)	23 000 (14 100–33 400)	1.9 (1.4–2.6)	4700 (3300–6400)
Western Asia	2.3 (1.5–4.0)	3000 (2000–5200)	5.4 (3.6–9.3)	2300 (1500–3900)	0.9 (0.6–1.4)	750 (480–1300)
Europe						
Central and eastern Europe	16.4 (13.3–19.4)	71 400 (57 800–84 200)	29.3 (24.2–33.7)	49 900 (41 100–57 300)	8.1 (6.3–10.2)	21 500 (16 700–26 900)
Northern Europe	12.1 (9.3–14.8)	24 800 (19 200–30 300)	21.4 (17.2–25)	15 600 (12 600–18 300)	6.9 (5.0–9.1)	9200 (6600–12 100)
Southern Europe	10.8 (8.4–13.1)	32 400 (25 200–39 400)	20.4 (16.2–24.2)	23 100 (18 300–27 400)	5.0 (3.7–6.4)	9300 (6900–12 000)
Western Europe	13.5 (10.6–16.2)	52 800 (41 300–63 500)	24.9 (20.0–29.2)	34 400 (27 500–40 300)	7.3 (5.4–9.1)	18 400 (13 800–23 200)
Americas						
Latin America and the Caribbean	8.9 (6.7–11.2)	39 300 (29 600–49 400)	19.7 (15.2–23.8)	26 800 (20 600–32 300)	4.1 (3.0–5.6)	12 600 (9100–17 100)
North America	10.3 (7.0–13.5)	59 600 (40 600–77 800)	20.9 (14.7–26.4)	38 500 (27 000–48 400)	5.4 (3.4–7.5)	21 200 (13 500–29 400)
Oceania						
Australia and New Zealand	12.9 (9.5–16.4)	6800 (5000–8600)	23.8 (18.2–28.7)	4200 (3200–5100)	7.4 (5.0–10.0)	2600 (1700–3500)
Melanesia, Micronesia (Federated States of), and Polynesia	3.1 (0.6–5.9)	190 (40–370)	6.7 (1.2–12.9)	160 (30–310)	0.9 (0.3–1.6)	30 (10–60)

CI, confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; PAF, population attributable fraction.

[a] Numbers > 10 are rounded to the nearest 10 or 100, depending on the value.

[b] Number of cases suppressed if < 5.

Data are from the Global Cancer Observatory (Rumgay et al., 2021b). For methodology, see Rumgay et al. (2021a).

When former alcohol consumption was included, the PAF and the number of alcohol-attributable new cancer cases globally in 2020 increased to 5.2% and 925 900 cases overall (7.7% and 713 200 cases among males, and 2.4% and 212 700 cases among females) (Rumgay et al., 2021a).

(ii) Regional and national patterns

The largest regional PAFs and numbers of alcohol-attributable new cancer cases in 2020 were in eastern Asia (5.7%; 332 100 cases) and central and eastern Europe (5.6%; 71 400 cases). The smallest regional PAFs in 2020 were in northern Africa (0.3%) and western Asia (0.7%) (Rumgay et al., 2021b) (Table 1.5; Fig. 1.5).

The largest regional PAFs among males were in eastern Asia (8.6%), European subregions (ranging from 4.7% in northern Europe to 7.8% in central and eastern Europe), south-central Asia (6.2%), southern Africa (5.7%), eastern Africa (4.9%), and Australia and New Zealand (4.8%), although the PAFs were not substantially smaller in four other regions (western Africa, middle Africa, Latin America and the Caribbean, and north America), where they ranged from 3.8% to 4.5% (Table 1.5). The smallest PAFs among males in 2020 were in the three remaining regions: northern Africa (0.6%), western Asia (1.0%), and Melanesia, the Federated States of Micronesia, and Polynesia (2.1%). Most of the countries with the largest PAFs among males were in eastern and south-eastern Asia and central and eastern Europe, but several countries in sub-Saharan Africa also had large PAFs among males (Fig. 1.5A).

In every region, PAFs of all new cancer cases in 2020 were smaller among females than among males (Table 1.5). The largest regional PAFs among females were in Europe (ranging from 2.3% in southern Europe to 3.4% in central and eastern Europe), Australia and New Zealand (3.3%), southern Africa (2.3%), and north America (2.2%). Most of the countries with the largest PAFs among females were in central and eastern Europe (Fig. 1.5B).

(b) Specific cancer sites

For all cancer sites associated with alcohol consumption, PAFs among both sexes in 2020 were largest in central and eastern Europe and smallest in northern Africa (Table 1.5). The regional variations in PAFs for each cancer site were generally similar to variations for all cancers combined (described previously), except for oesophageal cancer and colorectal cancer (see below). The largest regional PAFs among both males and females were generally in Europe, Australia and New Zealand, and southern Africa. In addition, the largest regional PAFs were in east and south-central Asia and eastern Africa among males, and in north America among females.

(i) Lip and oral cavity cancer

Globally, the proportion of new lip and oral cavity cancer cases in 2020 attributable to alcohol consumption was 20.2% (Table 1.5). The PAF was substantially larger among males (25.9%; 66 700 cases) than among females (7.3%; 8200 cases). The largest PAFs were in central and eastern Europe among both males (45.3%) and females (17.0%), and the smallest PAFs were in northern Africa among both males (4.0%) and females (0.4%).

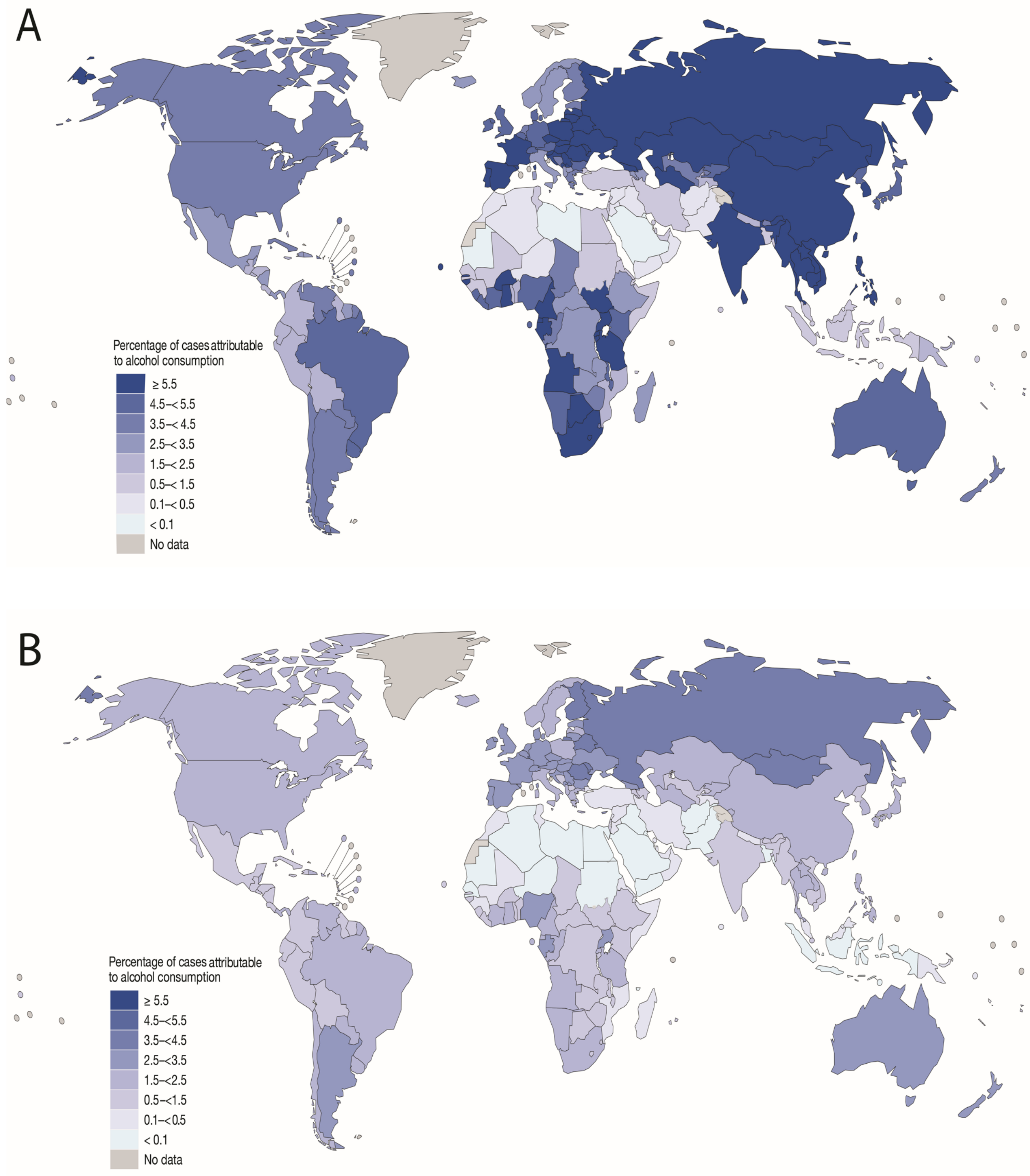
(ii) Pharyngeal cancer

Globally, the proportion of new pharyngeal cancer cases in 2020 attributable to alcohol consumption was 22.0% (Table 1.5). The PAF was substantially larger among males (25.3%; 37 000 cases) than among females (7.4%; 2500 cases). The largest PAFs were in central and eastern Europe among both males (40.3%) and females (15.9%), and the smallest PAFs were in northern Africa among both males (3.1%) and females (0.4%).

(iii) Laryngeal cancer

Globally, the proportion of new laryngeal cancer cases in 2020 attributable to alcohol consumption was 15.0% (Table 1.5). The PAF

Fig. 1.5 Proportion of new cancer cases in 2020 attributable to alcohol consumption by country, in males (A) and females (B)



From Rumgay et al. (2021b).

and the number of alcohol-attributable laryngeal cancer cases were larger among males (16.6%; 26 400 cases) than among females (4.7%; 1200 cases). The largest PAFs were in central and eastern Europe among both males (28.2%) and females (10.3%), and the smallest PAFs were in northern Africa among both males (2.1%) and females (0.2%).

(iv) Oesophageal cancer

Squamous cell carcinoma is the only subtype of oesophageal cancer that has an established association with alcohol consumption (IARC, 2012a), but previous studies have often reported the corresponding PAFs as the proportion of all oesophageal cancers. Globally, the largest PAF by cancer site in 2020 was for oesophageal cancer (31.6%), which contributed the most cases (189 700 cases) to the global burden of alcohol-attributable cancer cases (Table 1.5). The PAF was substantially larger among males (39.2%; 163 100 cases) than among females (14.3%; 26 600 cases).

Among males, regional patterns of PAFs for oesophageal cancer differed from patterns for all cancers combined (described previously). Notably, several additional subregions were among the regions with the largest PAFs for oesophageal cancer, including central and eastern Europe (53.5%), southern Africa (47.4%), eastern Asia (46.4%), southern Europe (38.7%), eastern Africa (37.3%), Latin America and the Caribbean (35.7%), middle Africa (35.7%), and south-eastern Asia (34.7%). In contrast, Australia and New Zealand (18.3%), northern Europe (15.6%), and north America (14.4%) – regions with relatively large PAFs for all cancers combined – were among the regions with relatively small PAFs for oesophageal cancer among males. This discrepancy may be due, in part, to the higher incidence rates for oesophageal adenocarcinoma (which has not been linked to alcohol consumption) in those three regions compared with the rest of the world, especially among males (Arnold et al., 2015; Li et al., 2022).

The smallest PAF for oesophageal cancer among males was in northern Africa (4.2%). The PAFs for oesophageal cancer among females ranged from 0.9% in northern Africa to 27.2% in central and eastern Europe. The regions with the largest PAFs for oesophageal cancer among females were those with the largest PAFs for all cancers combined (PAFs ≥ 13.3%), as well as eastern Asia (17.2%) and Latin America and the Caribbean (14.6%).

(v) Colorectal cancer

Globally, the proportions of new colon cancer cases (8.1%) and rectal cancer cases (9.0%) in 2020 attributable to alcohol consumption were comparable (Rumgay et al., 2021a). Globally, the proportion of new cases of colon and rectal cancer combined (colorectal cancer) in 2020 attributable to alcohol consumption was 8.4% (Table 1.5). The PAF was substantially larger among males (13.0%; 134 300 cases) than among females (2.7%; 22 400 cases). Unlike regional patterns for all cancers combined, no Asian or African subregions were among the regions with the largest PAFs for colorectal cancer among males, which included regions in Europe (ranging from 14.7% in southern Europe to 19.8% in central and eastern Europe), Australia and New Zealand (17.9%), and north America (14.8%). The PAF was ≤ 12.7% in all other regions and was smallest in northern Africa (1.3%). The PAFs for colorectal cancer among females ranged from 0.1% in northern Africa to 5.8% in central and eastern Europe. The regions with the largest PAFs for colorectal cancer among females were those with the largest PAFs for all cancers combined (PAFs ≥ 2.9%), as well as western Africa (3.0%).

(vi) Liver cancer

Hepatocellular carcinoma is the only subtype of liver cancer that has an established association with alcohol consumption (IARC, 2012a), but previous studies have often reported the corresponding PAFs as the proportion of all

liver cancers. Globally, the proportion of new liver cancer cases in 2020 attributable to alcohol consumption was 17.3% (Table 1.5). The PAF and the number of alcohol-attributable liver cancer cases were larger among males (22.7%; 141 300 cases) than among females (5.0%; 13 400 cases). The largest PAFs were in central and eastern Europe among both males (32.6%) and females (10.8%), and the smallest PAFs were in northern Africa among both males (2.1%) and females (0.2%).

(vii) Female breast cancer

In 2020, breast cancer was the most commonly diagnosed cancer among females worldwide and in most countries (154 of 185) (Sung et al., 2021). It also contributed the most alcohol-attributable cancer cases among females globally (98 300 cases) and in each region (Table 1.5). Globally, the proportion of new cases of female breast cancer in 2020 attributable to alcohol consumption was 4.4%. Similar to PAFs for all cancers combined, the largest PAFs for female breast cancer were in Europe (ranging from 5.4% in southern Europe to 8.3% in central and eastern Europe), Australia and New Zealand (7.7%), north America (5.6%), and southern Africa (4.6%). The smallest PAF for female breast cancer was in northern Africa (0.2%).

(viii) All seven cancer types associated with alcohol consumption combined

Globally, the 741 300 new cancer cases in 2020 that were attributable to alcohol consumption accounted for 11.7% of all cases of the seven cancer sites associated with alcohol consumption (lip and oral cavity, pharynx, larynx, oesophagus, colorectum, liver, and female breast) combined; this proportion was 21.6% among males and 4.7% among females (Table 1.5). Oesophageal cancer contributed the most alcohol-attributable cases globally in 2020 (189 700 cases, accounting for 25.6% of all cancer cases attributable to alcohol consumption), followed by colorectal cancer (156 7600 cases; 21.1%), liver cancer (154 700 cases; 20.9%), female breast cancer (98 300 cases; 13.3%), lip and oral cavity cancer (74 900 cases; 10.1%), pharyngeal cancer (39 400 cases; 5.3%), and laryngeal cancer (27 600 cases; 3.7%). The proportion of all seven alcohol-related cancers combined that were attributable to alcohol consumption was largest in central and eastern Europe among both males (29.3%) and females (8.1%) and smallest in northern Africa among both males (2.1%) and females (0.2%).

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2. ASSOCIATIONS OF CANCER RISK IN HUMANS

2.1 Methodological considerations

2.1.1 Study eligibility criteria

For this review and evaluation of human studies about the potential for reduction or cessation of alcoholic beverage consumption to reduce the risk of alcohol-related cancers, randomized controlled trials, individual case–control and cohort studies, meta-analyses, and pooled analyses were eligible for inclusion. No randomized controlled trials were identified that included cancer incidence or mortality as an outcome. The review and evaluation were limited to informative studies with data available to assess alcohol reduction, or duration of cessation or cessation compared with continuing consumption, in relation to the incidence of or mortality from cancers of the oral cavity, pharynx, larynx, oesophagus (squamous cell), colorectum, liver (hepatocellular), and female breast (i.e. collectively referred to here as alcohol-related cancers). The Working Group also reviewed informative studies of reduction, duration of cessation, and cessation in relation to the risk of upper aerodigestive tract cancers (i.e. cancers of the oral cavity, pharynx, larynx, and oesophagus combined), as well as the interaction (or effect modification) of cessation and alcohol-metabolizing gene variants on risk of alcohol-related cancers. (There were no studies of reduction or duration of cessation and alcohol-metabolizing gene interactions.) Table 2.1 shows the number of analyses for reduction, duration of cessation, and cessation by cancer site (excluding the analyses of cessation by gene interactions).

The Working Group did not review: (i) individual studies included in published meta-analyses or pooled analyses; (ii) meta-analyses or pooled analyses with overlapping studies; (iii) studies of precursor lesions (e.g. leukoplakia, erythroplakia, or colorectal adenomas); (iv) studies that compared cessation with abstention, but not continuing consumption with abstention; or (v) studies with fewer than 5 cancer cases that reported alcohol cessation overall or in subgroups (except for studies of alcohol cessation by gene interactions).

2.1.2 Overview of methodological issues

The important methodological issues that should be carefully considered when reviewing and inferring causality from observational studies of the reduction or cessation of alcoholic beverage consumption and cancer risk include selection bias, information bias, and confounding. Most of the observational studies reviewed focused primarily on associations between consumption and risk, and relative risks were usually presented with abstention as the reference category. However, in a randomized

Table 2.1 Number of analyses available for reduction and for duration of cessation and cessation of alcoholic beverage consumption compared with continuing consumption, in relation to risk of site-specific cancer

Cancer site	Types of analyses[a]		
	Reduction[b] (*n*)	Duration of cessation[c] (*n*)	Cessation[c] (*n*)
Oral cavity	0	1	8
Pharynx	0	2	9
Larynx	1	1	7
Oesophagus	1	9	15
Upper aerodigestive tract	2	3	6
Colorectum[d]	4	2	15
Liver	1	4	12
Female breast	4	0	18

[a] Some studies reported data for more than one type of analysis and/or for more than one cancer site.

[b] Analyses for reduction of alcohol consumption are based on at least two measures of consumption, one of which may be retrospectively recalled alcohol consumption history.

[c] Analyses for duration of cessation and cessation of alcoholic beverage consumption refer to those compared with continuing consumption. In the study of Andrade et al. (2015), risk of oral cancer for < 10 years of cessation was compared with ≥ 10 years of cessation, and in the study of White et al. (2017), risk of breast cancer for ≥ 15 years of cessation and 6–14 years of cessation was compared with ≤ 5 years of cessation. In these two studies, data were not available to compare cancer risk for categories of duration of cessation with continuing consumption. Therefore, the Working Group did not include these two studies in the counts of analyses for duration of cessation.

[d] Studies that reported evidence for colorectal cancer, colon cancer, and rectal cancer separately or for colon cancer and rectal cancer separately are counted only once for each type of analysis.

controlled trial designed to estimate the effect of alcohol cessation on cancer incidence or mortality, participant selection would be restricted to individuals who continue to consume alcoholic beverages, and they would be randomly assigned either to a cessation intervention group or to a control group. The target trial approach to the design and analysis of observational studies provides a useful framework for discussing the important methodological issues in case–control and cohort studies of alcohol cessation or reduction and cancer risk (Hernán et al., 2016; Hernán and Robins 2016; Moreno-Betancur, 2021). How well the observational studies reviewed in this *Handbook* emulate such a trial and the predicted direction of bias (assuming cessation is associated with lower cancer risk than continuing consumption) are included in the detailed discussion of the methodological issues below and summarized in Table 2.2. Because most of these studies reported results only for cessation, the discussion of methodological issues focuses primarily on cessation.

2.1.3 Selection bias

Selection bias relates to the selection, participation, or retention of study participants. In observational studies of alcohol cessation and cancer risk, selection bias can arise in one of two forms (Lu et al., 2022). The first form arises from conditioning on a common effect (or cause) of both the exposure and the outcome (Hernán et al., 2004). The second form arises from restricting the study to specific values or categories of an effect modifier of the relationship between the exposure and the outcome (Greenland, 1977; Hernán, 2017; Lu et al., 2022). Because smoking is an established effect modifier of the association between alcohol consumption and risk of

Table 2.2 Types and sources of bias in observational epidemiological studies of cessation of alcoholic beverage consumption compared with continuing consumption and risk of cancer, assuming that cessation is associated with a lower risk

Type of bias	Factor	Expected direction of bias[a] for measures of association[b] comparing cessation with continuing consumption	Comments
Selection bias (cohort studies)	Recruitment depends on alcohol cessation and presence of undiagnosed cancer	Unpredictable	Restriction to healthy participants used to avoid this bias
	Recruitment of elderly participants	Towards null	Sometimes considered to be an issue of generalizability
	Loss to follow-up that depends on both alcohol consumption status and case status	Unpredictable	Direction of bias will depend on loss to follow-up for both consumption status and likelihood of being diagnosed with the outcome Unlikely to be an issue when cancers are ascertained from population-based registries rather than from self-reports
Selection bias (case–control studies)	Hospital-based controls are likely to have elevated prevalence of alcohol cessation	Away from null	Individuals who cease consumption often do so because of ill health
	Response rates related to both alcohol consumption status and case status	Unpredictable	Direction of bias will depend on the response rates for both alcohol consumption status and case status
Selection bias (all studies)	Death from other causes related to alcohol (competing causes of death)	Towards null or a positive association	Only important if alcohol-related competing causes of death are common Important for liver cancer, for which cirrhosis is a precursor. Individuals with advanced cirrhosis who continue to consume alcohol are less likely to be diagnosed with cancer than those who cease consumption because they do not remain alive long enough to be diagnosed with cancer
Information bias (all studies)	Non-drinking reference category a mixture of lifetime abstention and alcohol cessation	No bias	Relative risks comparing alcohol cessation with "non-drinking" and continuing consumption with "non-drinking" will both be attenuated
	Misclassification of lifetime abstention as alcohol cessation	Away from null	Lifetime abstention is associated with a lower risk of alcohol-related cancer than alcohol cessation is
	Misclassification between alcohol cessation and continuing consumption	Towards null	
	Inadequate period of observation after alcohol cessation	Towards null	Benefit might take some time to manifest. Presentation of relative risks by duration of cessation would be useful
	Alcohol consumption status not measured at an etiologically relevant time	Towards null	Susceptibility to some cancer types (e.g. breast cancer) may vary through the life-course

Table 2.2 (continued)

Type of bias	Factor	Expected direction of bias[a] for measures of association[b] comparing cessation with continuing consumption	Comments
Information bias (all studies) (cont.)	Inclusion of histological or molecular subtypes of cancer that are not related to alcohol consumption	Towards null	
Information bias (cohort studies)	Long period of follow-up time with baseline measurement only	Towards null	Some participants will cease consumption during the follow-up time, but remain in the continuing consumption category
Information bias (case–control studies)	Measurement affected by case status (recall bias)	Uncertain	Direction depends on the magnitude and direction of measurement error for cases and controls
Confounding	Amount of alcohol consumed	Away from null	Assuming that individuals who report "light" consumption are more likely to cease consumption than those who continue to consume alcohol
	Amount of alcohol consumed	Towards null or a positive association	Assuming that individuals who report "heavy" consumption are more likely to cease consumption than those who continue to consume alcohol
	Smoking cessation (including duration of smoking cessation)	Away from null	Both alcohol cessation and quitting smoking may have common causes; quitting smoking reduces risk of cancer; this is an important issue for upper aerodigestive tract cancers
	Adiposity		Adiposity is positively associated with most alcohol-related cancers; unclear whether it is a mediator or a confounder of the association between alcohol cessation and risk of cancer
	Adiposity (weight loss)	Away from null (not likely to be strong)	Assuming that some individuals cease consumption to lose weight
	Diet	Depends on dietary risk factors for each cancer site (not likely to be strong)	
	Diet (adopting lower-risk diet)	Away from null (not likely to be strong)	Improving diet and alcohol cessation may have common causes; improving diet may reduce risk of cancer
Reverse causation	Alcohol reduction or cessation due to pre-diagnosis symptoms	Towards null or a positive association (could make cessation appear harmful)	Some individuals may cease consumption because of undiagnosed cancer Presenting relative risks by duration of cessation is useful for assessing potential reverse causation; ignoring at least the first year of follow-up time in statistical analysis is a strategy that could be used in cohort studies

[a] For direction of bias, "towards null" means that the association is underestimated or conservative, "away from null" means that it is overestimated (i.e. stronger inverse association), and "positive association" means that the bias is likely to result in a higher risk for cessation of alcohol consumption compared with continuing consumption.
[b] Measures of association: odds ratio, hazard ratio, risk ratio.

upper aerodigestive tract cancers, the implications of restricting analyses to never-smokers are discussed below under confounding and effect modification.

In cohort studies, selection bias might occur if recruitment is a common effect of alcohol consumption and symptoms of undiagnosed cancer. Most cohort studies restrict recruitment to healthy participants to avoid this type of selection bias. Selection bias can also arise when cohorts include substantial proportions of elderly participants, because they must have survived long enough to be included in the study. Loss to follow-up that differs by both exposure status and outcome (cancer) status would also introduce selection bias. Studies that identified participants who were diagnosed with cancer during the follow-up time from population-based cancer registries are less prone to selection bias than studies that ascertained self-reported diagnoses.

In case–control studies, the purpose of a control group is to provide a valid estimate of the prevalence of the exposure (e.g. alcohol cessation) in the source population from which the cases were ascertained. This is unlikely to be true for hospital-based case–control studies, in which controls are selected from among ill patients attending the same hospitals as the cases, because illness is a strong determinant of alcohol cessation. In many studies, individuals who became ill were more likely to quit than those who remained healthy. Early studies (Shaper et al., 1988; Wannamethee and Shaper, 1988) led to the "sick quitter" hypothesis as an explanation for why middle-aged individuals who do not consume alcohol had higher mortality rates than those who consumed less alcohol. In a large, prospective study, cessation was associated with a wide range of conditions (Sarich et al., 2019). Inclusion of controls likely to have ceased (or reduced) consumption will strengthen associations. The odds ratios from studies that restricted control selection to patients who only recently became ill or who had conditions unlikely to lead to reduction or cessation, and had a reference period for alcohol consumption before the onset of illness, are less likely to be biased. Similarly, if control selection is restricted to individuals who only recently became ill, associations for long-term cessation are less likely to be biased.

Low response rates in case–control studies that differ by both case status and exposure status, or a determinant of exposure, contribute to potential selection bias. Predicting the direction of bias requires knowledge about response rates by both case status and exposure status. For example, if controls (but not cases) who ceased consumption are more likely to participate than those who continue to consume alcohol, the bias would be away from the null.

Death due to other alcohol-related causes would prevent some people from being diagnosed with cancer and would bias associations between alcohol cessation and cancer risk towards the null or a positive association if cessation were also associated with the competing causes of death. Deaths due to other alcohol-related causes would need to be common for the bias to be important, which is unlikely to be the case for most cancers. However, for liver cancer, the bias could be important. Cirrhosis of the liver is a precursor to liver cancer, and individuals with advanced cirrhosis who continue to consume alcohol are less likely to be diagnosed with cancer than those who cease consumption because they do not remain alive long enough to be diagnosed with cancer.

2.1.4 Information bias (issues related to measurement)

(a) Assessment of alcoholic beverage consumption

Because there is little evidence that the association between alcoholic beverage consumption and cancer risk differs by the type of alcoholic beverage consumed (IARC, 2012a), this section pertains to total alcohol consumption.

For this *Handbook*, accurately distinguishing alcohol cessation (commonly referred to as former drinking in many studies) from lifetime abstention (commonly referred to as never drinking or non-drinking in many studies) is essential. The World Health Organization definition of "former drinking" is abstinence for at least the past 12 months (WHO, 2018). However, in epidemiological studies, the abstinence period is not always reported. A common approach for distinguishing cessation from lifetime abstention is to ask a study participant whether they consumed at least 12 alcoholic beverages in their lifetime. If the answer is no, then no further questions about consumption are asked and the person's consumption is categorized as abstention. Average consumption during a time period – typically the 12-month period before completing the questionnaire – is often measured using a food frequency questionnaire or a quantity–frequency questionnaire.

Neither a food frequency questionnaire nor a quantity–frequency questionnaire that measures consumption of alcoholic beverages over a single 12-month period provides information about reduction, duration of cessation, cessation, or amount of past alcoholic beverage consumption. Cessation can be assessed with a specific question, or by asking questions about consumption at different stages of life. Information about duration of cessation can be measured by asking questions about age at cessation or consumption at different stages of life. The amount of alcohol consumed and the change in consumption (e.g. reduction) require measurement of consumption at different time points. A few studies measured lifetime alcoholic beverage consumption retrospectively using questions about consumption at various stages of life, and some cohort studies used multiple waves of data collection.

The quantitative measurement of current and past alcoholic beverage consumption has important implications for interpreting associations between alcohol reduction or cessation and cancer risk. Although there is evidence that some individuals who ceased consumption report lifetime abstention (Fillmore et al., 2003), assuming that these individuals had similar amounts of past consumption to individuals who continued consuming alcohol, associations for cessation (compared with continuing consumption) and cancer risk would be unbiased. However, individuals who abstained throughout life are at lower risk of cancer, and including them in the cessation category would bias relative risks comparing cessation with continuing consumption away from the null. The measurement of past amount of alcohol consumed (e.g. drinks per day) facilitates control for confounding, which is discussed below in the section about confounding and effect modification.

Cancer is usually considered to have a long induction period, which means that if there is a benefit of alcohol cessation, it may take some time to manifest. Therefore, ideally, relative risks should be presented for categories of duration of cessation. Further, for some cancer sites, there might be specific stages of life during which an individual's susceptibility is increased. For these cancers, reduction or cessation must occur and be measured at the appropriate time. In cohort studies with long follow-up time and a single baseline measurement of alcohol consumption, an association between cessation and cancer risk may be underestimated if some participants who reported continuing consumption at baseline ceased consumption during the follow-up time.

In case–control studies, recall bias due to disease status that affects how alcohol consumption is measured can be problematic. However, the bias could be mitigated by blinding participants to the research questions, using standardized questionnaires, training interviewers, and/or blinding interviewers to case status (White et al., 2008). Participants with cancer may quit drinking after onset of symptoms and mistakenly state that they quit before then. The magnitude and direction of bias in estimates of odds

ratios for associations between alcohol cessation and cancer risk would depend on the degree of measurement error for cases and controls, which could be study- and population-specific.

(b) Outcome

For some cancer sites, the association between alcoholic beverage consumption and risk may vary by histological or molecular subtype. Therefore, any potential benefit of cessation is likely to be restricted to the subtypes that are alcohol-related. This may be an important issue for cancers of the oesophagus, liver, and breast.

Assessing associations of reduction or cessation of alcoholic beverage consumption with cancer incidence is preferable to assessing associations with cancer mortality. When mortality is the outcome, the relative risk is influenced by the risk of being diagnosed with and dying from cancer. If cessation affects the prognosis for a diagnosed cancer, the relative risk will not be the same as the relative risk of occurrence. This is less of an issue for oesophageal and liver cancers, which have low survival rates.

2.1.5 Issues related to statistical analysis

(a) Comparator (reference category)

In studies of alcohol cessation or duration of cessation in which the reference category was abstention (e.g. never drinking), the Working Group recalculated relative risks and their respective confidence intervals to permit a direct comparison of cancer risk between cessation and continuing consumption. The resulting relative risks were obtained by dividing the relative risks for cessation by the relative risk for continuing consumption. Throughout Section 2.2, these relative risks are referred to as "calculated" hazard ratios, rate ratios, risk ratios, or odds ratios for cessation or categories of duration of cessation compared with continuing consumption. Wherever possible, confidence intervals for the revised estimates accounted for the lack of independence due to the use of a common reference group. The method of Greenland and Longnecker (1992) was used to estimate covariances between relative risks. This method requires the number of cases and controls (person-years for a cohort study). Calculations were conducted with a user-written routine, drmeta (Orsini, 2021), in Stata version 17 (StataCorp, College Station, Texas, USA). When data needed for the calculations were not available, confidence intervals were calculated assuming independence using the same Stata routine. Ignoring the positive correlation between relative risk estimates leads to wider confidence intervals because the estimates are positively correlated (Greenland and Longnecker, 1992). For the few studies that presented floating confidence intervals (e.g. Im et al., 2021a, b), relative risk estimates were assumed to be uncorrelated, and therefore, no allowance for covariances was necessary (Easton et al., 1991). For each study that provided relative risks for several categories of amount of continuing consumption, the Working Group first calculated a single relative risk for single category of continuing consumption compared with abstention, and then calculated the relative risk comparing alcohol cessation with continuing consumption. The categories of amount of continuing consumption were combined using drmeta to perform a meta-analysis that allowed for the covariances between estimates. Because drmeta performs dose–response meta-analysis, all continuing consumption categories within a study were assigned the same value for alcohol consumption in the meta-analysis. For these calculations, continuing consumption of < 12 drinks per year was not included. For studies of alcohol reduction, no recalculations were necessary.

For one study of alcohol cessation and quitting smoking and risk of cancers of the head and neck (oral cavity, pharynx, and larynx) (Marron et al., 2010), two sets of calculations were conducted using data from Table 4 of the

study publication. Table 4 shows the interactions between categories of alcohol consumption status or duration of alcohol cessation and categories of tobacco smoking status or duration of quitting smoking on risk of head and neck cancers combined and separately using a common reference group of "current drinking and current smoking". To better understand the associations for duration of alcohol cessation, the relative risks were recalculated so that "current drinking" was the reference category in each smoking exposure stratum using the method of Greenland and Longnecker (1992) to account for the covariances. Next, to better understand the potential confounding effects of duration of smoking cessation on the association between duration of alcohol cessation and cancer risk, a random-effects meta-analysis was performed to calculate relative risks for duration of alcohol cessation adjusted for smoking status and duration of smoking cessation. No allowance for correlations between estimates was required.

(b) Confounding and effect modification

In observational studies, the exposures are not assigned randomly, and confounding is present when the groups being compared (e.g. cessation vs continuing consumption) have different distributions of other variables that affect the risk of the cancer being studied (VanderWeele, 2019).

The amount of alcohol consumed is a risk factor for alcohol-related cancers (IARC, 2012a), and individuals who ceased consumption may not have consumed the same amount of alcohol as individuals who continued to consume alcohol if the likelihood of quitting varied according to the amount consumed. In some cultures, people who consumed low amounts of alcohol may be the most likely to quit (Wannamethee and Shaper, 1988; Fillmore et al., 2003). In observational studies of cessation or duration of cessation, if this were the case, failure to measure and adjust for the amount of alcohol consumed would mean that associations comparing cessation with continuing consumption would be biased away from the null. If individuals who consumed higher amounts of alcohol were more likely to cease consumption than individuals who consumed lower amounts, the bias would be in the opposite direction. In studies of reduction, the amount of alcohol consumed is implicitly controlled for.

Another important potential confounding factor is tobacco smoking, which is an established risk factor for cancers of the oral cavity, pharynx, larynx, oesophagus, liver, and colorectum, and a positive association has been observed between tobacco smoking and risk of breast cancer (IARC, 2012a). Further, smoking cessation reverses smoking-related risk of upper aerodigestive tract cancers (IARC, 2007). When assessing reduction or cessation of alcoholic beverage consumption and cancer risk, adjustment for smoking status as never, former, and current is unlikely to fully prevent confounding by smoking. For upper aerodigestive tract cancers, adjusting for pack-years of smoking and duration of smoking cessation better reduces the confounding effects of smoking. Failure to adjust for these smoking data would be expected to strengthen any potential benefit of alcohol cessation, even long-term cessation. Assessing the association between alcohol cessation and cancer risk among individuals who never smoked may be the most appropriate means of controlling for smoking, although the relative risks might be imprecise because there are few cases. However, for cancers of the upper aerodigestive tract, alcohol consumption and tobacco smoking are synergistic (IARC, 2012a), and therefore relative risks for alcohol cessation from analyses restricted to never-smokers do not apply to everyone in the population (Lu et al., 2022).

Adiposity is a risk factor for cancers of the liver, colon, rectum, and female breast (in postmenopausal women). Whether it should be considered a confounder or a mediator of the

associations of alcohol reduction or cessation with risk of these cancers is uncertain. It would be a confounder if adiposity influenced reduction or cessation. It would be a mediator if reduction or cessation influenced adiposity. A further issue is that smoking cessation is associated with weight gain (Tian et al., 2015), which increases cancer risk, and could confound an association with alcohol reduction or cessation. Methods, known as g methods (generalized methods), have been developed when there was time-varying confounding, i.e. when a confounder at one time was subsequently affected by the exposure (Robins, 1986). No analyses of change in alcohol consumption and cancer risk using g methods were identified. Dietary factors are associated with risk of all alcohol-related cancers, although the specific dietary factors vary by cancer site (WCRF/AICR, 2018). These associations are generally weak to moderate and any bias due to confounding by dietary factors is likely to be minimal. Similar considerations apply to physical activity, which reduces risk of head and neck, colorectal, and breast cancers (Moore et al., 2016). Potentially important confounding factors for liver cancer that should be controlled for are chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. Screening for colorectal and breast cancer is common in many populations. If screening and alcohol cessation have shared antecedents (e.g. health consciousness), then failing to adjust for these antecedents, or for screening that occurred before cessation, could introduce confounding. Potential confounders are described at the beginning of the subsection for each of the alcohol-related cancer sites.

For an exposure to cause an outcome, it must precede the outcome. Reverse causation (also referred to as reverse causality) is a form of confounding in which the outcome precedes the exposure. In studies of cessation of alcoholic beverage consumption and cancer risk, reverse causation may occur if symptoms of undiagnosed cancer led to cessation, which could result in the appearance of a higher risk of cancer associated with cessation. A common strategy for mitigating the effects of reverse causation is to assess associations of cancer risk with categories of duration of alcohol cessation. In the presence of reverse causation, a short duration of cessation (e.g. < 5 years) may be associated with a higher risk of cancer compared with continuing consumption, but if there was a benefit to cessation, the higher risk should decrease with longer duration of cessation. In studies in which the relative risk of alcohol cessation compared with continuing consumption was > 1, and relative risks for categories of duration of cessation were not reported, or in cohort studies with short follow-up time, reverse causation is a likely explanation. Therefore, the studies that assessed associations for duration of cessation were influential in the evaluation, and more weight was given to associations for long-term cessation.

In case–control studies, bias due to reverse causation can be reduced by asking questions about alcoholic beverage consumption some time before diagnosis (e.g. 2 years). If the questions refer to consumption at the time of or after diagnosis, any benefit of quitting is likely to be underestimated, because people often quit after a diagnosis of cancer.

In cohort studies, excluding people with prevalent disease at baseline and beginning follow-up time ≥ 1 year after measuring consumption are strategies for reducing bias due to reverse causation. However, the former (i.e. excluding people with subclinical prevalent disease) generally is not possible, and the latter (beginning follow-up time ≥ 1 year after measuring consumption) is not consistent with a target trial approach (Hernán et al., 2016). Assessing the proportional hazards assumption (i.e. that the hazard ratio is constant over the follow-up time) in studies that assessed associations using Cox proportional hazards regression analysis is also useful for determining whether the relative risk varies by follow-up time.

2.2 Associations of reduction, duration of cessation, or cessation of alcoholic beverage consumption with cancer risk

2.2.1 Oral cancer

In this *Handbook*, oral cancer is defined primarily as cancer of the oral cavity, although some studies include cancer of the lip. Studies of oropharyngeal cancer are reviewed in the section on pharyngeal cancer (see Section 2.2.2), and the studies of oral cavity and oropharyngeal cancer combined are reviewed in the section on upper aerodigestive tract cancers (see Section 2.2.5). The International Classification of Diseases for Oncology, second edition (ICD-O-2) codes for oral cancer are ICD codes C00–C06, although C01 includes the oropharynx (Percy et al., 1990). Globally in 2020, the age-standardized (world population) incidence and mortality rates for oral cancer (including lip cancer) were 4.1 per 100 000 and 1.9 per 100 000, respectively (Ferlay et al., 2020).

The major risk factors for oral cancer are tobacco smoking, smokeless tobacco use, areca nut use, and alcohol consumption; there is a synergistic multiplicative effect of tobacco use and alcohol consumption combined on risk of oral cancer (IARC, 2012a, 2023).

(a) Cohort studies

The association between cessation of alcoholic beverage consumption compared with continuing consumption and risk of oral cancer was assessed in two cohort studies, one in India (Cancela et al., 2009) and one in China (Im et al., 2021a) (Table 2.3; Supplementary Table S2.4, web only; available from https://publications.iarc.who.int/638). There are no informative cohort studies with data to assess reduction or duration of cessation and risk of oral cancer.

The Trivandrum Oral Cancer Screening Trial in India included adults aged ≥ 35 years with no personal history of cancer (Cancela et al., 2009). Among eligible men, 32 771 participated in the first round of screening (1996–1998), and 32 347 men aged 35–100 years with alcohol consumption and follow-up data were included in the alcohol analysis. Incident cases of oral cavity cancer (*n* = 134) diagnosed between January 1996 and 30 June 2006 (mean follow-up time, 8.7 years) were ascertained through linkage with the Trivandrum population-based cancer registry or household interviews; oral cavity cancer deaths (*n* = 91) during the same time period were ascertained from municipal administration records or household interviews and cause of death was determined by a physician. Compared with never drinking, both current drinking and past drinking were associated with higher oral cancer incidence (hazard ratio [HR], 1.49; 95% confidence interval [CI], 1.01–2.21 for current drinking and HR, 1.90; 95% CI, 1.13–3.18 for past drinking) and higher oral cancer mortality (HR, 1.76; 95% CI, 1.08–2.86 for current drinking and HR, 2.04; 95% CI, 1.08–3.86 for past drinking). [Compared with continuing consumption, the calculated hazard ratio for cessation was 1.28 (95% CI, 0.73–2.23) for oral cancer incidence and 1.16 (95% CI, 0.59–2.29) for oral cancer mortality. The strength of this study is that the categories of drinking status were well defined. The limitations of this study are that the rationale for excluding women from this analysis is unclear, that the follow-up time after the second screening was limited (mean, 8.7 years), that the associations were adjusted for smoking status (ever, never) but not for detailed smoking history or the amount of alcohol consumed, and that there was no sensitivity analysis excluding at least the first year of follow-up time and no test of the proportional hazards assumption.]

Im et al. (2021a) assessed the association between alcohol consumption (and cessation) and cancer risk (including site-specific cancer risk) using data from the China Kadoorie Biobank. From 2004 to 2008, 512 715 men and women aged

Table 2.3 Cohort studies of cessation of alcoholic beverage consumption and risk of oral cancer

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Cancela et al. (2009) India Trivandrum Oral Cancer Screening Study 1996–2006	Analysis included n = 32 347 men aged 35–100 yr; follow-up time from January 1996 through June 2006 (average, 8.7 yr); cancer cases ascertained by cancer registry linkage or household visits; cancer deaths ascertained from municipal administration records and household interviews, and cause of death determined by a physician	Interviewer-administered questionnaire Drinking status: never was lifetime alcohol abstention; current was current drinking or cessation < 6 months before interview date; past was cessation ≥ 6 months before interview date	Oral (ICD-10 codes C02, other and unspecified parts of tongue; C03, gum; C04, floor of mouth; C05, palate; and C06, other and unspecified parts of the mouth)	Drinking status	Cases		Age, BMI, education, religion, occupation, standard of living index, betel quid chewing and smoking status (never, ever), vegetable and fruit intake	Limited follow-up time No adjustment for amount of alcohol consumed or detailed smoking history
				Never	61	1.0 (ref)		
				Current	52	1.49 (1.01–2.21)		
				Past	21	1.90 (1.13–3.18) P_{trend} = 0.006		
					Deaths			
				Never	43	1.0 (ref)		
				Current	34	1.76 (1.08–2.86)		
				Past	14	2.04 (1.08–3.86) P_{trend} = 0.008		
Im et al. (2021a) China China Kadoorie Biobank 2004–2016	Analysis included n = 209 237 men aged 30–79 yr; follow-up time from 2004 through 2016 (median, 10 yr); cancer cases ascertained by linkage with cancer registries and the national health insurance databases	Interviewer-administered questionnaire Drinking status: abstain was no drinking in the past year or in most weeks prior; ex-regular was drinking < weekly in the past year but drinking ≥ weekly prior; occasional was drinking < weekly in the past year and prior; current regular was drinking in most weeks in the past year	Lip and oral cavity (ICD-10 codes not specified for lip and oral cavity)	Drinking status			Age, study area, education, income, smoking (never, occasional, and for ever smoked, 3 categories of cigarettes per day in men and 2 in women), BMI, physical activity, fruit intake, and family history of cancer	Floating standard errors were used to estimate the CIs; abstention was the reference category No adjustment for amount of alcohol consumed or duration of smoking cessation
				Abstain	23	1.00 (0.65–1.53)		
				Ex-regular	12	1.06 (0.60–1.87)		
				Occasional	39	1.33 (0.96–1.86)		
				Current regular	66	1.89 (1.46–2.45)		

BMI, body mass index; CI, confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; ref, reference; yr, year or years.

30–79 years from 10 areas of China were enrolled. Unless otherwise noted in the description of this study for other cancer sites, the alcohol analyses included 209 237 men and 300 900 women with no personal history of cancer at baseline. Incident cancer cases diagnosed between enrolment and 1 January 2017 (median, 10 years) were identified through linkage with cancer registries and the National Health Insurance databases. Associations with risks of lip and oral cavity cancer, pharyngeal cancer (see Section 2.2.2), and laryngeal cancer (see Section 2.2.3) were assessed only for men, because too few women reported alcohol consumption to assess risk of these cancers for women separately. Associations with all head and neck cancers combined (see Section 2.2.5) are shown only for men, because among women there were fewer than 5 cases of head and neck cancer in the ex-drinking category. Among the men included in the analysis, 140 incident cases of lip and oral cavity cancer were identified. Compared with abstaining, ex-regular drinking was not associated with risk of lip and oral cavity cancer (HR, 1.06; 95% CI, 0.60–1.87), and current-regular drinking was associated with a higher risk (HR, 1.89; 95% CI, 1.46–2.45). [The calculated hazard ratio for cessation compared with continuing consumption was 0.56 (95% CI, 0.30–1.05).] A sensitivity analysis showed that, among men, the association between ex-drinking (compared with abstaining) and risk of all alcohol-related cancers combined was similar without (HR, 1.30; 95% CI, 1.20–1.40) and with (HR, 1.27; 95% CI, 1.16–1.40) exclusion of the first 3 years of follow-up time. [The strengths of this study are that the cohort was large, that the categories of drinking status were well defined, and that the hazard ratios for the first 5 years of follow-up time were similar to that for subsequent years, indicating no evidence of violation of the proportional hazards assumption. The limitations of this study are that the ex-regular-drinking category included less than weekly consumption during the previous year, that the associations were not adjusted for the amount of alcohol consumed or the duration of smoking cessation, that the sensitivity analysis excluding the first 3 years of follow-up time was not conducted for individual cancer sites (except for liver cancer, which was reported separately; see Section 2.2.7), and that it is unclear whether the examination of the proportional hazards assumption assessed potential differences for ex-regular drinking.]

(b) Case–control studies

The associations of duration of cessation and cessation of alcoholic beverage consumption compared with continuing consumption with risk of oral cancer were assessed in a large international pooled analysis of case–control studies (Marron et al., 2010). The association between cessation and risk also was assessed in five individual case–control studies in Brazil (Andrade et al., 2015), China (Zheng et al., 1997), Taiwan (China) (Ko et al., 1995; Huang et al., 2017), and Uruguay (De Stefani et al., 2007), not included in the pooled analysis (Table 2.5; Supplementary Table S2.4 and Table S2.6, web only; available from https://publications.iarc.who.int/638). Duration of cessation was also assessed in the study of Andrade et al. (2015); however, the data were not available to compare categories of duration of cessation with continuing consumption.

The associations of duration of cessation and cessation of alcoholic beverage consumption with risks of oral cavity cancer, oropharyngeal or hypopharyngeal cancer (see Section 2.2.2), laryngeal cancer (see Section 2.2.3), and combined head and neck cancers (see Section 2.2.5) were assessed in pooled analyses of individual-level data from European, Latin American, United States, and international-based case–control studies within the International Head and Neck Cancer Epidemiology (INHANCE) consortium (Marron et al., 2010). Included in the analysis for oral cavity cancer were data from 2615 cases and 12 359 controls who participated in

Table 2.5 Pooled analysis and individual case–control studies of duration of cessation and cessation of alcoholic beverage consumption and risk of oral cancer

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases or deaths	Odds ratio (95% CI)	Adjustment factors	Comments
Marron et al. (2010) INHANCE consortium ~1980s–early 2000s	Men and women with incident oral cavity cancer (n = 2615) who participated in population-based case–control studies in Seattle, Washington (USA), Los Angeles, California (USA), Boston, Massachusetts (USA), or Puerto Rico (USA), or hospital-based case–control studies in Italy, Switzerland, Iowa (USA), North Carolina (USA), Tampa, Florida (USA), Houston, Texas (USA), Latin America, or an international multicentre study	Hospital-based and population-based controls (n = 12 359 men and women) In one population-based study, controls were individually matched to cases on decade of age, sex, and neighbourhood; in the hospital-based studies, controls were frequency-matched to cases on age, sex, and other factors (e.g. study centre, hospital, and race or ethnicity)	Interviewer-administered questionnaires in all studies except self-administered in the Iowa study Drinking status: current was consumption within the past year; former was cessation ≥ 1 yr; never was responding no to ever drinking Duration of cessation: difference between age at reference date (interview or diagnosis) and age at cessation	Drinking status			Age, sex, race or ethnicity, study centre, education, pack-years of tobacco smoking, and number of alcoholic drinks per day	Pooled analysis of individual participant data Most data came from hospital-based case–control studies (n = 8), compared with population-based case–control studies (n = 4) No details reported about selection of hospital-based controls Participation rates not reported
				Current	1131	1.0 (ref)		
				Former	610	0.60 (0.43–0.84)		
				Never	737	0.64 (0.36–1.15)		
				Missing	137			
				Duration of cessation				
				Current	1131	1.0 (ref)		
				> 1–4 yr	132	0.81 (0.61–1.07)		
				5–9 yr	149	0.77 (0.52–1.15)		
				10–19 yr	174	0.66 (0.47–0.92)		
				≥ 20 yr	155	0.45 (0.26–0.78)		
				Never	737	0.65 (0.36–1.16)		
						P_{trend} = 0.05		
				Duration of cessation stratified by drinks per day				
				< 1 drink/day				
				Current	256	1.0 (ref)		
				> 1–4 yr	30	1.51 (0.80–2.87)		
				5–9 yr	22	1.06 (0.39–2.88)		
				10–19 yr	40	0.80 (0.37–1.75)		
				≥ 20 yr	57	0.98 (0.54–1.77)		
				Never	727	0.86 (0.39–1.89)		
				1–2 drinks/day				
				Current	234	1.0 (ref)		
				> 1–4 yr	24	0.67 (0.33–1.35)		
				5–9 yr	36	1.22 (0.43–3.43)		
				10–19 yr	30	0.34 (0.15–0.80)		
				≥ 20 yr	29	0.59 (0.22–1.57)		
				Never	717	0.58 (0.26–1.28)		

Table 2.5 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases or deaths	Odds ratio (95% CI)	Adjustment factors	Comments
Marron et al. (2010) (cont.)				≥ 3 drinks/day				
				Current	589	1.0 (ref)		
				> 1–4 yr	77	0.79 (0.54–1.14)		
				5–9 yr	90	0.85 (0.51–1.41)		
				10–19 yr	102	0.82 (0.50–1.34)		
				≥ 20 yr	69	0.43 (0.28–0.67)		
				Never	727	0.19 (0.09–0.39)		
Ko et al. (1995) Taiwan (China) 1992–1993	Men and women (n = 107), aged 18–86 yr with histologically confirmed oral cancer (ICD-9 codes 140–141, 143–145); diagnosed in the dentistry department of Kaohsiung Medical College Hospital	Hospital-based controls (n = 200), matched 2:1 for 93 cases and 1:1 for 14 cases on sex, age, and treatment period; without peptic ulcer, and treated in the same hospital as the cases	Interviewer-administered questionnaire Drinking status: no drinking and ex-drinking were not defined; yes was regular alcohol drinking > 4 days/week	Drinking status			Education, occupation, cigarette smoking status (no, ex, yes), and betel quid chewing status	Limited information about selection of hospital-based controls No adjustment for amount of alcohol consumed or detailed smoking history Participation rates not reported Reference date for drinking status not reported
				No	25	1.0 (ref)		
				Ex	14	1.0 (0.3–3.3)		
				Yes [drinking]	68	2.2 (1.0–4.9)		
Zheng et al. (1997) China 1988–1989	Men and women (n = 111) aged 20–80 yr with newly diagnosed, histologically confirmed tongue cancer; diagnosed at 1 of 7 hospitals in the Beijing area; 100% participation rate	Hospital-based controls (n = 111) individually matched to cases on sex and age (± 5 yr); patients from same hospital as cases or from the cases' referral hospital with conditions unrelated to smoking or alcohol consumption; 100% participation rate	Interviewer-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	Drinking status			Tobacco smoking, years of education, and matching factors	Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption No adjustment for amount of alcohol consumed Unclear what categories of smoking were controlled for
				Never	64	1.0 (ref)		
				Current	40	1.20 (0.58–2.50)		
				Ex	7	0.94 (0.28–3.22)		

Table 2.5 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases or deaths	Odds ratio (95% CI)	Adjustment factors	Comments
De Stefani et al. (2007) Uruguay 1998–2000	Men (*n* = 335) aged 30–78 yr with newly diagnosed, microscopically confirmed oral SCC; identified from the 4 major public hospitals in Montevideo, Uruguay; 97.4% participation rate	Hospital-based controls (*n* = 1501 men) matched to cases on time period and hospital; patients with non-neoplastic conditions unrelated to smoking or alcohol consumption, and without recent changes in their diet; 97.1% participation rate	Interviewer-administered questionnaire Drinking status: never was drinking occasionally (social) and < once per month; current was drinking at time of interview or quit < 1 yr before interview date; former was all others	Drinking status			Age, residence, urban or rural status, hospital, diagnosis year, education, first-degree family history of cancer, occupation, total vegetable, fruit, and maté intake, smoking status, years since quitting smoking, and current number of cigarettes per day	Excluded cancers of the lip Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption No adjustment for amount of alcohol consumed
				Never	34	1.0 (ref)		
				Former	91	3.0 (1.9–4.7)		
				Current	210	3.4 (2.3–5.2)		

Table 2.5 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases or deaths	Odds ratio (95% CI)	Adjustment factors	Comments
Andrade et al. (2015) Brazil 2002–2012	Men and women (n = 127) aged 23–96 yr with histopathologically confirmed SCC of the tongue, floor of mouth, lower lip, alveolar ridge, retromolar region, buccal mucosa, and hard palate; treated at the Universidade Estadual de Feira de Santana; 100% participation rate	Hospital-based controls (n = 254 men and women) from the same reference centre; excluded patients with confirmed or potentially malignant oral lesions or history of cancer	Medical record abstraction Drinking status: no definitions were reported for categories of drinking status	Drinking status				Limited information about selection of hospital-based controls No adjustment for any potential confounding factors, including smoking or amount of alcohol consumed Participation rate for controls not reported
				Non [drinking]	27	1.0 (ref)		
				Former	56	2.73 (1.73–4.31)		
				Current	44	1.07 (0.69–1.68)		
				Duration of cessation				
				≥ 10 yr	20	1.0 (ref)		
				< 10 yr	36	4.61 (2.08–10.22)		
Huang et al. (2017) Taiwan (China) 2010–2016	Men and women (n = 509) aged ≥ 20 yr with newly diagnosed, pathologically confirmed SCC of the oral cavity; treated at the National Cheng Kung University Hospital	Hospital-based controls (n = 940 men and women) frequency-matched to cases on sex and age (± 5 yr); patients from otolaryngology and stomatology departments diagnosed with non-cancer head and neck diseases unrelated to alcohol consumption, betel quid chewing, or cigarette smoking	Interviewer-administered questionnaire Drinking status: never was self-reported as such; occasional was not defined; regular was drinking ≥ once per week and was categorized as former regular (quit for > 6 months) and current regular	Drinking status			Age, sex, education, cigarette smoking (pack-year categories), and betel quid chewing (pack-year categories)	Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption No adjustment for amount of alcohol consumed or duration of smoking cessation Participation rates not reported
				Never/ occasional	195	1.0 (ref)		
				Former regular	61	0.77 (0.51–1.17)		
				Current regular	253	1.29 (0.97–1.73)		

CI, confidence interval; ICD-9, International Statistical Classification of Diseases and Related Health Problems, 9th revision; INHANCE, International Head and Neck Cancer Epidemiology; ref, reference; SCC, squamous cell carcinoma; yr, year or years.

four population-based and eight hospital-based case–control studies. Compared with current drinking, there was a lower risk of oral cancer associated with former drinking (odds ratio [OR], 0.60; 95% CI, 0.43–0.84). Longer duration of cessation was inversely associated with risk; the odds ratios were 0.81 (95% CI, 0.61–1.07) for > 1–4 years of cessation, 0.77 (95% CI, 0.52–1.15) for 5–9 years of cessation, 0.66 (95% CI, 0.47–0.92) for 10–19 years of cessation, and 0.45 (95% CI, 0.26–0.78) for ≥ 20 years of cessation (long-term cessation). The odds ratio for long-term alcohol cessation was substantially lower in the 1–2 drinks per day stratum (OR, 0.59; 95% CI, 0.22–1.57) and in the ≥ 3 drinks per day stratum (OR, 0.43; 95% CI, 0.28–0.67) than in the < 1 drink per day stratum (OR, 0.98; 95% CI, 0.54–1.77). In the subset of study participants with detailed alcohol consumption and smoking history data (2066 cases and 9471 controls), compared with the single reference category of current drinking and current smoking, long-term alcohol cessation was associated with a lower risk in each smoking stratum (OR, 0.40; 95% CI, 0.18–0.88 in the current-smoking stratum; range of ORs, 0.15–0.44 in the strata of duration of smoking cessation; and OR, 0.34; 95% CI, 0.12–0.93 in the never-smoking stratum). [In the Working Group re-analysis with continuing consumption as the reference category within each smoking stratum, the calculated odds ratios for long-term cessation were weaker but remained < 1 (range, 0.64–0.83) across all strata of duration of smoking cessation; in the never-smoking stratum, the calculated odds ratio for long-term alcohol cessation was 2.00 (95% CI, 0.70–5.75). After meta-analytic adjustment for smoking status and duration of smoking cessation, the calculated odds ratio for long-term cessation was 0.75 (95% CI, 0.43–1.33). The strengths of this study are that it is a large, robust pooled analysis of harmonized data on duration of alcohol cessation compared with continuing consumption, that the categories of drinking status were well defined, that the primary analysis included adjustment for pack-years of smoking and number of drinks per day (current and past), and that analyses were presented stratified by the number of drinks per day and by smoking status or duration of smoking cessation. The limitations of this study are that there is significant heterogeneity among studies (although sensitivity analyses showed that the associations from the two-stage random-effects model and the fixed-effects model were similar and the summary estimates were not dependent on one study), that most studies were hospital-based and there was no information on selection of hospital-based controls, and that in most duration of smoking cessation and never-smoking strata, there were few cases of oral cavity cancer in the long-term alcohol cessation category (range, *n* = 5–10).]

A hospital-based case–control study in Taiwan (China) (Ko et al., 1995) included 107 men and women aged 18–86 years with histologically confirmed oral cancer who were diagnosed in 1992 and 1993. The controls were 200 men and women matched on sex, age, and time of treatment (2 controls per case for 93 cases, and 1 control per case for 14 cases). Compared with "no drinking", there was no association for "ex-drinking" (OR, 1.0; 95% CI, 0.3–3.3) and a higher risk for "yes drinking" (OR, 2.2; 95% CI, 1.0–4.9). [Compared with continuing consumption, the calculated odds ratio for cessation was 0.46 (95% CI, 0.15–1.39). The strength of this study is that the analysis included adjustment for categories of betel quid chewing status. The limitations of this study are that the time between diagnosis and the interview date was not reported, that the categories of no drinking and ex-drinking were not defined, that there was limited information about selection of hospital-based controls, and that the associations were adjusted for cigarette smoking status (no, ex, yes) but not for detailed smoking history or the amount of alcohol consumed.]

A hospital-based case–control study in China (Zheng et al., 1997) included 111 men and women aged 20–80 years newly diagnosed with histologically confirmed tongue cancer in 1988–1989 at one of seven hospitals in the Beijing area. The controls were 111 men and women individually matched to cases on sex and age (± 5 years). Compared with never drinking, the odds ratio for current drinking was 1.20 (95% CI, 0.58–2.50) and for ex-drinking was 0.94 (95% CI, 0.28–3.22). [Compared with continuing consumption, the calculated odds ratio for cessation was 0.78 (95% CI, 0.21–2.90). The strength of this study is that the controls were selected from among patients with conditions thought to be unrelated to alcohol consumption. The limitations of this study are that the cases were interviewed before surgery but it is unclear when the controls were interviewed, that the categories of drinking status were not defined, that it is unclear what smoking categories were controlled for, that the associations were not adjusted for the amount of alcohol consumed, and that there were few cases of tongue cancer in the ex-drinking category (n = 7).]

The associations of alcohol cessation with risk of oral and pharyngeal (see Section 2.2.2) squamous cell carcinoma (SCC) among men were assessed by De Stefani et al. (2007) using data from a hospital-based case–control study in Uruguay. The analysis for oral cancer included 335 men aged 30–78 years newly diagnosed in 1988–2000 with microscopically confirmed SCC of the mouth. The controls were patients who did not have cancer (n = 1501 men), from the same time period and hospital as cases with conditions unrelated to smoking or alcohol consumption, and who had no recent dietary changes. Compared with never drinking, both former and current drinking were associated with a higher risk of oral cancer (former drinking OR, 3.0; 95% CI, 1.9–4.7 and current drinking OR, 3.4; 95% CI, 2.3–5.2). [Compared with continuing consumption, the calculated odds ratio for cessation was 0.88 (95% CI, 0.63–1.24). The strengths of this study are that there were a large number of controls, that controls were selected from among patients with conditions thought to be unrelated to alcohol consumption, that all participants were interviewed shortly after being admitted to the hospital, that categories of drinking status were well defined, and that the analysis adjusted for multiple potential confounders, including duration of smoking cessation. The limitation of this study is that the associations were not adjusted for the amount of alcohol consumed.]

In a hospital-based case–control study in north-eastern Brazil (Andrade et al., 2015), the cases included 127 men and women aged 23–96 years with histologically confirmed SCC of the tongue, floor of the mouth, lower lip, alveolar ridge, retromolar region, buccal mucosa, and hard palate who were treated from 2002 to 2012. The controls (2 per case) included 254 men and women. Compared with non-drinking, former drinking was associated with a higher risk of oral cancer (OR, 2.73; 95% CI, 1.73–4.31), whereas drinking was not associated with a higher risk (OR, 1.07; 95% CI, 0.69–1.68). [Compared with continuing consumption, cessation was associated with a higher risk of oral cancer (calculated OR, 2.55; 95% CI, 1.62–4.01).] There was a higher risk of oral cancer for < 10 years compared with ≥ 10 years of cessation, (OR, 4.61; 95% CI, 2.08–10.22). [The strength of this study is that there was histological confirmation of oral SCC. The limitations of this study are that there was limited information about selection of hospital-based controls, that the time between diagnosis and the interview date was not reported, that the categories of drinking status were not defined, that the associations were not adjusted for any potential confounding factors, including detailed smoking history and the amount of alcohol consumed, and that the comparison of risk between the two categories of duration of cessation does not provide the data needed

to recalculate risk for duration of cessation compared with continuing consumption.]

In a more recent hospital-based case–control study in Taiwan (China) (Huang et al., 2017), associations of alcohol cessation with risks of oral cavity cancer, oropharyngeal and hypopharyngeal cancer (see Section 2.2.2), laryngeal cancer (see Section 2.2.3), and combined head and neck cancers (see Section 2.2.5) were assessed. The cases were men and women aged ≥ 20 years with pathologically confirmed SCC of the head and neck, treated from September 2010 to August 2016. A total of 811 cases of head and neck cancer were enrolled; 509 cases of oral cavity cancer were included in the analysis. The controls (n = 940) were frequency-matched to cases on age (± 5 years) and sex. Compared with never and occasional drinking, the odds ratio was 0.77 (95% CI, 0.51–1.17) for former-regular drinking and 1.29 (95% CI, 0.97–1.73) for current-regular drinking. [Compared with continuing consumption, cessation was associated with a lower risk (calculated OR, 0.60; 95% CI, 0.39–0.92). The strengths of this study are that it was a large, hospital-based case–control study and that the controls were selected from among patients with conditions thought to be unrelated to alcohol consumption. The limitations of this study are that the category of never and occasional consumption was not defined and that the associations were not adjusted for duration of smoking cessation or the amount of alcohol consumed.]

2.2.2 Pharyngeal cancer

Pharyngeal cancer includes cancers of the oropharynx (ICD codes C09–C10), hypopharynx (ICD codes C12–C13), and nasopharynx (ICD code C11) (Percy et al., 1990). Globally in 2020, the age-standardized (world population) incidence and mortality rates for oropharyngeal cancer were 1.1 per 100 000 and 0.51 per 100 000, respectively; for hypopharyngeal cancer were 0.91 per 100 000 and 0.41 per 100 000, respectively; and for nasopharyngeal cancer were 1.5 per 100 000 and 0.88 per 100 000, respectively (Ferlay et al., 2020).

The major risk factors for oropharyngeal and hypopharyngeal cancer are smoking tobacco, chewing smokeless tobacco, and consuming alcohol; there is a synergistic multiplicative effect of alcohol consumption and tobacco smoking combined on risk of pharyngeal cancer (IARC, 2012a). In addition, there is sufficient evidence in humans for the causal role of human papillomavirus in the etiology of oropharyngeal cancer (IARC, 2012b). Epstein–Barr virus and dietary consumption of Chinese-style salted fish are established causes of nasopharyngeal cancer, whereas alcohol consumption may have a more limited role (IARC, 2010, 2012a, b).

(a) Cohort studies

The association between cessation of alcoholic beverage consumption compared with continuing consumption and risk of pharyngeal cancer was assessed in two cohort studies, one in India (Jayalekshmi et al., 2013) and one in China (Im et al., 2021a) (Table 2.7; Supplementary Table S2.8, web only; available from https://publications.iarc.who.int/638). There are no informative cohort studies with data to assess reduction or duration of cessation and risk of pharyngeal cancer.

From January 1990 to December 1997, 359 614 men and women were enrolled in the Karunagappally cohort study in India (Jayalekshmi et al., 2013). Included in the alcohol analysis were 65 553 men aged 30–84 years with no personal history of cancer at enrolment. Women were not included in the analysis because rates of pharyngeal cancer (and of laryngeal cancer; see Section 2.2.3) are low in the Karunagappally population. Incident cancer cases were ascertained by cancer registry linkage and cancer deaths were ascertained from the death registry supplemented by home visits. Among the men included in the analysis, 52 cases

Table 2.7 Cohort studies of cessation of alcoholic beverage consumption and risk of pharyngeal cancer

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Jayalekshmi et al. (2013) India Karunagappally cohort 1990–unclear	Analysis included *n* = 65 553 men aged 30–84 yr; follow-up time began in January 1990, but end date was unclear; cancer cases ascertained by cancer registry linkage; cancer deaths ascertained from death registry supplemented with house visits	Interviewer-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	Hypo-pharynx (ICD-9 code 148)	Drinking status			Attained age, income, and education	No adjustment for amount of alcohol consumed or smoking Excluded individuals who died within the first 3 yr of follow-up time End of follow-up was unclear
				Never	23	1.0 (ref)		
				Former	9	1.2 (0.6–2.6)		
				Current	20	1.3 (0.7–2.4)		
Im et al. (2021a) China China Kadoorie Biobank 2004–2016	Analysis included *n* = 209 237 men aged 30–79 yr; follow-up time from 2004 through 2016 (median, 10 yr); cancer cases ascertained by linkage with cancer registries and the national health insurance databases	Interviewer-administered questionnaire Drinking status: abstain was no drinking in the past year or in most weeks prior; ex-regular was drinking < weekly in the past year but drinking ≥ weekly prior; occasional was drinking < weekly in the past year and prior; current regular was drinking in most weeks in the past year	Pharynx (excluding nasophar-ynx)	Drinking status			Age, study area, education, income, smoking (never, occasional, and for ever smoked, 3 categories of cigarettes per day in men and 2 in women), BMI, physical activity, fruit intake, and family history of cancer	Floating standard errors were used to estimate the CIs; abstention was the reference category No adjustment for amount of alcohol consumed or duration of smoking cessation
				Abstain	10	1.00 (0.53–1.89)		
				Ex-regular	9	1.81 (0.93–3.50)		
				Occasional	15	1.18 (0.69–2.00)		
				Current regular	33	2.05 (1.42–2.96)		

BMI, body mass index; CI, confidence interval; ICD-9, International Statistical Classification of Diseases and Related Health Problems, 9th revision; ref, reference; yr, year or years.

of hypopharyngeal cancer were identified. Compared with never drinking, the relative risk was 1.2 (95% CI, 0.6–2.6) for former drinking and 1.3 (95% CI, 0.7–2.4) for current drinking. [Compared with continuing consumption, the calculated relative risk for cessation was 0.92 (95% CI, 0.42–2.04). The strength of this study is the large cohort. The limitations of this study are that the categories of drinking status were not defined, that the end date for follow-up was inconsistently reported in the paper (the abstract states that the follow-up period was 1990–2009, the cancer case ascertainment section states that cancer incidence was assessed in 1997–2009, and the statistical analysis section states that the observation period was 1990–2005 and the end of follow-up was 31 December 2005), that there were few cases of hypopharyngeal cancer in the former-drinking category (n = 9), and that the associations were not adjusted for smoking status or the amount of alcohol consumed.]

In the study of Im et al. (2021a) (described in Section 2.2.1), 67 incident cases of oropharyngeal and hypopharyngeal cancer (combined) among men were included in the analysis. Compared with abstaining, the hazard ratio was 1.81 (95% CI, 0.93–3.50) for ex-regular drinking and 2.05 (95% CI, 1.42–2.96) for current-regular drinking. [Compared with continuing consumption, the calculated hazard ratio for cessation was 0.88 (95% CI, 0.41–1.88). The strengths and limitations of this study are described in Section 2.2.1.]

(b) Case–control studies

The associations of duration of cessation and cessation of alcoholic beverage consumption compared with continuing consumption with risk of oropharyngeal and hypopharyngeal cancer (combined) were assessed in the international pooled analysis of case–control studies (Marron et al., 2010), and with risk of hypopharyngeal cancer were assessed in an individual case–control study in Japan (Takezaki et al., 2000) that was not included in the pooled analysis. Cessation and risk of pharyngeal cancer was assessed in the study in Uruguay (De Stefani et al., 2007), and hypopharyngeal and oropharyngeal cancer were the outcomes in two individual case–control studies in Taiwan (China) (Lee et al., 2005b; Huang et al., 2017). Cessation and risk of nasopharyngeal cancer was assessed in two other individual studies in China (Feng et al., 2021) and in Thailand (Fachiroh et al., 2012) (Table 2.9; Supplementary Table S2.8 and Table S2.10, web only; available from https://publications.iarc.who.int/638).

The international pooled analysis of case–control studies (Marron et al., 2010) (described in Section 2.2.1) included individual-level data from 3219 cases of oropharyngeal and hypopharyngeal cancer (combined) and 12 593 controls from nine hospital-based and four population-based case–control studies. Compared with current drinking, the risk of oropharyngeal and hypopharyngeal cancer (combined) was not associated with former drinking (OR, 0.98; 95% CI, 0.69–1.39). The odds ratio for long-term cessation (≥ 20 years) was suggestive of a lower risk (OR, 0.74; 95% CI, 0.50–1.09), but the odds ratios were near or above 1 for categories of shorter duration of cessation (OR range, 0.95–1.15). There was no clear pattern of risk reduction associated with duration of cessation in strata of drinks per day. In the subset of study participants with detailed alcohol consumption and smoking history data (n = 1864 cases and n = 7569 controls), compared with the single reference category of current drinking and current smoking, the odds ratio for long-term alcohol cessation was 0.82 (95% CI, 0.42–1.6) in the current-smoking stratum. The odds ratios ranged from 0.37 to 0.75 among the strata of duration of smoking cessation, and the odds ratio was 0.51 (95% CI, 0.07–3.73) in the never-smoking stratum. [In the Working Group re-analyses with continuing consumption as the reference category within each smoking stratum, the calculated odds ratios for long-term cessation ranged from 0.82 to 1.76. After meta-analytic

Table 2.9 Pooled analysis and individual case–control studies of duration of cessation and cessation of alcoholic beverage consumption and risk of pharyngeal cancer

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases or deaths	Odds ratio (95% CI)	Adjustment factors	Comments
Oropharyngeal and/or hypopharyngeal cancer								
Marron et al. (2010) INHANCE consortium ~1980s–early 2000s	Men and women with incident oropharyngeal and hypopharyngeal cancer (*n* = 3219) who participated in population-based case–control studies in Seattle, Washington (USA), Los Angeles, California (USA), Boston, Massachusetts (USA), or Puerto Rico (USA), or hospital-based case–control studies in France, Italy, Switzerland, Iowa (USA), North Carolina (USA), Tampa, Florida (USA), Houston, Texas (USA), Latin America, or an international multicentre study	Hospital-based and population-based controls (*n* = 12 593) In the Los Angeles population-based study, controls were individually matched to cases on decade of age, sex, and neighbourhood; in the hospital-based studies, controls were frequency-matched to cases on age, sex, and other factors (e.g. study centre, hospital, and race or ethnicity	Interviewer-administered questionnaires in all studies except self-administered in the Iowa study Drinking status: current was consumption within the past year; former was cessation ≥ 1 yr before interview date; never was responding no to ever drinking Duration of cessation: difference between age at reference date (interview or diagnosis) and age at cessation	Drinking status			Age, sex, race or ethnicity, study centre, education, pack-years of tobacco smoking, and number of alcoholic drinks per day	Pooled analysis of individual participant data Most data came from hospital-based case–control studies (*n* = 9), compared with population-based case–control studies (*n* = 4) No details reported about selection of hospital-based controls Participation rates not reported
				Current	1703	1.0 (ref)		
				Former	1014	0.98 (0.69–1.39)		
				Never	406	0.64 (0.41–1.00)		
				Missing	96			
				Duration of cessation				
				Current	1703	1.0 (ref)		
				> 1–4 yr	213	1.04 (0.73–1.48)		
				5–9 yr	240	0.95 (0.61–1.49)		
				10–19 yr	340	1.15 (0.92–1.43)		
				≥ 20 yr	221	0.74 (0.50–1.09)		
				Never	406	0.65 (0.42–1.02)		
						P_{trend} = 0.18		
				Duration of cessation stratified by drinks per day				
				< 1 drink/day				
				Current	338	1.0 (ref)		
				> 1–4 yr	29	2.02 (1.07–3.80)		
				5–9 yr	28	1.44 (0.65–3.16)		
				10–19 yr	67	1.49 (0.96–2.34)		
				≥ 20 yr	60	1.16 (0.65–2.05)		
				Never	406	0.97 (0.59–1.58)		
				1–2 drinks/day				
				Current	335	1.0 (ref)		
				> 1–4 yr	38	1.09 (0.65–1.82)		
				5–9 yr	33	1.09 (0.55–2.16)		
				10–19 yr	55	1.06 (0.67–1.68)		
				≥ 20 yr	45	0.80 (0.47–1.37)		
				Never	400	0.49 (0.30–0.81)		

Table 2.9 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases or deaths	Odds ratio (95% CI)	Adjustment factors	Comments
Marron et al. (2010) (cont.)				≥ 3 drinks/day				
				Current	926	1.0 (ref)		
				> 1–4 yr	141	1.05 (0.69–1.59)		
				5–9 yr	174	1.12 (0.60–2.08)		
				10–19 yr	213	1.15 (0.73–1.81)		
				≥ 20 yr	115	0.77 (0.45–1.30)		
				Never	397	0.19 (0.10–0.37)		
Takezaki et al. (2000) Japan 1988–1997	Men ($n = 62$) aged 40–79 yr with histopathologically or clinically confirmed hypopharyngeal cancer (ICD-9 code 148 or ICD-10 code C13); diagnosed within 1 yr of completing a first-visit outpatient questionnaire at ACCH from 1988 to 1997	Hospital-based controls ($n = 11\,936$ men) aged 40–79 yr; completed questionnaire as first-visit outpatients at ACCH and confirmed to be cancer-free by diagnostic procedures from 1988 to 1997	Self-administered questionnaire Drinking status: almost never was not defined; former was quit ≥ 1 yr previously; current was drinking ≥ 4 times/week Duration of cessation: years since quitting	Drinking status			Age, year, and season of visit, smoking (never, former, and for current, < 30 and ≥ 30 pack-years), and consumption of raw vegetables	Limited information about selection of hospital-based controls No adjustment for amount of alcohol consumed or duration of smoking cessation 98.6% of first-visit outpatients returned the survey
				Almost never	5	1.0 (ref)		
				Former	7	7.9 (2.5–25.3)		
				Current	50	4.7 (1.9–12.0)		
				Duration of cessation				
				Almost never	NR	1.0 (ref)		
				1–9 yr		7.8 (2.1–29.6)		
				≥ 10 yr		10.0 (1.8–57.4)		

Table 2.9 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases or deaths	Odds ratio (95% CI)	Adjustment factors	Comments
Lee et al. (2005b) Taiwan (China) 2000–2003	Men (*n* = 148) aged 41–80 yr with histologically confirmed SCC of the hypopharynx (ICD-10 code C13) and oropharynx (ICD-10 code C10); recruited from 2 teaching hospitals in southern Taiwan (China); 97.9% participation rate	Hospital-based, controls (*n* = 255 men) aged 40–92 yr; otolaryngology outpatients or inpatients at one of the hospitals during the same study period as cases; without conditions associated with betel quid chewing, cigarette smoking, or alcohol consumption; 88.2% participation rate	Interviewer-administered questionnaires Drinking status: non was lifetime abstention; ex was abstaining for > 1 yr before interview; current was drinking at time of interview or quit < 1 yr before interview date	Drinking status			Cigarette smoking, betel quid chewing, and age	Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption No adjustment for amount of alcohol consumed Unclear what categories of smoking were controlled for
				Non	28	1.0 (ref)		
				Ex	22	7.4 (2.8–20.3)		
				Current	98	6.4 (3.3–13.9)		
De Stefani et al. (2007) Uruguay 1988–2000	Men (*n* = 441) aged 30–78 yr with microscopically confirmed SCC of the pharynx; identified from the 4 major public hospitals in Montevideo, Uruguay; 97.4% participation rate	Hospital-based controls (*n* = 1501 men) matched to cases on time period and hospital; patients with non-neoplastic conditions unrelated to smoking or drinking, and with no recent changes in their diet; 97.1% participation rate	Interviewer-administered questionnaire Drinking status: never was drinking occasionally (social) and < once per month; current was drinking at time of interview or quit < 1 yr before interview date; former was all others	Drinking status			Age, residence, urban or rural status, hospital, diagnosis year, education, first-degree family history of cancer, occupation, total vegetable, fruit, and maté intake, smoking status, years since quitting smoking, and current number of cigarettes per day	Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption No adjustment for amount of alcohol consumed
				Never	33	1.0 (ref)		
				Former	116	3.9 (2.5–6.1)		
				Current	292	4.5 (3.0–6.8)		

Table 2.9 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases or deaths	Odds ratio (95% CI)	Adjustment factors	Comments
Huang et al. (2017) Taiwan (China) 2010–2016	Men and women (*n* = 118) aged ≥20 yr with newly diagnosed pathologically confirmed SCC of the oropharynx (ICD-10 code C10) or hypopharynx (ICD-10 code C13); treated at the National Cheng Kung University Hospital	Hospital-based controls (*n* = 940 men and women), frequency-matched to cases on sex and age (± 5 yr); patients from otolaryngology and stomatology departments diagnosed with non-cancer head and neck diseases unrelated to alcohol consumption, betel quid chewing, and cigarette smoking	Interviewer-administered questionnaire Drinking status: never was self-reported as such; occasional was not defined; regular was drinking ≥ once per week and was categorized as former regular (quit for > 6 months) and current regular	Drinking status	Oropharynx		Age, sex, education, cigarette smoking (pack-year categories), and betel quid chewing (pack-year categories)	Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption No adjustment for amount of alcohol consumed or duration of smoking cessation Participation rates not reported
				Never/occasional	29	1.0 (ref)		
				Former regular	20	2.83 (1.39–5.76)		
				Current regular	69	4.23 (2.38–7.52)		
					Hypopharynx			
				Never/occasional	4	1.0 (ref)		
				Former regular	19	14.02 (4.38–44.85)		
				Current regular	66	21.55 (7.36–63.15)		
Nasopharyngeal cancer								
Fachiroh et al. (2012) Thailand 2005–2010	Men and women (*n* = 681), mean age 49.8 yr, with newly diagnosed clinically and pathologically confirmed primary nasopharyngeal cancer (ICD-O code C11); identified from 7 regional cancer centres	Friend- or family-based controls (*n* = 1078 men and women), mean age 46.9 yr; healthy individuals who visited patients admitted to one of the centres	Interviewer-administered questionnaire Drinking status: never was not defined; former was quit for ≥ 2 yr before interview (controls) or diagnosis (cases); current was continuous drinking for ≥ 1 yr	Drinking status			Sex, age group (10-yr groups), centre, education, and smoking status (never, former, current)	No adjustment for amount of alcohol consumed or detailed smoking history Participation rates not reported
				Never	295	1.0 (ref)		
				Former	106	1.40 (0.95–2.06)		
				Current	280	1.02 (0.78–1.34) P_{trend} = 0.98		

Table 2.9 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases or deaths	Odds ratio (95% CI)	Adjustment factors	Comments
Feng et al. (2021) China 2010–2014	Men (*n* = 1785) and women (*n* = 656) aged 20–74 yr with histopathologically confirmed incident nasopharyngeal cancer; ascertained by a rapid reporting system in 3 regions in southern China; 83.8% participation rate	Population-based controls (*n* = 1869 men and *n* = 677 women) frequency-matched to cases on sex and age (± 5 yr) by geographical region; randomly selected every 6–12 months from total population registries within each geographical region; 82.7% participation rate	Interviewer-administered questionnaire Drinking status: never was no habitual (≥ once per week for 6 months) alcohol consumption; former was ever drinking and > 2 yr since cessation; current was all others	Drinking status	All		Age (10-yr groups), area of residence, sex, education, current housing type, current occupation, current smoking (ever or never), tea drinking (never, former, or current, for alcohol analysis only), BMI at age 20 yr, salt-preserved fish, vegetable, and herbal soup consumption, nasopharyngeal cancer among first-degree relatives, frequency of tooth brushing	No adjustment for amount of alcohol consumed or detailed smoking history Former drinking was defined as cessation for > 2 yr
				Never	1686	1.0 (ref)		
				Former	130	1.31 (0.99–1.74)		
				Current	625	1.08 (0.93–1.25)		
					Women			
				Never	620	1.0 (ref)		
				Former	12	1.72 (0.70–4.26)		
				Current	24	0.94 (0.51–1.73)		
					Men			
				Never	1066	1.0 (ref)		
				Former	118	1.29 (0.95–1.74)		
				Current	601	1.08 (0.93–1.25)		

ACCH, Aichi Cancer Center Hospital; BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; INHANCE, International Head and Neck Cancer Epidemiology; NR, not reported; ref, reference; SCC, squamous cell carcinoma; yr, year or years.

adjustment for smoking status and duration of smoking cessation, the calculated odds ratio for long-term cessation was 0.95 (95% CI, 0.56–1.61). The strengths and limitations of this study are described in Section 2.2.1.]

In 1988–1997, men and women were asked to complete a questionnaire during their first outpatient visit at the Aichi Cancer Center Hospital in Nagoya (Japan). Among 67 854 men and women aged ≥ 18 years who were asked to participate, 66 885 (98.6%) completed the survey (Takezaki et al., 2000). Only men aged 40–79 years were included in the alcohol analysis, because there were too few data about younger cases and female cases for analysis, and the reliability of the study questionnaire was lower among older cases. Data from the questionnaires were linked to the hospital cancer registry 1 year after the first visit to obtain information about confirmed diagnosis. The cases were patients diagnosed with histologically or clinically confirmed cancer of the hypopharynx (or oesophagus; see Section 2.2.4). Among eligible patients who responded to the questionnaire, 62 men were diagnosed with hypopharyngeal cancer. The controls (n = 11 936 men) were selected from all first-visit outpatients who completed the questionnaire and were aged 40–79 years and confirmed to be cancer-free. Compared with almost-never drinking, there were higher risks associated with former drinking (OR, 7.9; 95% CI, 2.5–25.3) and current drinking (OR, 4.7; 95% CI, 1.9–12.0). [Compared with continuing consumption, the calculated odds ratio for cessation was 1.68 (95% CI, 0.73–3.86).] In analyses of duration of cessation, compared with almost-never drinking, there were higher risks for 1–9 years of cessation (OR, 7.8; 95% CI, 2.1–29.6) and ≥ 10 years of cessation (OR, 10.0; 95% CI, 1.8–57.4). [Compared with continuing consumption, the calculated odds ratio for 1–9 years of cessation was 1.66 (95% CI, 0.33–8.92) and for ≥ 10 years of cessation was 2.13 (95% CI, 0.30–15.12). The strengths of this study are that alcohol consumption data were collected before cancer diagnosis, and that the former-drinking and current-drinking categories were well defined. The limitations of this study are that there was limited information about selection of hospital-based controls, that the associations were adjusted for pack-years of smoking but not for duration of smoking cessation or the amount of alcohol consumed, that no information was provided about the number of cases in each of the duration of cessation categories, and that there were few cases of hypopharyngeal cancer in the never-drinking category (n = 5) and the former-drinking category (n = 7).]

A hospital-based case–control study in Taiwan (China) (Lee et al., 2005b) included men aged 40–80 years (n = 276) diagnosed from November 2000 to December 2003 with histologically confirmed hypopharyngeal and oropharyngeal (combined) and laryngeal (see Section 2.2.3) SCC. Included in the analysis for pharyngeal cancer were 148 cases. The controls (n = 255) were men aged 40–92 years. Compared with non-drinking, the odds ratio was 7.4 (95% CI, 2.8–20.3) for ex-drinking and 6.4 (95% CI, 3.3–13.9) for current drinking. [Compared with continuing consumption, the calculated odds ratio for cessation was 1.16 (95% CI, 0.41–3.27). The strengths of this study are that the controls were selected from among patients with conditions thought to be unrelated to alcohol consumption and that the categories of drinking status were well defined. The limitations of the study are that it is unclear what smoking categories were controlled for and that the associations were not adjusted for the amount of alcohol consumed.]

In the hospital-based case–control study of De Stefani et al. (2007) (described in Section 2.2.1), 441 men with pharyngeal SCC and 1501 controls were included in the analysis. Compared with never consumption, both former consumption and current consumption were associated with a higher risk of pharyngeal cancer (OR, 3.9; 95% CI, 2.5–6.1 for former consumption and OR, 4.5; 95% CI, 3.0–6.8 for

current consumption). [The calculated odds ratio for cessation compared with continuing consumption was 0.87 (95% CI, 0.63–1.18). The strengths and limitations of this study are described in Section 2.2.1.]

In another case–control study in Taiwan (China) (Huang et al., 2017) (described in Section 2.2.1), 118 cases of oropharyngeal SCC, 89 cases of hypopharyngeal SCC, and 940 controls were included in the analysis. Compared with never drinking and occasional drinking, both former-regular drinking and current-regular drinking were associated with higher risk of oropharyngeal cancer (OR, 2.83; 95% CI, 1.39–5.76 for former-regular drinking and OR, 4.23; 95% CI, 2.38–7.52 for current-regular drinking). [The calculated odds ratio for cessation compared with continuing consumption was 0.67 (95% CI, 0.35–1.29).] Similarly, compared with never drinking and occasional drinking, both former-regular drinking and current-regular drinking were associated with higher risk of hypopharyngeal cancer (OR, 14.02; 95% CI, 4.38–44.85 for former-regular drinking and OR, 21.55; 95% CI, 7.36–63.15 for current-regular drinking). [The calculated odds ratio for cessation compared with continuing consumption was 0.65 (95% CI, 0.33–1.29). The strengths and limitations of this study are described in Section 2.2.1. In addition, in the analysis of hypopharyngeal cancer, there were few cases in the never or occasional consumption category (n = 4).]

In a friend- or family-based case–control study in Thailand (Fachiroh et al., 2012), cases included 681 men and women (mean age, 49.8 years) with clinically and pathologically confirmed nasopharyngeal cancer, who were recruited from January 2005 to May 2010. The controls (n = 1078) were healthy men and women (mean age, 46.9 years) who visited patients admitted to one of the centres. Compared with never drinking, the odds ratio was 1.40 (95% CI, 0.95–2.06) for former drinking and 1.02 (95% CI, 0.78–1.34) for current drinking. [Compared with continuing consumption, the calculated odds ratio for cessation was 1.37 (95% CI, 0.92–2.06). The strengths of this study are that it was a large case–control study and that former drinking was defined as cessation for ≥ 2 years. The limitations of this study are that never drinking was not defined and that the associations were adjusted for smoking status (never, former, current) but not for detailed smoking history or the amount of alcohol consumed.]

In a population-based case–control study in China (Feng et al., 2021), cases were ascertained from 2010 to 2014 by a rapid reporting system and included men (n = 1785) and women (n = 656) aged 20–74 years with histopathologically confirmed, incident nasopharyngeal cancer. Population-based controls (n = 1869 men, n = 677 women) were randomly selected from total population registries and were frequency-matched to cases on sex and age (± 5 years) by geographical region. Compared with never drinking, the odds ratios for former drinking were 1.31 (95% CI, 0.99–1.74) among women and men combined, 1.72 (95% CI, 0.70–4.26) among women, and 1.29 (95% CI, 0.95–1.74) among men. The odds ratios for current drinking ranged from 0.94 among women to 1.08 among women and men combined and among men only. [Compared with continuing consumption, the calculated odds ratio for cessation was 1.21 (95% CI, 0.90–1.64) among men and women combined, 1.83 (95% CI, 0.62–5.38) among women, and 1.19 (95% CI, 0.87–1.63) among men. The strengths of this study are that it was a large population-based case–control study and that former drinking was defined as cessation for > 2 years. The limitation of this study is that the associations were adjusted for smoking status (ever, never) but not for detailed smoking history or the amount of alcohol consumed.]

2.2.3 Laryngeal cancer

Laryngeal cancer includes malignancies of the glottis (vocal cord), supraglottis, and subglottis, as well as the laryngeal cartilage (ICD code C32) (Percy et al., 1990). Globally in 2020, the age-standardized (world population) incidence and mortality rates for laryngeal cancer were 2.0 per 100 000 and 1.0 per 100 000, respectively (Ferlay et al., 2020).

As mentioned above, the major risk factors for head and neck cancers are tobacco smoking, smokeless tobacco use, and alcohol consumption; when consumed together, there is a synergistic multiplicative effect of tobacco use and alcohol consumption on risk of head and neck cancer (IARC, 2012a). Alcohol consumption is more strongly associated with oral cavity and pharyngeal cancer than with laryngeal cancer, whereas smoking is more strongly associated with laryngeal cancer (Lubin et al., 2009). The synergistic multiplicative effect of alcohol consumption and tobacco use is also greater for oral cavity and pharyngeal cancers than for laryngeal cancer (Hashibe et al., 2009).

(a) Cohort studies

The associations of both reduction and cessation of alcoholic beverage consumption with risk of laryngeal cancer were assessed in one cohort study in the Republic of Korea (Yoo et al., 2022). The association between cessation and risk was assessed in two other cohort studies, one in China and one in India (Jayalekshmi et al., 2013; Im et al., 2021a) (Table 2.11; Supplementary Table S2.12, web only; available from https://publications.iarc.who.int/638). There are no informative cohort studies with data to assess duration of cessation and risk of laryngeal cancer.

The associations of reduction and cessation of alcoholic beverage consumption with cancer risk were assessed in a large population-based cohort study from the Korean National Health Insurance Service database, which covers 97% of the population (Yoo et al., 2022). Included in the analysis were 4 513 746 men and women aged ≥ 40 years who underwent biennial national health screenings, including measurement of alcohol consumption, in 2009 and in 2011, did not have a personal history of cancer at the time of the 2011 screening, and did not die within 1 year of the 2011 screening. For each measurement, the amount of alcohol consumed was classified as none (0 g of ethanol per day), mild (< 15 g per day), moderate (15–29.9 g per day), or heavy (≥ 30 g per day). To assess change in consumption, the associations for levels of consumption in 2011 were stratified on level of consumption in 2009 and the reference category for each comparison was a stable level of consumption in 2009 and in 2011 (none in 2009/none in 2011, mild in 2009/mild in 2011, etc.). Incident cancer cases diagnosed from 1 year after the 2011 screening until the end of 2018 (median, 6.4 years) were ascertained through the Korean National Health Insurance Service database. Among the men and women included in the analysis, 1642 cases of laryngeal cancer were identified. In analyses of alcohol reduction, compared with stable moderate consumption, the hazard ratio for reduction from moderate consumption in 2009 to mild consumption in 2011 was 1.11 (95% CI, 0.85–1.45); compared with stable heavy consumption, the hazard ratio for reduction from heavy to mild consumption was 2.10 (95% CI, 1.55–2.85) and for reduction from heavy to moderate consumption was 0.75 (95% CI, 0.54–1.03). Compared with stable mild, stable moderate, and stable heavy consumption, the hazard ratios for cessation from each level of consumption in 2009 to none in 2011 were 1.10 (95% CI, 0.86–1.41), 1.65 (95% CI, 1.12–2.41), and 1.51 (95% CI, 0.95–2.41), respectively. [The strengths of this study are that loss to follow-up was minimal, that it was a large study, that the analysis is strengthened by stratifying on consumption reported during the first screening, that the associations were adjusted for many potential confounding variables, including

Table 2.11 Cohort studies of reduction and cessation of alcoholic beverage consumption and risk of laryngeal cancer

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Jayalekshmi et al. (2013) India Karunagappally cohort 1990–unclear	Analysis included *n* = 65 553 men aged 30–84 yr; follow-up time began in January 1990, but end date was unclear; cancer cases ascertained by cancer registry linkage; cancer deaths ascertained from death registry supplemented with house visits (proportion of death-only cases ranged from 14% in 1990–1994 to 4.3% in 1998–2002)	Interviewer-administered questionnaire Drinking status: no definitions for categories of drinking status were reported	Larynx (ICD-9 code 161)	Drinking status Never Former Current	 27 19 39	 1.0 (ref) 2.0 (1.1–3.7) 2.1 (1.3–3.5)	Attained age, income, and education	No adjustment for amount of alcohol consumed or smoking Excluded individuals who died within the first 3 yr of follow-up time End of follow-up was unclear
Im et al. (2021a) China China Kadoorie Biobank 2004–2016	Analysis included *n* = 209 237 men aged 30–79 yr; follow-up time from 2004 through 2016 (median, 10 yr); cancer cases ascertained by linkage with cancer registries and the national health insurance databases	Interviewer-administered questionnaire Drinking status: abstain was no drinking in the past year or in most weeks prior; ex-regular was drinking < weekly in the past year but drinking ≥ weekly prior; occasional was drinking < weekly in the past year and prior; current regular was drinking in most weeks in the past year	Larynx (ICD-10 code C32)	Drinking status Abstain Ex-regular Occasional Current regular	 18 19 36 91	 1.00 (0.62–1.61) 2.05 (1.30–3.23) 1.50 (1.07–2.11) 3.30 (2.64–4.13)	Age, study area, education, income, smoking (never, occasional, and for ever smoked, 3 categories of cigarettes per day in men and 2 in women), BMI, physical activity, fruit intake, and family history of cancer	Floating standard errors were used to estimate the CIs; abstention was the reference category No adjustment for amount of alcohol consumed

Table 2.11 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Yoo et al. (2022) Republic of Korea NHIS 2009–2018	Analysis included n = 4 513 746 men and women aged ≥ 40 yr with drinking status data from 2 consecutive (2009 and 2011) biennial NHIS health screenings; follow-up time through 2018 (median, 6.4 yr); cancer cases ascertained through the NHIS billing system	Self-administered questionnaires in 2009 and 2011 Alcohol intake in 2009 and 2011: for each survey, alcohol intake was first classified by amount of ethanol consumed: none, mild (< 15 g/day), moderate (15–29.9 g/day), and heavy (≥ 30 g/day); then associations for each level of consumption in 2011 were assessed with stratification based on level of consumption in 2009; the reference group for each stratum was the stable group at each level of consumption (e.g. 2009/2011 none/none)	Larynx (ICD-10 code C32)	Alcohol intake in 2009/2011	1642 total		Age, sex, socioeconomic position, smoking status, physical activity, comorbidities (hypertension, diabetes, dyslipidaemia, chronic kidney disease, and chronic obstructive pulmonary disease), and Charlson Comorbidity Index	Excluded the first year of follow-up time No information about alcohol consumption before the first wave of reporting Limited follow-up time No adjustment for detailed smoking history, including duration of smoking cessation
				None/none		1.0 (ref)		
				None/mild		1.01 (0.79–1.29)		
				None/moderate		1.10 (0.76–1.60)		
				None/heavy		1.31 (0.88–1.95)		
				Mild/none		1.10 (0.86–1.41)		
				Mild/mild		1.0 (ref)		
				Mild/moderate		0.73 (0.55–0.95)		
				Mild/heavy		1.10 (0.80–1.53)		
				Moderate/none		1.65 (1.12–2.41)		
				Moderate/mild		1.11 (0.85–1.45)		
				Moderate/moderate		1.0 (ref)		
				Moderate/heavy		0.93 (0.69–1.24)		
				Heavy/none		1.51 (0.95–2.41)		
				Heavy/mild		2.10 (1.55–2.85)		
				Heavy/moderate		0.75 (0.54–1.03)		
				Heavy/heavy		1.0 (ref)		

BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; NHIS, National Health Insurance Service; ref, reference; yr, year or years.

the Charlson Comorbidity Index, and that the first year of follow-up time was excluded from the analysis. The limitations of this study are that there was no information about alcohol consumption before the first screening in 2009, that the follow-up time after the second screening was limited (median, 6.4 years), that the number of cases in each category was not shown, that sex-specific associations were not reported (except for female breast cancer), and that the associations were adjusted for categories of smoking status and pack-years but not for duration of smoking cessation.]

In the Karunagappally cohort study (Jayalekshmi et al., 2013) (described in Section 2.2.2), 85 cases of laryngeal cancer were identified among the men included in the analysis. Compared with never drinking, both former drinking and current drinking were associated with higher risk of laryngeal cancer (relative risk [RR], 2.0; 95% CI, 1.1–3.7 for former drinking and RR, 2.1; 95% CI, 1.3–3.5 for current drinking). [Compared with continuing consumption, the calculated relative risk for cessation was 0.95 (95% CI, 0.53–1.73). The strengths and limitations of this study are described in Section 2.2.2.]

In the study of Im et al. (2021a) (described in Section 2.2.1), 164 incident cases of laryngeal cancer were identified among the men included in the analysis. Compared with abstaining, the hazard ratios were 2.05 (95% CI, 1.30–3.23) for ex-regular drinking and 3.30 (95% CI, 2.64–4.13) for current-regular drinking. [Compared with continuing-regular consumption, the calculated hazard ratio for cessation was 0.62 (95% CI, 0.37–1.03). The strengths and limitations of this study are described in Section 2.2.1.]

(b) Case–control studies

The associations of duration of cessation and cessation of alcoholic beverage consumption with risk of laryngeal cancer were assessed in the international pooled analysis (Marron et al., 2010), and the associations between cessation and risk were assessed in two individual case–control studies in Taiwan (China) (Lee et al., 2005b; Huang et al., 2017) and an individual study in Uruguay (De Stefani et al., 2004) (Table 2.13; Supplementary Table S2.12 and Table S2.14, web only; available from https://publications.iarc.who.int/638).

The international pooled analysis of case–control studies (Marron et al., 2010) (described in Section 2.2.1) included individual-level data from 2006 cases of laryngeal cancer and 9555 controls who participated in seven hospital-based and two population-based case–control studies. Compared with current drinking, there was a lower risk of laryngeal cancer associated with former drinking (OR, 0.79; 95% CI, 0.57–1.08). There was a greater reduction in risk for long-term cessation (≥ 20 years) (OR, 0.69; 95% CI, 0.52–0.91) than for shorter durations of cessation (OR, 0.88; 95% CI, 0.65–1.19 for 5–9 years and OR, 0.93; 95% CI, 0.64–1.36 for 10–19 years). In analyses stratified on the amount of alcohol consumed, the odds ratio for long-term cessation was lowest in the highest stratum of consumption (≥ 3 drinks per day) (OR, 0.28; 95% CI, 0.09–0.86), with no association observed in the < 1 drink per day stratum (OR, 0.99; 95% CI, 0.56–1.74). In the subset of study participants with detailed alcohol consumption and smoking history data (n = 1628 cases and n = 6689 controls), compared with the single reference category of current drinking and current smoking, the odds ratio for long-term cessation in the current-smoking stratum was 0.74 (95%, 0.46–1.20). Among strata of duration of smoking cessation, the odds ratios ranged from 0.14 to 0.84, and in the never-smoking stratum, the odds ratio was 0.24 (95% CI, 0.07–0.85). [In the Working Group re-analyses with continuing consumption as the reference category within each smoking stratum, the calculated odds ratios ranged from 0.61 to 1.01 across strata of duration of smoking cessation, and the odds ratio was 1.85 (95% CI, 0.43–7.96) in the never-smoking stratum. After meta-analytic

Table 2.13 Pooled analysis and individual case–control studies of duration of cessation and cessation of alcoholic beverage consumption and risk of laryngeal cancer

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases or deaths	Odds ratio (95% CI)	Adjustment factors	Comments
Marron et al. (2010) INHANCE consortium ~1980s–early 2000s	Men and women with incident laryngeal cancer (n = 2006) who participated in population-based case–control studies in Boston, Massachusetts (USA), or Los Angeles, California (USA), or hospital-based case–control studies in Italy, Switzerland, Iowa (USA), North Carolina (USA), Tampa, Florida (USA), Houston, Texas (USA), or Latin America	Hospital-based and population-based controls (n = 9555) In the Los Angeles population-based study, controls were individually matched to cases on decade of age, sex, and neighbourhood; in the hospital-based studies, controls were frequency-matched to cases on age, sex, and other factors (e.g. study centre, hospital, and race or ethnicity	Interviewer-administered questionnaires in all studies except self-administered in the Iowa study Drinking status: current was consumption within the past year; former was cessation ≥ 1 yr before interview date; never was responding no to ever drinking Duration of cessation: difference between age at reference date (interview or diagnosis) and age at cessation	Drinking status			Age, sex, race or ethnicity, study centre, education, pack-years of tobacco smoking, and number of alcoholic drinks per day	Pooled analysis of individual participant data Most data came from hospital-based case–control studies (n = 7), compared with population-based case–control studies (n = 2) No details reported about selection of hospital-based controls Participation rates not reported
				Current	1103	1.0 (ref)		
				Former	609	0.79 (0.57–1.08)		
				Never	243	0.67 (0.42–1.07)		
				Missing	51			
				Duration of cessation				
				Current	1103	1.0 (ref)		
				> 1–4 yr	141	1.16 (0.82–1.63)		
				5–9 yr	112	0.88 (0.65–1.19)		
				10–19 yr	199	0.93 (0.64–1.36)		
				≥ 20 yr	157	0.69 (0.52–0.91)		
				Never	243	0.69 (0.43–1.09)		
						P_{trend} = 0.28		
				Duration of cessation stratified by drinks per day				
				< 1 drink/day				
				Current	207	1.0 (ref)		
				> 1–4 yr	23	2.38 (1.11–5.11)		
				5–9 yr	18	1.47 (0.70–3.11)		
				10–19 yr	33	1.26 (0.73–2.19)		
				≥ 20 yr	34	0.99 (0.56–1.74)		
				Never	243	0.86 (0.48–1.55)		
				1–2 drinks/day				
				Current	213	1.0 (ref)		
				> 1–4 yr	37	1.81 (1.01–3.24)		
				5–9 yr	15	0.91 (0.39–2.11)		
				10–19 yr	33	1.00 (0.53–1.89)		
				≥ 20 yr	28	0.78 (0.39–1.55)		
				Never	233	0.67 (0.28–1.57)		

Table 2.13 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases or deaths	Odds ratio (95% CI)	Adjustment factors	Comments
Marron et al. (2010) (cont.)				≥ 3 drinks/day				
				Current	751	1.0 (ref)		
				> 1–4 yr	85	0.70 (0.34–1.44)		
				5–9 yr	80	0.91 (0.50–1.66)		
				10–19 yr	132	0.78 (0.42–1.44)		
				≥ 20 yr	94	0.28 (0.09–0.86)		
				Never	249	0.26 (0.12–0.57)		
De Stefani et al. (2004) Uruguay 1988–2000	Men (*n* = 481) aged 30–89 yr with newly diagnosed, microscopically confirmed SCC of the larynx (supraglottis, *n* = 304; glottis, *n* = 177); diagnosed at the Cancer Institute or School of Medicine of Montevideo; 97.2% participation rate	Hospital-based controls (*n* = 481 men) frequency-matched to cases on age (10-yr interval), residence (Montevideo, other counties), and urban or rural status; hospitalized for conditions unrelated to alcohol consumption or tobacco smoking, and with no recent changes in their diet; 98.7% participation rate	Interviewer-administered questionnaire Drinking status: never was drinking occasionally (social) and < once per month; current was drinking at time of interview or quit < 1 yr before interview date; former was all others	Drinking status		Supraglottis	Age (categorical), residence, urban or rural status, education (categorical), period of diagnosis, centre, and pack-years of smoking (categorical)	Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption No adjustment for amount of alcohol consumed or duration of smoking cessation
				Never	27	1.0 (ref)		
				Former	46	1.2 (0.6–2.2)		
				Current	231	3.9 (2.3–6.7)		
						Glottis		
				Never	26	1.0 (ref)		
				Former	47	1.3 (0.7–2.3)		
				Current	104	2.1 (1.2–3.7)		

Table 2.13 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases or deaths	Odds ratio (95% CI)	Adjustment factors	Comments
Lee et al. (2005b) Taiwan (China) 2000–2003	Men (n = 128) aged 43–89 yr with histologically confirmed SCC of the larynx (ICD-10 code C32); recruited from 2 teaching hospitals in southern Taiwan (China); 97.9% participation rate	Hospital-based controls (n = 255 men) aged 40–92 yr; otolaryngology outpatients or inpatients at one of the hospitals during the same study period as cases; without conditions associated with betel quid chewing, cigarette smoking, or alcohol consumption; 88.2% participation rate	Interviewer-administered questionnaires Drinking status: non was lifetime abstention; ex was abstaining for > 1 yr before interview; current was drinking at time of interview or quit < 1 yr before interview date	Drinking status			Cigarette smoking, betel quid chewing, and age	Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption No adjustment for amount of alcohol consumed Unclear what categories of smoking were controlled for
				Non	56	1.0 (ref)		
				Ex	12	3.0 (0.2–3.4)		
				Current	60	4.1 (2.5–8.8)		
Huang et al. (2017) Taiwan (China) 2010–2016	Men and women (n = 95) aged ≥ 20 yr with newly diagnosed, pathologically confirmed SCC of the larynx (ICD-10 code C32); treated at the National Cheng Kung University Hospital	Hospital-based controls (n = 940 men and women) frequency-matched to cases on sex and age (± 5 yr); patients from otolaryngology and stomatology departments diagnosed with non-cancer head and neck diseases unrelated to alcohol consumption, betel quid chewing, or cigarette smoking	Interviewer-administered questionnaire Drinking status: never was self-reported as such; occasional was not defined; regular was drinking ≥ once per week and was categorized as former regular (quit for > 6 months) and current regular	Drinking status			Age, sex, education, cigarette smoking (pack-year categories), and betel quid chewing (pack-year categories)	Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption No adjustment for amount of alcohol consumed or duration of smoking cessation Participation rates not reported
				Never/occasional	35	1.0 (ref)		
				Former regular	11	0.86 (0.40–1.85)		
				Current regular	49	1.84 (1.09–3.11)		

CI, confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; INHANCE, International Head and Neck Cancer Epidemiology; ref, reference; SCC, squamous cell carcinoma; yr, year or years.

adjustment for smoking status and duration of smoking cessation, the calculated odds ratio for long-term cessation was 0.80 (95% CI, 0.56–1.13). The strengths and limitations of this study are described in Section 2.2.1.]

In a hospital-based case–control study in Uruguay (De Stefani et al., 2004), the cases were men aged 30–89 years with newly diagnosed and microscopically confirmed SCC of the larynx in 1988–2000 (n = 304 with supraglottis and n = 177 with glottis lesions). The controls were men (n = 481) who were frequency-matched to cases (1:1) on age (10-year intervals), residence (Montevideo, other counties), and urban or rural status. Compared with never drinking, there was a higher risk of supraglottic cancer associated with both former drinking (OR, 1.2; 95% CI, 0.6–2.2) and current drinking (OR, 3.9; 95% CI, 2.3–6.7). [Compared with continuing consumption, cessation was associated with a lower risk (calculated OR, 0.31; 95% CI, 0.19–0.51).] Former drinking (OR, 1.3; 95% CI, 0.7–2.3) and current drinking (OR, 2.1; 95% CI, 1.2–3.7) also were associated with a higher risk of glottal cancer. [Compared with continuing consumption, cessation was associated with a lower risk (calculated OR, 0.62; 95% CI, 0.38–1.02). The strengths of this study are that it was a large case–control study, that the controls were selected from among patients with conditions thought to be unrelated to alcohol consumption, and that the alcohol consumption categories were well defined. The limitation of this study is that the associations were adjusted for pack-years of smoking but not for duration of smoking cessation or the amount of alcohol consumed.]

In the hospital-based case–control study in Taiwan (China) (Lee et al., 2005b) (described in Section 2.2.2), 128 men with SCC of the larynx and 255 controls were included in the analysis. Compared with non-drinking, former drinking (OR, 3.0; 95% CI, 0.2–3.4) and current drinking (OR, 4.1; 95% CI, 2.5–8.8) were associated with higher risks of laryngeal SCC. [Compared with continuing consumption, the calculated odds ratio for cessation was 0.73 (95% CI, 0.17–3.07). The strengths and limitations of this study are described in Section 2.2.2.]

In another hospital-based case–control study in Taiwan (China) (Huang et al., 2017) (described in Section 2.2.1), 95 cases of SCC of the larynx and 940 controls were included in the analysis. Compared with never and occasional drinking, the odds ratio was 0.86 (95% CI, 0.40–1.85) for former-regular drinking and 1.84 (95% CI, 1.09–3.11) for current-regular drinking. [Compared with continuing consumption, there was a lower risk for cessation (calculated OR, 0.47; 95% CI, 0.21–1.03). The strengths and limitations of this study are described in Section 2.2.1.]

2.2.4 Oesophageal cancer

Oesophageal cancer (ICD code C15) is the eighth most commonly diagnosed type of cancer and the sixth leading cause of cancer death globally (Sung et al., 2021). Globally in 2020, the age-standardized (world population) incidence and mortality rates for oesophageal cancer were 6.3 per 100 000 and 5.6 per 100 000, respectively (Ferlay et al., 2020). The most common histological subtype is oesophageal SCC (85%) and the remainder of the cases are oesophageal adenocarcinomas, although there is some variability in the distribution of histological subtypes among countries (Morgan et al., 2022).

Consumption of alcoholic beverages is an established cause of oesophageal SCC but not of oesophageal adenocarcinoma (IARC, 2012a). Tobacco smoking is also an established cause of oesophageal SCC, and there is evidence that alcohol consumption and tobacco use have a synergistic effect on risk (IARC, 2012a); consumption of red meat and processed meat probably increases risk (Vingeliene et al., 2017). Studies of alcohol cessation and oesophageal adenocarcinoma only were not eligible for inclusion in this review. However, studies assessing

alcohol consumption and cessation and risk of oesophageal SCC and oesophageal adenocarcinoma combined were included. When they were described in the original publication, the distributions of each histological subtype are included in the study description.

(a) Cohort studies

The associations of reduction and cessation of alcoholic beverage consumption with risk of oesophageal cancer were assessed in one cohort study (Yoo et al., 2022); cessation only was assessed in three other cohort studies (Ishikawa et al., 2006; Jayalekshmi et al., 2021, Im et al., 2021a), and duration of cessation and cessation and risk of oesophageal cancer mortality were assessed using data from another cohort (Ozasa et al., 2007; Yaegashi et al., 2014) (Table 2.15; Supplementary Table S2.16, web only; available from https://publications.iarc.who.int/638). In the cohort study in India, 82% of cases with known histology were oesophageal SCC (Jayalekshmi et al., 2021). The distribution of histological subtypes was not specified in the other cohort studies (Ishikawa et al., 2006; Ozasa et al., 2007; Yaegashi et al., 2014; Im et al., 2021a; Yoo et al., 2022); however, these studies were conducted in countries where oesophageal SCC is substantially more common than oesophageal adenocarcinoma (Morgan et al., 2022).

In the study of Yoo et al. (2022) (described in Section 2.2.3), among the men and women included in the analysis, 3009 cases of oesophageal cancer were identified during the follow-up time. In analyses of alcohol reduction, compared with stable moderate consumption, the hazard ratio for reduction from moderate consumption in 2009 to mild consumption in 2011 was 1.38 (95% CI, 1.13–1.70). Compared with stable heavy consumption, the hazard ratio for reduction from heavy to mild consumption was 2.23 (95% CI, 1.74–2.86) and for reduction from heavy to moderate consumption was 1.03 (95% CI, 0.83–1.29). Compared with stable mild, stable moderate, and stable heavy consumption, the hazard ratios for cessation from each level of consumption in 2009 to none in 2011 were 1.13 (95% CI, 0.92–1.38), 2.38 (95% CI, 1.79–3.17), and 3.66 (95% CI, 2.77–4.83), respectively. [The strengths and limitations of this study are described in Section 2.2.3. In addition, the association for oesophageal SCC was not reported separately.]

In 1988–1990, the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC) enrolled a cohort of 109 778 men and women aged 40–79 years who were living in one of 45 areas of Japan and cancer-free (Tamakoshi et al., 2007). Follow-up for cancer incidence, vital status, and date and cause of death was achieved by cancer registry linkage or review of death certificates (Ogimoto et al., 2004; Wakai et al., 2005). A JACC study that assessed associations of alcohol consumption with oesophageal cancer mortality included 42 408 men who were followed up for cause-specific mortality from enrolment until 2009 (except in four areas, where follow-up ended in 1999; in another four areas, follow-up ended in 2003, and in two areas, follow-up ended in 2008), during which 196 oesophageal cancer deaths were identified (Yaegashi et al., 2014). Women were not included in the analysis because there were too few who consumed alcohol. Compared with non-drinking, the hazard ratio was 2.10 (95% CI, 0.99–4.42) for ex-drinking and 2.28 (95% CI, 1.40–3.72) for current drinking. [Compared with continuing consumption, the calculated hazard ratio for cessation was 0.92 (95% CI, 0.50–1.70).] In an earlier analysis from this cohort (Ozasa et al., 2007), the association between duration of cessation and oesophageal cancer mortality was assessed; among men, 153 oesophageal cancer deaths were identified during follow-up until 2003 (except in three areas, where follow-up ended in 1999) (Tamakoshi et al., 2007). Compared with rare/none, there was a 3.7-fold higher risk for < 5 years of cessation (HR, 3.75; 95% CI, 1.16–12.1) and no association for ≥ 15 years of cessation

Table 2.15 Cohort studies of reduction, duration of cessation, and cessation of alcoholic beverage consumption and risk of oesophageal cancer

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comment
Ishikawa et al. (2006) Japan Miyagi cohorts Cohort 1: 1984–1992 Cohort 2: 1990–1997	Analysis included: Cohort 1, n = 9008 men, aged ≥ 40 yr who lived in 3 municipalities; follow-up time from 1984 through 1992 (up to 9 yr); Cohort 2, n = 17 715 men, aged ≥ 40–64 yr who lived in 14 municipalities; follow-up time from June 1990 through 1997 (up to 7.6 yr); cancer cases ascertained by cancer registry linkage	Self-administered questionnaire Drinking status: never was not defined; occasional was drinking < 5 days/week; former was not defined; daily was drinking ≥ 5 days/week	Oesophagus (ICD-O-2 codes C15.0–C15.9; histology not specified)	Drinking status			Age, cigarette smoking (never, past, current 1–19 cigarettes per day, or current ≥ 20 cigarettes per day), and green tea, coffee, and black tea intake	Pooled analysis Limited follow-up time No adjustment for amount of alcohol consumed or duration of smoking cessation
				Never/occasional	16	1.0 (ref)		
				Former	5	1.55 (0.58–4.14)		
				Daily	57	2.73 (1.55–4.81)		
						P_{trend} = 0.0002		
Ozasa et al. (2007); Yaegashi et al. (2014) Japan Japan Collaborative Cohort Study for Evaluation of Cancer Risk 1988–2009	Analysis for drinking status (Yaegashi et al., 2014) included n = 42 408 men aged 40–79 yr; follow-up time from 1988 through 2009 in most of the 45 areas of data collection but ended in 1999 in 4 areas, 2003 in 4 areas, and 2008 in 2 areas. Analysis of duration of cessation (Ozasa et al., 2007) included follow-up through 2003 (except in 3 areas, where it ended in 1999) (Tamakoshi et al., 2007); cause of death ascertained by death certificate review	Self-administered questionnaire Drinking status: no definitions were reported for categories of drinking status Duration of cessation: self-reported	Oesophagus (deaths) (ICD-10 codes C15.0–C15.9; histology not specified)	Drinking status	Deaths		Age, centre, and vegetable and fruit intake	No adjustment for amount of alcohol consumed or smoking Women were not included in the drinking status analysis, and there were no women who died of oesophageal cancer in any of the duration of cessation categories
				Non-drinking	18	1.0 (ref)		
				Ex-drinking	12	2.10 (0.99–4.42)		
				Drinking	166	2.28 (1.40–3.72)		
				Duration of cessation				
				Rare/none	14	1.0 (ref)		
				< 5 yr	4	3.75 (1.16–12.1)		
				5–15 yr	3	2.76 (0.76–10.0)		
				≥ 15 yr	1	1.03 (0.13–8.12)		

Table 2.15 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comment
Jayalekshmi et al. (2021) India Karunagappally cohort 1990–2013	Analysis included n = 65 528 men aged 30–84 yr; follow-up time from January 1990 through 2013; cancer cases ascertained by cancer registry linkage; cancer deaths ascertained from death registry supplemented with house visits (proportion of death-only cases was 14% in 1990–1994 and decreased to 1% in subsequent years)	Interviewer-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	Oesophagus (ICD-O-3 codes not specified)	Drinking status	All		Age, calendar time, family income, and education	81.8% OSCC in a subset of cases No adjustment for amount of alcohol consumed or smoking Excluded individuals who died within the first 3 yr of follow-up time
				Never	65	1.0 (ref)		
				Former	24	1.2 (0.7–1.9)		
				Current	69	1.6 (1.1–2.3)		
				Drinking status	OSCC			
				Never	32	1 (ref)		
				Former	12	1.2 (0.6–2.4)		
				Current	45	2.0 (1.3–3.2)		
Im et al. (2021a) China China Kadoorie Biobank 2004–2016	Analysis included n = 209 237 men and n = 300 900 women aged 30–79 yr; follow-up time from 2004 through 2016 (median, 10 yr); cancer cases ascertained by linkage with cancer registries and the national health insurance databases	Interviewer-administered questionnaire Drinking status: abstain was no drinking in the past year or in most weeks prior; ex-regular was drinking < weekly in the past year but drinking ≥ weekly prior; occasional was drinking < weekly in the past year and prior; current regular was drinking in most weeks in the past year	Oesophagus (ICD-10 code C15)	Drinking status	Men		Age, study area, education, income, smoking (never, occasional, and for ever smoked, 3 categories of cigarettes per day in men and 2 in women), BMI, physical activity, fruit intake, and family history of cancer	Floating standard errors were used to estimate the CIs; abstention is the reference category No adjustment for amount of alcohol consumed or duration of smoking cessation
				Abstain	243	1.00 (0.88–1.14)		
				Ex-regular	152	1.23 (1.05–1.44)		
				Occasional	558	1.05 (0.96–1.15)		
				Current regular	655	1.80 (1.66–1.96)		
					Women			
				Abstain	340	1.00 (0.89–1.13)		
				Ex-regular	8	1.17 (0.57–2.41)		
				Occasional	377	0.99 (0.88–1.12)		
				Current regular	15	1.23 (0.73–2.06)		

Table 2.15 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comment
Yoo et al. (2022) Republic of Korea NHIS 2009–2018	Analysis included n = 4 513 746 men and women aged ≥ 40 yr with drinking status data from 2 consecutive (2009 and 2011) biennial NHIS health screenings; follow-up time through 2018 (median, 6.4 yr); cancer cases ascertained through the NHIS billing system	Self-administered questionnaires in 2009 and 2011 Alcohol intake in 2009 and 2011: for each survey, alcohol intake was first classified by amount of ethanol consumed: none, mild (< 15 g/day), moderate (15–29.9 g/day), and heavy (≥ 30 g/day); then associations for each level of consumption in 2011 were assessed stratified on level of consumption in 2009; the reference group for each stratum was the stable group at each level of consumption (e.g. 2009/2011 none/none)	Oesoph-agus (ICD-10 code C15; histology not specified)	Alcohol intake in 2009/2011	3009 total		Age, sex, socioeconomic position, smoking status, physical activity, comorbidities (hypertension, diabetes, dyslipidaemia, chronic kidney disease, and chronic obstructive pulmonary disease), and Charlson Comorbidity Index	Excluded the first year of follow-up time No information about alcohol consumption before the first wave of reporting Limited follow-up time No adjustment for detailed smoking history, including duration of smoking cessation
				None/none		1.0 (ref)		
				None/mild		0.92 (0.76–1.12)		
				None/moderate		1.07 (0.81–1.41)		
				None/heavy		1.01 (0.79–1.29)		
				Mild/none		1.13 (0.92–1.38)		
				Mild/mild		1.0 (ref)		
				Mild/moderate		0.80 (0.66–0.98)		
				Mild/heavy		0.74 (0.59–0.92)		
				Moderate/none		2.38 (1.79–3.17)		
				Moderate/mild		1.38 (1.13–1.70)		
				Moderate/moderate		1.0 (ref)		
				Moderate/heavy		0.73 (0.61–0.88)		
				Heavy/none		3.66 (2.77–4.83)		
				Heavy/mild		2.23 (1.74–2.86)		
				Heavy/moderate		1.03 (0.83–1.29)		
				Heavy/heavy		1.0 (ref)		

BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; NHIS, National Health Insurance Service; OSCC, oesophageal squamous cell carcinoma; ref, reference; yr, year or years.

(HR, 1.03; 95% CI, 0.13–8.12). [Compared with continuing consumption, risk decreased with longer duration of cessation (calculated HR, 1.66; 95% CI, 0.84–3.28 for < 5 years of cessation, and calculated HR, 0.46; 95% CI, 0.15–1.37 for ≥ 15 years of cessation). The strength of this study is the long follow-up time (up to 21 years). The limitations of this study are that the categories of drinking status were not defined, that the associations were not adjusted for smoking or the amount of alcohol consumed, that there were few oesophageal cancer deaths among men in the ex-drinking category (*n* = 5), and that there was no sensitivity analysis excluding at least the first year of follow-up time and no test of the proportional hazards assumption in the analysis of Yaegashi et al. (2014) or Ozasa et al. (2007).]

The association between alcohol cessation and risk of oesophageal cancer was assessed in a pooled analysis of data from two cohorts in Miyagi Prefecture in Japan (Ishikawa et al., 2006). For Miyagi Cohort 1, a questionnaire was mailed to residents aged ≥ 40 years living in three municipalities in January 1984; 93.7% of the surveys were returned. For Miyagi Cohort 2, a questionnaire was mailed to residents aged 40–64 years living in 14 municipalities between June and August 1990; 91.7% of the surveys were returned. For both cohorts, incident cancer cases were ascertained through linkage with the Miyagi Prefectural Cancer Registry. Women were excluded from the analysis because they seldom consumed alcohol, as were men with a personal history of cancer at enrolment or who had incomplete data for analysis. In Miyagi Cohort 1, among 9008 men included in the analysis, 38 cases of oesophageal cancer were identified during the follow-up from enrolment until 1992 (9 years). In Miyagi Cohort 2, among 17 715 men included in the analysis, 40 cases of oesophageal cancer were identified during the follow-up from enrolment until December 1997 (7.6 years). Compared with never or occasional drinking, the hazard ratio for former drinking was 1.55 (95% CI, 0.58–4.14) and for [current] daily drinking was 2.73 (95% CI, 1.55–4.81). [The calculated hazard ratio for cessation compared with continuing consumption was 0.57 (95% CI, 0.18–1.76). The strength of this study is the high participation rates in each cohort. The limitations of this study are that neither never drinking nor former drinking were defined, that the follow-up time was limited in each cohort (9 years in Miyagi Cohort 1 and 7.6 years in Miyagi Cohort 2), that the associations were not adjusted for smoking or the amount of alcohol consumed, that there were few cases in the former-drinking category (*n* = 5), and that there was no sensitivity analysis excluding at least the first year of follow-up time and no test of the proportional hazards assumption.]

In the Karunagappally cohort study in India (Jayalekshmi et al., 2021) (described in Section 2.2.2), among 65 528 men included in the analysis, 158 oesophageal cancer cases or deaths were identified between completion of the baseline survey from 1990 to 1997 and December 2013. Compared with never drinking, the relative risk for former drinking was 1.2 (95% CI, 0.7–1.9) for all oesophageal cancers and 1.2 (95% CI, 0.6–2.4) for oesophageal SCC. Compared with never drinking, the relative risk for current drinking was 1.6 (95% CI, 1.1–2.3) for all oesophageal cancers and 2.0 (95% CI, 1.3–3.2) for oesophageal SCC. [Compared with continuing consumption, the calculated relative risk for cessation was 0.75 (95% CI, 0.45–1.25) for all oesophageal cancer and 0.60 (95% CI, 0.32–1.14) for oesophageal SCC. The strength of this study is that the associations for oesophageal SCC were assessed separately. The limitations of this study are that the categories of drinking status were not defined, that it is unclear why women were excluded from the analysis, and that the associations were not adjusted for smoking or the amount of alcohol consumed.]

In the study of Im et al. (2021a) (described in Section 2.2.1), 1608 incident cases of oesophageal

cancer among 209 237 men and 740 incident cases among 300 900 women were identified during the follow-up time. Among men, compared with abstaining, there was a higher risk of oesophageal cancer associated with ex-regular drinking (HR, 1.23; 95% CI, 1.05–1.44) and with current-regular drinking (HR, 1.80; 95% CI, 1.66–1.96). Among women, compared with abstaining, the hazard ratio was 1.17 (95% CI, 0.57–2.41) for ex-regular drinking and 1.23 (95% CI, 0.73–2.06) for current-regular drinking. [Compared with continuing consumption, there was a lower risk for cessation among men (calculated HR, 0.68; 95% CI, 0.57–0.82) but not among women (calculated HR for cessation, 0.95; 95% CI, 0.39–2.31). The strengths and limitations of this study are described in Section 2.2.1. In addition, the association for oesophageal SCC was not reported separately, and among women there were very few cases in the ex-regular-drinking category (n = 8).]

(b) Meta-analysis

Rehm et al. (2007) assessed the association between duration of cessation of alcoholic beverage consumption and risk of oesophageal cancer with adjustment for tobacco smoking in a meta-analysis of four hospital-based case–control studies (Cheng et al., 1995; Castellsagué et al., 1999; Bosetti et al., 2000; Zambon et al., 2000), in two of which an adjustment was made for the amount of alcohol consumed (Cheng et al., 1995; Bosetti et al., 2000) (Supplementary Table S2.16, web only; available from https://publications.iarc.who.int/638; Table 2.17). The four studies included 1812 cases of oesophageal cancer (78% SCC) and 4898 controls in Argentina, Brazil, Hong Kong Special Administrative Region (China), Italy, Paraguay, Switzerland, and Uruguay. Compared with current drinking, there was a higher risk of oesophageal cancer for > 0–2 years (OR, 2.50; 95% CI, 2.23–2.80), and for 2–5 years of cessation (OR, 1.10; 95% CI, 1.03–1.18), whereas the odds ratios for categories of longer duration of cessation were < 1 with substantially lower risk for long-term cessation (OR, 0.35; 95% CI, 0.31–0.39 for ≥ 15 years of cessation). In each of the two case–control studies included in the meta-analysis that also adjusted for the amount of alcohol consumed, there was a lower risk of oesophageal cancer associated with ≥ 15 years of cessation (OR, 0.2; 95% CI, 0.1–0.6, Cheng et al., 1995; and OR, 0.53; 95% CI, 0.15–1.85, Bosetti et al., 2000). In one case–control study included in the meta-analysis (Castellsagué et al., 1999), a further analysis showed that adjusting for duration of smoking cessation had little impact on the strength of the association between duration of alcohol cessation and risk (Castellsagué et al., 2000). [The meta-analysis by Rehm et al. (2007) was preferred to that by Jarl and Gerdtham (2012) because the analysis allowed for modelling of the reverse causation in the first few years after alcohol cessation. The strengths of this study are that smoking-adjusted associations for categories of duration of cessation, including long-term cessation, were assessed and that it included geographical diversity. The limitations of this study are that there was no information about the selection of hospital-based controls, that it is unclear what smoking categories were controlled for, and that the associations for oesophageal SCC were not reported separately.]

(c) Case–control studies

The associations of duration of cessation only or duration of cessation and cessation of alcoholic beverage consumption compared with continuing consumption with risk of oesophageal cancer were assessed in seven individual case–control studies that were not included in the meta-analysis (Launoy et al., 1997; Takezaki et al., 2000; Lee et al., 2005a; Vioque et al., 2008; Szymańska et al., 2011; Wu et al., 2011; Yang et al., 2017), and the association for cessation only was assessed in four other individual case–control studies (Gao et al., 1994; Yokoyama et al., 2002; Yang et al., 2005; Wu et al., 2006) (Supplementary

Table 2.17 Meta-analyses and pooled analyses of duration of cessation of alcoholic beverage consumption and risk of oesophageal cancer

Reference	Description Type of analysis; no. and type of studies; total no. of cases and controls (or total cohort and no. of cases)	Study population characteristics	Exposure categories	Odds ratio (95% CI)	Adjustment factors	Comments
Rehm et al. (2007)	Meta-analysis of 4 hospital-based case–control studies with data about duration of alcohol cessation and analyses adjusted for smoking; *n* = 1812 cases (78% OSCC) and *n* = 4898 controls	Men and women in 3 studies; only men in 1 study Participants from Argentina, Brazil, Hong Kong Special Administrative Region (China), Italy, Paraguay, Switzerland, and Uruguay	Drinking status		All studies adjusted for smoking	The 4 case–control studies that adjusted for smoking were: Bosetti et al. (2000); Castellsagué et al. (1999); Cheng et al. (1995); Zambon et al. (2000) No details reported about selection of hospital-based controls. Two studies also adjusted for amount of alcohol consumed: Bosetti et al. (2000); Cheng et al. (1995)
			Current	1.0 (ref)		
			Never	0.37 (0.35–0.39)		
			Duration of cessation			
			> 0–2 yr	2.50 (2.23–2.80)		
			2–5 yr	1.10 (1.03–1.18)		
			5–10 yr	0.85 (0.79–0.92)		
			10–15 yr	0.85 (0.79–0.92)		
			> 15 yr	0.35 (0.31–0.39)		

CI, confidence interval; OSCC, oesophageal squamous cell carcinoma; ref, reference; yr, year or years.

Table S2.16, web only; available from https://publications.iarc.who.int/638; Table 2.18). Among the 11 individual case–control studies, six included only histologically confirmed cases of oesophageal SCC (Launoy et al., 1997; Yokoyama et al., 2002; Lee et al., 2005a; Wu et al., 2006; Szymańska et al., 2011; Yang et al., 2017); in three studies, the percentage of cases with oesophageal SCC was 67% (Gao et al., 1994), 96% (Yang et al., 2005), and 79% (Vioque et al., 2008). The distribution of histological subtypes was not reported in studies in Japan (Takezaki et al., 2000) and China (Wu et al., 2011), where oesophageal SCC is much more common than oesophageal adenocarcinoma (Morgan et al., 2022).

A hospital-based case–control study conducted in France from 1991 to April 1994 (Launoy et al., 1997) included 208 men aged < 85 years with histologically confirmed oesophageal SCC who were treated at three university hospitals. The controls included 399 men who were patients admitted to the same hospitals during the same period as the cases and matched to cases on age and hospital. Compared with current drinking, the odds ratios were 2.23 (95% CI, 1.01–4.89) for 1–5 years of cessation, 1.86 (95% CI, 0.58–5.87) for 6–10 years of cessation, and 1.15 (95% CI, 0.63–3.24) for ≥ 11 years of cessation. [The strength of this study is that patients hospitalized for trauma were excluded from the control group. The limitations of this study are that the participation rate among controls was not reported, that the categories of drinking status were not defined, that the associations were not adjusted for smoking or the amount of alcohol consumed, and that there were few cases in the two highest categories of duration of cessation (n = 7 for 6–10 years of cessation, and n = 5 for ≥ 11 years of cessation).]

The hospital-based case–control study of Takezaki et al. (2000) (described in Section 2.2.2) included 284 cases of oesophageal cancer and 11 936 controls. Compared with almost-never drinking, the odds ratio for former drinking was 4.4 (95% CI, 2.5–7.9), which was similar to that for current drinking (OR, 4.4; 95% CI, 2.9–6.7). [Compared with continuing consumption, cessation was not associated with risk of oesophageal cancer (calculated OR, 1.00; 95% CI, 0.63–1.59).] Compared with almost-never drinking, there were higher risks for 1–9 years of cessation (OR, 5.1; 95% CI, 2.6–10.0) and for ≥ 10 years of cessation (OR, 3.5; 95% CI, 1.4–9.1). [Compared with continuing consumption, the calculated odds ratio for 1–9 years of cessation was 1.16 (95% CI, 0.52–2.56) and for ≥ 10 years of cessation was 0.80 (95% CI, 0.29–2.22). The strengths and limitations of this study are described in Section 2.2.2. An additional limitation is that the association with oesophageal SCC was not reported separately.]

In a hospital-based case–control study in Taiwan (China), 513 histologically confirmed cases of oesophageal SCC, aged 28–89 years, diagnosed from July 1996 to December 2003 at three hospitals were enrolled (Lee et al., 2005a). The controls were aged 26–89 years, received routine physical check-ups at the same hospitals as the cases within 4 weeks of when the cases were identified, and were matched to the cases on sex and age (± 3 years). Among 818 controls, 224 were matched 1 per case, 243 were matched 2 per case, and 108 were matched 3 per case. Compared with never drinking, the odds ratio for former drinking was 5.5 (95% CI, 3.6–8.6), and for current drinking, the odds ratio was 7.6 (95% CI, 5.2–11.1). [The calculated odds ratio for cessation compared with continuing consumption was 0.72 (95% CI, 0.46–1.14).] Compared with current drinking, the odds ratios decreased with longer duration of cessation: 1.3 (95% CI, 0.7–2.4) for 1–5 years of cessation, 0.8 (95% CI, 0.4–1.8) for 6–10 years of cessation, and 0.3 (95% CI, 0.1–0.6) for > 10 years of cessation. [The strength of this study is that it assessed long-term cessation. The limitations of this study are that there was limited information about selection of hospital-based controls and that the associations

Table 2.18 Case–control studies of duration of cessation and cessation of alcoholic beverage consumption and risk of oesophageal cancer

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Gao et al. (1994) China 1990–1993	Men (n = 513) aged 30–74 yr; histologically confirmed oesophageal cancer (67% OSCC); residents of urban Shanghai; 88.8% participation rate	Population-based controls (n = 799 men) frequency-matched to cases on age; randomly selected from the urban Shanghai population	Interviewer-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	Drinking status			Age, education, birthplace, tea drinking, dietary factors, cigarette smoking	No adjustment for amount of alcohol consumed Unclear what categories of smoking were controlled for Participation rate for controls not reported Results for women not shown here because there were 3 cases in the ex-drinking category
				Non	196	1.0 (ref)		
				Ex	27	1.6 (0.8–3.1)		
				Current	290	1.4 (1.1–1.9)		
Launoy et al. (1997) France 1991–1994	Men (n = 208) aged < 85 yr; 100% histologically confirmed OSCC; admitted to 1 of 3 university hospitals in France; 93.3% participation rate	Hospital-based controls (n = 399 men), matched to cases on age and hospital; admitted to the rheumatology or orthopaedic units; excluded trauma patients during the same period	Interviewer-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	Duration of cessation			Interviewer, age, place of residence, occupation, education level, and marital status	Limited information about selection of hospital-based controls No adjustment for amount of alcohol consumed or smoking Participation rate for controls not reported
				Current	181	1.0 (ref)		
				1–5 yr	14	2.23 (1.01–4.89)		
				6–10 yr	7	1.86 (0.58–5.87)		
				≥ 11 yr	5	1.15 (0.63–3.24)		
						P_{trend} = 0.25		

Table 2.18 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Takezaki et al. (2000) Japan 1988–1997	Men (n = 284) aged 40–79 yr; 93% histopathologically or clinically confirmed oesophageal cancer (ICD-9 code 150 or ICD-10 code C15); diagnosed within 1 yr of completing a first-visit outpatient questionnaire at ACCH	Hospital-based controls (n = 11 936 men) aged 40–79 yr; completed questionnaire as first-visit outpatients at ACCH and confirmed to be cancer-free by diagnostic procedures	Self-administered questionnaire Drinking status: almost never was not defined; former was quit ≥ 1 yr previously; current was drinking ≥ 4 times/week Duration of cessation: years since quitting	Drinking status			Age, year, and season of visit, smoking (never, former, and for current, < 30 and ≥ 30 pack-years), and consumption of raw vegetables	Limited information about selection of hospital-based controls No adjustment for amount of alcohol consumed or duration of smoking cessation 98.6% of first-visit outpatients returned the survey
				Almost never	31	1.0 (ref)		
				Former	31	4.4 (2.5–7.9)		
				Current	284	4.4 (2.9–6.7)		
				Duration of cessation				
				Almost never	NR	1.0 (ref)		
				1–9 yr		5.1 (2.6–10.0)		
				≥ 10 yr		3.5 (1.4–9.1)		
Yokoyama et al. (2002) Japan 2000–2001	Men (n = 234) aged 40–79 yr; 100% histologically confirmed OSCC; diagnosed within 3 yr before study registration and treated at 1 of 4 hospitals; 99.2% participation rate	Hospital-based controls (n = 634 men) aged 40–79 yr; outpatients registered at 2 Tokyo clinics for annual health check-ups; 86% participation rate	Self-administered questionnaire Drinking status: self-reported never, current, or ex-drinker status Current consumption was categorized as light (1–8.9 units/week), moderate (9–17.9 units/week), or heavy (≥ 18 units/week), where 1 unit = 22 g of ethanol	Drinking status			Age, frequency of drinking strong alcoholic beverages, pack-years of smoking, consumption of green–yellow vegetables, and fruit intake	Limited information about selection of hospital-based controls No adjustment for duration of smoking cessation
				Never/rare	5	0.17 (0.05–0.56)		
				Ex	13	9.44 (3.29–27.08)		
				Current				
				Light	24	1.0 (ref)		
				Moderate	86	8.22 (4.42–15.28)		
				Heavy	106	13.74 (7.18–26.29)		

Table 2.18 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Lee et al. (2005a) Taiwan (China) 1996–2003	Men and women (n = 513) aged 28–89 yr; 100% histologically confirmed OSCC; ascertained from 3 hospitals in Taiwan (China); 65.5% participation rate	Hospital-based controls (n = 818 men and women) aged 26–89 yr; healthy outpatients attending for physical check-up: matched on sex, age (± 3 yr), and hospital (1:1 for 224 cases, 2:1 for 243 cases, and 3:1 for 36 cases); 95.0% participation rate	Interviewer-administered questionnaire Drinking status: never was no consumption ≥ once per week for ≥ 6 months; ever was any consumption ≥ once per week for ≥ 6 months and was categorized as current (consumption within the year before diagnosis or interview) and former (quit for ≥ 1 yr before diagnosis or interview)	Drinking status			Age, sex, study hospital, education, consumption of vegetables and fruits, pack-years of cigarette smoking, and betel quid chewing	Limited information about selection of hospital-based controls No adjustment for amount of alcohol consumed or duration of smoking cessation
				Never	110	1.0 (ref)		
				Former	114	5.5 (3.6–8.6)		
				Current	289	7.6 (5.2–11.1)		
						P_{trend} < 0.0001		
				Duration of cessation				
				Current	289	1.0 (ref)		
				1–5 yr	66	1.3 (0.7–2.4)		
				6–10 yr	22	0.8 (0.4–1.8)		
				> 10 yr	26	0.3 (0.1–0.6)		
						P_{trend} = 0.002		
				Never	110	0.1 (0.1–0.2)		
Yang et al. (2005) Japan 2001–2004	Men and women (n = 165) aged 18–80 yr with histologically confirmed oesophageal cancer (96% OSCC); completed a first-visit outpatient questionnaire at ACCH	Hospital-based controls (n = 495 men and women) randomly selected and matched (3:1) on age and sex; first-visit outpatients at ACCH during the same period and confirmed to be cancer-free	Self-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	Drinking status			Age and sex	Limited information about selection of hospital-based controls No adjustment for amount of alcohol consumed or smoking 95% of first-visit outpatients completed the questionnaire
				Never	8	1.0 (ref)		
				Former	12	6.20 (2.34–16.4)		
				Current	145	9.44 (4.36–20.4)		

Table 2.18 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Wu et al. (2006) Taiwan (China) Dates not specified	Men (*n* = 165) aged 35–92 yr with histologically confirmed OSCC; ascertained from 2 hospitals in southern Taiwan (China)	Hospital-based controls (*n* = 255 men) aged 40–92 yr, age-matched; with no malignant tumours or conditions associated with betel quid chewing, smoking, or alcohol consumption; 88.2% participation rate	Interviewer-administered Drinking status: ever was drinking > 4 times/week for ≥ 1 yr; current was drinking > 4 times/week within the past year; ex-drinking was quit > 1 yr before diagnosis or interview	Drinking status			Cigarette smoking, betel quid chewing, age, and years of education	Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption Unclear what categories of smoking were controlled for No adjustment for amount of alcohol consumed Participation rate for cases was not reported
				Non-drinking	17	1 (ref)		
				Ex	13	5.4 (1.9–15.4)		
				Current	135	23.3 (12.0–47.7)		
Vioque et al. (2008) Spain The PANESOES project 1995–1999	Men and women (*n* = 202) aged 30–80 yr with histologically confirmed oesophageal cancer (79.2% OSCC); hospitalized in any of 9 participating hospitals; 96% participation rate	Hospital-based controls (*n* = 455 men and women) aged 30–80 yr; selected from the same hospitals as cases, frequency-matched on age group, sex, and province; selected based on having diseases unrelated to tobacco use, alcohol consumption, or diet; 99.6% participation rate	Interviewer-administered questionnaire Drinking status: never was having consumed < 1 drink/month; former was quit ≥ 1 yr before interview; current was not defined Duration of cessation: no information reported about how this was estimated	Drinking status	OSCC		Sex, age, education level, province, and tobacco smoking (never, past, < 20, 20–49, or ≥ 50 pack-years), energy-adjusted intake of fruit and vegetables in tertiles, and energy intake	Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption No adjustment for amount of alcohol consumed or duration of smoking cessation
				Never	6	1.0 (ref)		
				Former	31	11.03 (3.73–32.62)		
				Current	123	4.48 (1.69–11.84)		
				Duration of cessation				
				Current	123	1.0 (ref)		
				< 5 yr	14	5.89 (2.01–17.25)		
				≥ 5 yr	17	1.70 (0.79–3.66)		
				Drinking status	All			
				Never	16	1.0 (ref)		
				Former	38	4.28 (1.92–9.56)		
				Current	148	2.06 (1.04–4.08)		
				Duration of cessation				
				Current	148	1.0 (ref)		
				< 5 yr	16	3.60 (1.34–9.69)		
				≥ 5 yr	22	1.71 (0.86–3.41)		

Table 2.18 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Szymańska et al. (2011) Brazil 1998–unclear	Men and women (*n* = 171) with 100% histologically confirmed OSCC (ICD-O code C15); recruited from 1 of 2 centres in Brazil	Hospital-based controls (*n* = 496), frequency-matched on sex, age, and centre; patients with a recent diagnosis of diseases not related to tobacco use or alcohol consumption	Interviewer-administered questionnaire Drinking status: never was not defined; ever was having consumed alcohol ≥ once per month; former was quit > 1 yr before the interview (for controls) or the diagnosis date (for cases) Duration of cessation: no information reported about how this was estimated	Drinking status			Sex, age, centre, education, pack-years of tobacco smoking, and fruit and cruciferous vegetable consumption ORs for duration of cessation also adjusted for amount of alcohol consumed (g/day)	Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption No adjustment for duration of smoking cessation Cases and controls were part of a larger multicentre study; overall, participation rates were 95% for cases and 86% for controls
				Never	23	1.0 (ref)		
				Former	70	4.24 (2.26–7.94)		
				Current	78	4.10 (2.19–7.69)		
				Duration of cessation				
				Current	77	1.0 (ref)		
				2–4 yr	28	2.15 (1.10–4.21)		
				5–9 yr	15	0.89 (0.43–1.85)		
				10–19 yr	18	0.75 (0.36–1.55)		
				≥ 20 yr	9	0.46 (0.19–1.16)		
				OR per 10 yr of cessation		0.72 (0.54–0.96)		

Table 2.18 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Wu et al. (2011) China 2003–2007	Men and women (n = 1191 men, mean age 65.3 yr; n = 329 women, mean age 67.4 yr) with newly diagnosed oesophageal cancer; residents of Dafeng and Ganyu for ≥ 5 yr, ascertained from local population-based cancer registries in Dafeng; 68% participation rate in Dafeng and 75% participation rate in Ganyu	Population-based controls (n = 2916 men, mean age 64.2 yr; n = 963 women, mean age 64.9 yr); identified from county demographic databases, frequency-matched to cases on sex and age (± 5 yr); 87% participation rate in Dafeng and 85% participation rate in Ganyu	Interviewer-administered questionnaire Drinking status: never was drinking < once per month; current was drinking at time of interview or quit < 1 yr before interview; former was not clearly defined Duration of cessation: if quit drinking was reported at time of interview, duration of cessation was also recorded	Drinking status	All		Age, sex, study area, previous income, BMI, pack-years of smoking, and family history of cancer	No adjustment for amount of alcohol consumed or duration of smoking cessation Among women, results were not reported for categories of duration of cessation
				Never	490	1.0 (ref)		
				Former	454	5.16 (4.23–6.29)		
				Current	576	0.94 (0.80–1.10)		
					Men			
				Never	221	1.0 (ref)		
				Former	424	6.43 (5.14–8.04)		
				Current	546	1.10 (0.92–1.33)		
					Women			
				Never	269	1.0 (ref)		
				Former	30	2.19 (1.30–3.71)		
				Current	30	0.52 (0.34–1.02)		
				Duration of cessation	All			
				Never	490	1.0 (ref)		
				≥ 10 yr	32	1.80 (1.14–2.85)		
				5–< 10 yr	27	2.22 (1.32–3.75)		
				< 5 yr	237	5.28 (4.19–6.65)		
						P_{trend} < 0.001		
					Men			
				Never	221	1.0 (ref)		
				5–< 10 yr	26	2.33 (1.36–4.02)		
				< 5 yr	223	5.46 (4.29–6.96)		
						P_{trend} < 0.001		

Table 2.18 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Yang et al. (2017) China 2010–2013	Men (n = 921) aged 40–85 yr; 100% histologically confirmed OSCC; residents of Taixing for ≥ 5 yr, identified by medical record review in endoscopy clinic at 1 of 4 large hospitals or from local cancer registry	Population-based controls (n = 1352 men) randomly selected from the local population registry and frequency-matched (1.3:1) on 5-yr age groups and sex	Interviewer-administered questionnaire Drinking status: ever was drinking ≥ once per week for 6 months; ex-drinking was quit ≥ 2 yr before interview date Duration of cessation: difference between age at permanently quit and age at interview	Drinking status			Age, smoking status (never, ex, current), education, marital status, occupation, family wealth score, energy intake and BMI 10 yr ago, missing or filled teeth, tooth brushing, tea temperature, and first-degree family history of oesophageal cancer	No adjustment for amount of alcohol consumed or detailed smoking history Overall participation rates among men and women combined were 78.3% for cases and 70.4% for controls Results for women were reported only for ever compared with never drinking
				Never	235	1.0 (ref)		
				Ex	40	1.51 (0.96–2.38)		
				Current	646	2.24 (1.82–2.76)		
						P_{trend} < 0.001		
				Duration of cessation				
				Never	235	1.0 (ref)		
				≤ 7 yr	20	1.55 (0.83–2.91)		
				> 7 yr	20	1.63 (0.86–3.12)		

ACCH, Aichi Cancer Center Hospital; BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; NR, not reported; OR, odds ratio; OSCC, oesophageal squamous cell carcinoma; PANESOES, Adherence to Pro-Vegetarian Food Patterns and Risk of Oesophagus, Stomach, and Pancreas Cancers; ref, reference; yr, year or years.

were adjusted for pack-years of smoking but not for duration of smoking cessation or the amount of alcohol consumed.]

In a hospital-based case–control study in Spain, associations of duration of cessation and cessation with risk of oesophageal cancer overall and with oesophageal SCC were assessed (Vioque et al., 2008). Between January 1995 and March 1999, 202 men and women aged 30–80 years with histologically confirmed oesophageal cancer (79.2% oesophageal SCC) were identified at nine hospitals in Valencia and Alicante (which include about 90% of cases in both provinces). The controls were selected from among patients with diseases unrelated to tobacco use, alcohol consumption, and diet, were treated at the same hospitals and during the same time period as the cases, and were frequency-matched to the expected distribution of cases on age group, sex, and province. Among eligible controls, 455 completed the interviews (99.6%). Compared with never drinking, the risk of oesophageal SCC was higher for former drinking (OR, 11.03; 95% CI, 3.73–32.62) and for current drinking (OR, 4.48; 95% CI, 1.69–11.83). The risk of all oesophageal cancers also was higher for former drinking (OR, 4.28; 95% CI, 1.92–9.56) and for current drinking (OR, 2.06; 95% CI, 1.04–4.08). [Compared with continuing consumption, cessation was associated with a higher risk of oesophageal SCC (calculated OR, 2.46; 95% CI, 1.11–5.44) and all oesophageal cancers (calculated OR, 2.08; 95% CI, 1.03–4.18).] In an analysis of oesophageal SCC, compared with current drinking, the odds ratio for < 5 years of cessation was 5.89 (95% CI, 2.01–17.25) and for ≥ 5 years of cessation was 1.70 (95% CI, 0.79–3.66). For all oesophageal cancers, compared with current drinking, the odds ratio for < 5 years of cessation was 3.60 (95% CI, 1.34–9.69) and for ≥ 5 years of cessation was 1.71 (95% CI, 0.86–3.41). [The strength of this study is selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption. The limitations of this study are that the highest category of duration of cessation was ≥ 5 years and that the associations were adjusted for categories of pack-years of smoking but not for duration of smoking cessation or the amount of alcohol consumed.]

Szymańska et al. (2011) assessed duration of cessation and cessation in relation to oesophageal SCC using data from two centres in Brazil which were part of a larger multicentre hospital-based case–control study in Latin America that was initiated in 1998 and was originally designed to assess risk factors for all upper aerodigestive tract cancers. Included in this analysis were 171 men and women with histologically confirmed oesophageal SCC and 496 controls who were frequency-matched to cases on age, sex, and centre, and were inpatients or outpatients with conditions unrelated to tobacco use or alcohol consumption. Compared with never drinking the risk was higher for both former drinking (OR, 4.24; 95% CI, 2.26–7.94) and current drinking (OR, 4.10; 95% CI, 2.19–7.69). [Compared with continuing consumption, the calculated odds ratio for cessation was 1.03 (95% CI, 0.66–1.63).] For categories of duration of cessation, compared with current consumption, there was a higher risk for 2–4 years of cessation (OR, 2.15; 95% CI, 1.10–4.21), but the odds ratios were < 1 across categories of longer duration of cessation (e.g. OR, 0.46; 95% CI, 0.19–1.16 for ≥ 20 years of cessation). Modelled as a continuous variable, duration of cessation was inversely associated with risk (OR, 0.72; 95% CI, 0.54–0.96 per 10 years of cessation). [The strengths of this study are the selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption and that the associations for duration of cessation were further adjusted for the amount of alcohol consumed. The limitations of this study are that the associations were adjusted for tobacco pack-years but not for duration of smoking cessation and that there were few cases in the long-term cessation category (n = 9).]

In a large, population-based case–control study in China (Wu et al., 2011), patients with primary oesophageal cancer that was newly diagnosed from 2003 to 2007 were ascertained from local population-based cancer registries. Included in the analysis were 1520 cases of oesophageal cancer (*n* = 1191 men, mean age, 65.3 years; *n* = 329 women, mean age, 67.4 years). The controls were randomly selected from the county demographic database and frequency-matched to cases on sex and age (± 5 years). Included in the analysis were 3879 controls (*n* = 2916 men, mean age, 64.2 years; *n* = 963 women, mean age, 64.9 years). Among men and women combined, compared with never drinking, the odds ratio for current drinking was 0.94 (95% CI, 0.80–1.10) and for former drinking was 5.16 (95% CI, 4.23–6.29). The odds ratios were > 1 for all categories of duration of cessation (e.g. OR, 5.28; 95% CI, 4.19–6.95 for < 5 years and OR, 1.80; 95% CI, 1.14–2.85 for ≥ 10 years of cessation). [Compared with continuing consumption, there was a higher risk associated with cessation (calculated OR, 5.49; 95% CI, 4.51–6.68), but the higher risks decreased with longer duration of cessation: the calculated OR was 5.62 (95% CI, 4.75–6.64) for < 5 years of cessation and 1.91 (95% CI, 1.21–3.03) for ≥ 10 years of cessation.] Odds ratios for cessation among men and women separately were similar to that among men and women combined. Odds ratios for duration of cessation among men also were similar to those among men and women combined. Among women, there were too few cases to assess duration of cessation. [The strength of this study is that it was large and population-based. The limitations of this study are that all oesophageal cancer cases were included, that former drinking was not clearly defined, that there were too few cases among women to assess duration of cessation, and that the associations were adjusted for pack-years of smoking but not for duration of smoking cessation or the amount of alcohol consumed.]

In a large, population-based case–control study in Taixing (China) conducted from 2010 to 2013, cases were histologically confirmed oesophageal SCC identified by medical record review in an endoscopy clinic at one of four large hospitals or in a local cancer registry (Yang et al., 2017). Overall, 921 men and 432 women aged 40–85 years were included in the alcohol analysis. The controls were randomly selected from the local population registry and frequency-matched on 5-year age group and sex (1.3 controls per case). Overall, 1352 male controls and 609 female controls were included in the analysis. Among women, results were only reported for never drinking compared with ever drinking. Among men, compared with never drinking, the odds ratio for ex-drinking was 1.51 (95% CI, 0.96–2.38) and for current drinking was 2.24 (95% CI, 1.82–2.76). [Cessation was associated with a lower risk compared with continuing consumption (calculated OR, 0.67; 95% CI, 0.43–1.05).] Compared with never drinking, the odds ratio for ≤ 7 years of cessation was 1.55 (95% CI, 0.83–2.91) and for > 7 years of cessation was 1.63 (95% CI, 0.86–3.12). [Compared with continuing consumption, the calculated odds ratio for ≤ 7 years of cessation was 0.69 (95% CI, 0.37–1.28) and for > 7 years of cessation was 0.73 (95% CI, 0.39–1.37). The strengths of this study are that it was large and population-based and that the cases were limited to oesophageal SCC. The limitations of this study are that there were too few cases among women to assess cessation or duration of cessation and that the associations were not adjusted for detailed smoking history or the amount of alcohol consumed.]

In a population-based case–control study in Shanghai (China), cases of oesophageal cancer aged 30–74 years and diagnosed between 1 October 1990 and 31 January 1993 were identified from the Shanghai Cancer Registry rapid reporting system (Gao et al., 1994). Among eligible cases, 902 were interviewed (88.8%), and 605 (67% of those interviewed) had pathologically

confirmed oesophageal SCC. Among men, 513 cases of oesophageal cancer were included in the alcohol analysis. Among women, there were 3 cases in the ex-drinking category; therefore, results for women are not described here. The controls were randomly selected from the urban Shanghai population and frequency-matched to the age and sex distribution of cases in the Shanghai Cancer Registry from 1986 to 1987. Among controls interviewed, 799 men were included in the alcohol analysis. Higher risks of oesophageal cancer were associated with ex-drinking than with non-drinking (OR, 1.6; 95% CI, 0.8–3.1) and with current drinking than with non-drinking (OR, 1.4; 95% CI, 1.1–1.9). [The calculated OR for cessation compared with continuing consumption was 1.14 (95% CI, 0.58–2.25). The strength of this study is that it was population-based. The limitations of this study are that the participation rate among controls was not reported, that the categories of drinking status were not defined, that it is unclear what smoking categories were controlled for, and that the associations were not adjusted for the amount of alcohol consumed.]

In a hospital-based case–control study in Japan (Yokoyama et al., 2002), cases included (*n* = 234) men aged 40–79 years who were diagnosed with oesophageal SCC within 3 years of study enrolment between September 2000 and December 2001 and treated at one of four hospitals. The controls (*n* = 634) were outpatients at one of two Tokyo clinics for annual health check-ups during the same time period. The odds ratio for ex-drinking compared with light-drinking was 9.44 (95% CI, 3.29–27.08). [Compared with continuing consumption, the calculated odds ratio for cessation was 1.02; 95% CI, 0.42–2.48). The strengths of this study are that the associations were adjusted for consumption of strong alcoholic beverages and that the cases were limited to oesophageal SCC. The limitations of this study are that there was limited information about selection of hospital-based controls, that the associations were adjusted for categories of pack-years of smoking but not for duration of smoking cessation, and that there were few cases in the never/rare reference category (*n* = 5).]

In another hospital-based case–control study in Japan, the cases included 165 men and women aged 18–80 years who were diagnosed with oesophageal cancer between January 2001 and August 2004 and had completed a first outpatient questionnaire at the Aichi Cancer Center Hospital (Yang et al., 2005). The controls (*n* = 495 men and women), who were randomly selected from among all first-visit outpatients who completed the questionnaire during the same time period, were cancer-free and matched to cases (3:1) on age and sex. Compared with never drinking, there was a higher risk for former drinking (OR, 6.20; 95% CI, 2.34–16.4) and for current drinking (OR, 9.44; 95% CI, 4.36–20.4). [Compared with continuing consumption, the calculated odds ratio for cessation was 0.66 (95% CI, 0.34–1.29). The strength of this study is that it included men and women. The limitations of this study are that there was limited information available about selection of hospital-based controls, that the associations were not adjusted for smoking or the amount of alcohol consumed, and that there were few cases in the never-drinking category (*n* = 8).]

In a hospital-based case–control study in Taiwan (China), the cases included 165 men aged 35–92 years who were diagnosed with histologically confirmed oesophageal SCC at one of two hospitals (Wu et al., 2006). The controls (*n* = 255) were men aged 40–92 years who were inpatients or outpatients at the Otolaryngology Department at one of the hospitals during the study period and who did not have cancer or conditions associated with betel quid chewing, cigarette smoking, or alcohol consumption. Compared with non-drinking, there was a higher risk for ex-drinking (OR, 5.4; 95% CI, 1.9–15.4) and for current drinking (OR, 23.3; 95% CI, 12.0–47.7). [Compared with continuing

consumption, cessation was associated with a substantially lower risk (calculated OR, 0.23; 95% CI, 0.08–0.65). The strength of this study is the selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption. The limitations of this study are that the participation rate among controls was not reported, that it is unclear what smoking categories were controlled for, and that the associations were not adjusted for the amount of alcohol consumed.]

2.2.5 Combined cancers of the upper aerodigestive tract

"Upper aerodigestive tract cancers" is a collective term that is used to describe oesophageal cancer and cancers of the head and neck, which itself is a collective term that typically includes cancers of the oral cavity, pharynx, and larynx (ICD codes C00–C15, C32). Other sites of the head and neck (e.g. thyroid) can be included in some clinical definitions; however, these were not included in this review because they are not alcohol-related cancers. Furthermore, oral cavity and pharyngeal cancers (or cancer in subsites of the pharynx such as the oropharynx) are combined in some studies. Risk factors for combined head and neck cancers, or for different subgroups of or all upper aerodigestive tract cancers, are often assessed in epidemiological studies, in part because of a shared etiology with risk factors such as tobacco smoking and alcohol consumption, or because of a limited number of cases for a single cancer site. Therefore, it is important that anatomical subsites are clearly specified in studies of upper aerodigestive tract cancers combined.

(a) Cohort studies

The association between reduction of alcoholic beverage consumption and risk of upper aerodigestive tract cancers combined was assessed in two cohort studies (Thygesen et al., 2007; Yoo et al., 2022). The association between cessation and risk was assessed in three cohort studies (Weikert et al., 2009; Im et al., 2021a; Yoo et al., 2022) (Table 2.19; Supplementary Table S2.20, web only; available from https://publications.iarc.who.int/638). There are no informative cohort studies of duration of cessation and risk.

In 1976–1978, 14 223 men and women who were randomly selected within age strata of the Central Copenhagen population participated in the Copenhagen City Heart Study (Thygesen et al., 2007). Included in the alcohol analysis were 10 355 participants who were re-examined in 1981–1983, for whom complete alcohol data were available at each examination and who had no history of cancer at the time of the second examination. Among the participants included in the analysis, 105 incident cases of upper aerodigestive tract cancer (i.e. tongue, oral cavity, pharyngeal, laryngeal, and oesophageal cancer; 84% SCC) were identified during the follow-up time between the date of the second examination and 31 December 2002 (up to 21 years) through linkage with the Danish Cancer Registry. Compared with stable consumption (change of −0.9 to +0.9 drinks per week), the hazard ratio for reducing consumption by 1–6.9 drinks per week was 1.2 (95% CI, 0.5–2.7) and for reducing consumption by ≥ 7 drinks per week was 0.5 (95% CI, 0.1–2.5). [The strengths of this study are that the associations were adjusted for initial alcohol intake and for detailed changes in smoking habits and that no violation of the proportional hazards assumption was detected. The limitation of this study is that there were few cases in the highest reduction category ($n = 2$).]

In the study of Yoo et al. (2022) (described in Section 2.2.3), among the men and women included in the analysis, 3884 cases of lip, oral cavity, and pharyngeal cancer (combined) were identified during the follow-up time. In the analysis of alcohol reduction, compared with stable moderate consumption, the hazard ratio

Table 2.19 Cohort studies of reduction and cessation of alcoholic beverage consumption and risk of cancers of the upper aerodigestive tract

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Thygesen et al. (2007) Denmark Copenhagen City Heart Study 1976–2002	Analysis included n = 10 355 men and women enrolled in 1976–1978 and re-examined in 1981–1983; follow-up time through 2002 (up to 21 yr after re-examination); cancer cases ascertained by cancer registry linkage	Self-administered questionnaire at enrolment and re-examination Change in intake: difference in the number of drinks per week between the first and second examinations	Tongue (ICD-7 codes 141.0, 141.1, 141.8); oral cavity (ICD-7 143.0, 144.0, 144.2); pharynx (ICD-7 145.0, 145.8, 146.0, 146.4, 147.0, 148.0); larynx (ICD-7 161.0, 161.1); and oesophagus (ICD-7 150.0–150.2)	Change in drinks/week			Age, alcohol intake at first examination, sex, and detailed change in smoking	No information was obtained about drinking history at either the first or second examination
				≥ −7	2	0.5 (0.1–2.5)		
				−6.9 to −1	22	1.2 (0.5–2.7)		
				−0.9 to +0.9	14	1.0 (ref)		
				+1 to +6.9	20	1.3 (0.6–2.7)		
				+7 to +14	12	1.4 (0.6–3.3)		
				> +14	35	2.5 (1.1–5.3)		
						P_{trend} < 0.0001		
Weikert et al. (2009) 6 European countries (Denmark, Germany, Italy, the Netherlands, Spain, and the United Kingdom) European Prospective Investigation into Cancer and Nutrition 1992–2005	Analysis included n = 98 505 men and n = 172 748 women aged 35–70 yr; mean follow-up time, 8.6 yr; cancer cases ascertained by cancer registry linkage in 5 countries, and through insurance records, cancer and pathology registries, and active follow-up of participants or their next-of-kin in the 6th country	Self-administered questionnaire; intake at baseline and retrospective intake for ages 20, 30, 40, and 50 yr Lifetime intake: never was no consumption at any age or at baseline; former was alcohol consumption at ages 20, 30, 40, or 50 yr but not during the 12 months before enrolment;	SCC of the tongue (ICD-O-2 codes C01–C06), oropharynx (ICD-O-2 codes C09–C10), hypo-pharynx (ICD-O-2 codes C13–C14), oesophagus (ICD-O-2 code C15), and larynx (ICD-O-2 code C32)	Lifetime intake	Men		Centre, age, duration of smoking (continuous), smoking status (former smoking quitting ≥ 10 yr, former smoking quitting < 10 yr, former smoking with unknown quit, current smoking < 15, ≥ 15–< 25, and ≥ 25 cigarettes per day, and unknown quantity),	Limited follow-up time No adjustment for amount of alcohol consumed
				Never	1	0.51 (0.07–3.80)		
				Former	36	4.14 (2.38–7.19)		
				Current (g/day)				
				> 0.1–≤ 6	23	1.0 (ref)		
				> 6–≤ 18	44	0.78 (0.47–1.31)		
				> 18–≤ 30	46	1.10 (0.65–1.86)		
				> 30–≤ 60	70	1.65 (1.00–2.71)		
				> 60–≤ 96	30	2.20 (1.23–3.95)		
				> 96	32	4.63 (2.52–8.48)		
						P_{trend} < 0.0001		

Table 2.19 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Weikert et al. (2009) (cont.)		average lifetime intake for those who reported current drinking was a weighted average of g/day		Lifetime intake	Women		education, BMI, fruit and vegetable intake	
				Never	9	2.22 (0.99–4.99)		
				Former	9	2.01 (0.91–4.43)		
				Current (g/day)				
				> 0.1–≤ 6	34	1.0 (ref)		
				> 6–≤ 18	38	1.67 (1.03–2.69)		
				> 18–≤ 30	11	1.84 (0.90–3.75)		
				> 30	12	6.05 (2.98–12.3)		
						$P_{trend} < 0.0001$		
Im et al. (2021a) China China Kadoorie Biobank 2004–2016	Analysis included *n* = 209 237 men aged 30–79 yr; follow-up time from 2004 through 2016 (median, 10 yr); cancer cases ascertained by linkage with cancer registries and the national health insurance databases	Interviewer-administered questionnaire Drinking status: abstain was no drinking in the past year or in most weeks prior; ex-regular was drinking < weekly in the past year but drinking ≥ weekly prior; occasional was drinking < weekly in the past year and prior; current regular was drinking in most weeks in the past year	Mouth and throat (ICD-10 codes C00–C14, C32)	Drinking status			Age, study area, education, income, smoking (never, occasional, and for ever smoked, 3 categories of cigarettes per day in men and 2 in women), BMI, physical activity, fruit intake, and family history of cancer	Floating standard errors were used to estimate the CIs; abstention was the reference category No adjustment for amount of alcohol consumed or duration of smoking cessation Results for women not shown here because there were 4 cases in the ex-regular drinking category
				Abstain	90	1.00 (0.81–1.24)		
				Ex-regular	61	1.46 (1.13–1.88)		
				Occasional	154	1.22 (1.03–1.44)		
				Current regular	236	1.73 (1.51–1.99)		

Table 2.19 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Yoo et al. (2022) Republic of Korea NHIS 2009–2018	Analysis included n = 4 513 746 men and women aged ≥ 40 yr with drinking status data from 2 consecutive (2009 and 2011) biennial NHIS health screenings; follow-up time through 2018 (median, 6.4 yr); cancer cases ascertained through the NHIS billing system	Self-administered questionnaires in 2009 and 2011 Alcohol intake in 2009 and 2011: for each survey, alcohol intake was first classified by amount of ethanol consumed: none, mild (< 15 g/day), moderate (15–29.9 g/day), and heavy (≥ 30 g/day); then associations for each level of consumption in 2011, with stratification on level of consumption in 2009; the reference group for each stratum was the stable group at each level of consumption (e.g. 2009/2011 none/none)	Oral cavity and pharynx (ICD-10 codes C01–C10, C12–C14)	Alcohol intake in 2009/2011	3884 total		Age, sex, socioeconomic position, smoking status, physical activity, comorbidities (hypertension, diabetes, dyslipidaemia, chronic kidney disease, and chronic obstructive pulmonary disease), and Charlson Comorbidity Index	Excluded the first year of follow-up time No information about alcohol consumption before the first wave of reporting Limited follow-up time No adjustment for detailed smoking history, including duration of smoking cessation eTable 2 lists lip, oral cavity, and pharynx in the definition for the organ sites included
				None/none		1.0 (ref)		
				None/mild		0.94 (0.80–1.11)		
				None/moderate		1.00 (0.74–1.35)		
				None/heavy		1.13 (0.83–1.55)		
				Mild/none		1.20 (1.04–1.38)		
				Mild/mild		1.0 (ref)		
				Mild/moderate		0.98 (0.81–1.19)		
				Mild/heavy		1.11 (0.87–1.42)		
				Moderate/none		1.21 (0.90–1.63)		
				Moderate/mild		1.15 (0.96–1.38)		
				Moderate/moderate		1.0 (ref)		
				Moderate/heavy		0.96 (0.77–1.20)		
				Heavy/none		1.47 (1.06–2.05)		
				Heavy/mild		1.22 (0.92–1.61)		
				Heavy/moderate		0.93 (0.73–1.18)		
				Heavy/heavy		1.0 (ref)		

BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; NHIS, National Health Insurance Service; ref, reference; SCC, squamous cell carcinoma; yr, year or years.

for a reduction from moderate consumption in 2009 to mild consumption in 2011 was 1.15 (95% CI, 0.96–1.38). Compared with stable heavy consumption, the hazard ratio for a reduction from heavy to mild consumption was 1.22 (95% CI, 0.92–1.61) and for reduction from heavy to moderate consumption was 0.93 (95% CI, 0.73–1.18). Compared with stable mild, stable moderate, and stable heavy consumption, the hazard ratios for cessation from each level of consumption in 2009 to none in 2011 were 1.20 (95% CI, 1.04–1.38), 1.21 (95% CI, 0.90–1.63), and 1.47 (95% CI, 1.06–2.05), respectively. [The strengths and limitation of this study are described in Section 2.2.3.]

A multicentre cohort study of alcohol consumption in six countries in the European Prospective Investigation into Cancer and Nutrition (EPIC) study included 271 253 men and women who were cancer-free at baseline for whom complete alcohol intake and other data were available and who were followed up for a mean of 8.6 years (Weikert et al., 2009). During the follow-up time, 392 cases of incident primary SCC of the upper aerodigestive tract (i.e. tongue, oropharynx, hypopharynx, larynx, and oesophagus) were identified through linkage with population-based cancer registries in five countries or a combination of health insurance records, cancer and pathology registries, and active follow-up of study subjects and their next-of-kin in the sixth country. The reference group among the current drinkers had an average lifetime consumption of > 0–≤ 6 g per day. Cessation was associated with a higher risk among men (RR, 4.14; 95% CI, 2.38–7.19) and women (RR, 2.01; 95% CI, 0.91–4.43). [Compared with continuing consumption that included all amounts of lifetime consumption, the calculated relative risk for cessation was 2.68 (95% CI, 0.28–25.07) among men and 1.10 (95% CI, 0.32–3.74) among women. The strengths of this study are that it was a multicountry European study, that it captured lifetime alcohol intake, and that the associations were adjusted for detailed smoking history, including categories of time since quitting among former smokers and numbers of cigarettes per day among current smokers. The limitations of this study are that the follow-up time was limited (mean, 8.6 years), that there were few women with upper aerodigestive tract cancers in the former-drinking category ($n = 9$), that the associations were not adjusted for the amount of alcohol consumed, and that there was no sensitivity analysis excluding at least the first year of follow-up time and no test of the proportional hazards assumption.]

In the study of Im et al. (2021a) (described in Section 2.2.1), 541 incident cases of lip, oral cavity, pharyngeal, and laryngeal cancer (combined) among men were included in the analysis. Compared with abstaining, the hazard ratio was 1.46 (95% CI, 1.13–1.88) for ex-regular drinking and 1.73 (95% CI, 1.51–1.99) for current-regular drinking. [Compared with continuing consumption, the calculated hazard ratio for cessation was 0.84 (95% CI, 0.63–1.13). The strengths and limitations of this study are described in Section 2.2.1.]

(b) Case–control studies

The associations of duration of cessation and cessation of alcoholic beverage consumption with risk of upper aerodigestive tract cancers combined were assessed in the international pooled analysis (Marron et al., 2010) and in two individual case–control studies (Takezaki et al., 1996; Huang et al., 2017) (Table 2.21; Supplementary Table S2.20 and Table S2.22, web only; available from https://publications.iarc.who.int/638).

In the international pooled analysis (Marron et al., 2010) (described in Section 2.2.1), individual-level data from all 9176 cases of oral cavity, oropharyngeal, hypopharyngeal, and laryngeal cancer (combined) and 12 593 controls who participated in nine hospital-based and four population-based case–control studies were

Table 2.21 Case–control studies of duration of cessation and cessation of alcoholic beverage consumption and risk of cancers of the upper aerodigestive tract combined

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Marron et al. (2010) INHANCE consortium ~1980s–early 2000s	Men and women with incident oral, oropharyngeal, and hypopharyngeal cancer and laryngeal cancer (*n* = 9167) who participated in population-based case–control studies in Seattle, Washington (USA), Los Angeles, California (USA), Boston, Massachusetts (USA), or Puerto Rico (USA), or hospital-based case–control studies in France, Italy, Switzerland, Iowa (USA), North Carolina (USA), Tampa, Florida (USA), Houston, Texas (USA), Latin America, or an international multicentre study	Hospital-based and population-based controls (*n* = 12 593) In the Los Angeles population-based study, controls were individually matched to cases on decade of age, sex, and neighbourhood; in the hospital-based studies, controls were frequency-matched to cases on age, sex, and other factors (e.g. study centre, hospital, and race or ethnicity)	Interviewer-administered questionnaires in all studies except self-administered in the Iowa study Drinking status: current was consumption within the past year; former was cessation ≥ 1 yr before interview date; never was responding no to ever drinking Duration of cessation: difference between age at reference date (interview or diagnosis) and age at cessation	Drinking status			Age, sex, race or ethnicity, study centre, education, pack-years of tobacco smoking, and number of alcoholic drinks per day	Pooled analysis of individual participant data Most data came from hospital-based case–control studies (*n* = 9), compared with population-based case–control studies (*n* = 4) ORs for ≥ 20 yr of cessation (compared with current drinking) and risk of all head and neck cancers combined were 0.45 (95% CI, 0.25–0.81) in the hospital-based studies and 0.89 (95% CI, 0.45–1.45) in the population-based studies No details reported about selection of hospital-based controls Participation rates not reported
				Current	4668	1.0 (ref)		
				Former	2521	0.85 (0.63–1.14)		
				Never	1602	0.73 (0.51–1.06)		
				Missing	376			
				Duration of cessation				
				Current	4668	1.0 (ref)		
				> 1–4 yr	564	0.99 (0.69–1.43)		
				5–9 yr	575	0.90 (0.62–1.30)		
				10–19 yr	790	0.94 (0.75–1.18)		
				≥ 20 yr	591	0.60 (0.40–0.89)		
				Never	1602	0.74 (0.51–1.06)		
						P_{trend} = 0.05		

Table 2.21 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Takezaki et al. (1996) Japan 1988–1993	Men and women (n = 266) aged 20–79 yr, with histologically confirmed cancer of the oral cavity (ICD-9 codes 141, 143–145), oropharynx (ICD-9 code 146), and hypopharynx (ICD-9 code 148); completed a first-visit outpatient questionnaire at ACCH	Hospital-based controls (n = 36 527 men and women) aged 20–79 yr; first-visit outpatients at ACCH and confirmed to be cancer-free by diagnostic procedures	Self-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	Drinking status			Age, sex, year of visit, and smoking	No adjustment for amount of alcohol consumed Unclear what categories of smoking were controlled for Participation rates not reported
				Almost never	97	1.0 (ref)		
				Never quit	138	1.2 (0.9–1.6)		
				Duration of cessation				
				0–4 yr	9	2.4 (1.1–5.1)		
				5–14 yr	4	1.7 (0.6–4.8)		
				≥ 15 yr	4	3.4 (1.2–9.9)		
Huang et al. (2017) Taiwan (China) 2010–2016	Men and women (n = 811) aged ≥ 20 yr with newly diagnosed, pathologically confirmed SCC of the oral cavity, oropharynx, hypopharynx, and larynx (ICD-10 codes C00–C10, C12–C14, C32); treated at the National Cheng Kung University Hospital	Hospital-based controls (n = 940 men and women) frequency-matched to cases on sex and age (± 5 yr); patients from otolaryngology and stomatology departments diagnosed with non-cancer head and neck diseases unrelated to alcohol consumption, betel quid chewing, or cigarette smoking	Interviewer-administered questionnaire Drinking status: never was self-reported as such; occasional was not defined; regular was drinking ≥ once per week and was categorized as former regular (quit for > 6 months) and current regular	Drinking status			Age, sex, education, cigarette smoking (pack-year categories), and betel quid chewing (pack-year categories)	Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption No adjustment for amount of alcohol consumed or duration of smoking cessation Participation rates not reported
				Never/occasional	263	1.0 (ref)		
				Former regular	111	1.14 (0.80–1.62)		
				Current regular	437	1.81 (1.41–2.34)		
				Duration of cessation				
				Current regular	437	1.0 (ref)		
				< 5 yr	50	0.76 (0.46–1.26)		
				5–9.9 yr	23	0.79 (0.42–1.50)		
				> 10 yr	34	0.46 (0.27–0.79)		
				Never/occasional	263	0.55 (0.43–0.71)		

Table 2.21 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Huang et al. (2017) (cont.)				Duration of cessation stratified by past consumption				
				Former light or moderate				
				Current regular	398	1.0 (ref)		
				< 5 yr	16	0.57 (0.26–1.24)		
				5–9.9 yr	11	0.76 (0.32–1.79)		
				> 10 yr	13	0.31 (0.14–0.65)		
				Never/occasional	235	0.54 (0.41–0.71)		
				Former heavy				
				Current regular	398	1.0 (ref)		
				< 5 yr	26	1.08 (0.50–2.33)		
				5–9.9 yr	10	1.10 (0.35–3.45)		
				> 10 yr	15	0.75 (0.30–1.87)		
				Never/occasional	235	0.54 (0.42–0.71)		

ACCH, Aichi Cancer Center Hospital; CI, confidence interval; ICD, International Classification of Diseases; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio; ref, reference; SCC, squamous cell carcinoma; yr, year or years.

included in the analysis of head and neck cancers combined. Compared with current drinking, the odds ratio for former drinking was 0.85 (95% CI, 0.63–1.14). Long-term cessation (≥ 20 years) was associated with a lower risk of head and neck cancer (OR, 0.60; 95% CI, 0.40–0.89), but shorter durations of cessation were not. The odds ratios for long-term alcohol cessation were 0.45 (95% CI, 0.25–0.81) in the nine hospital-based case–control studies and 0.89 (95% CI, 0.54–1.45) in the four population-based case–control studies. For long-term alcohol cessation, risk was lower in the ≥ 3 drinks per day stratum (OR, 0.54; 95% CI, 0.31–0.94) than in the 1–2 drinks per day stratum (OR, 0.76; 95% CI, 0.52–1.12), and there was no association in the < 1 drink per day stratum (OR, 1.00; 95% CI, 0.72–1.39). Detailed data about alcohol consumption and smoking history were available for a subset of study participants (n = 7213 cases and n = 9471 controls). Among this population, compared with the single reference category of current drinking and current smoking, long-term alcohol cessation was associated with a lower risk in each smoking strata (OR, 0.53; 95% CI, 0.32–0.88 in the current-smoking stratum and odds ratios ranging from 0.25 to 0.55 among all other smoking strata). [In the Working Group re-analysis with continuing consumption as the reference category within each smoking stratum, associations for long-term cessation were weaker but remained < 1 (calculated ORs, 0.73–0.93) across all strata of duration of smoking cessation, whereas in the never-smoking stratum, the calculated odds ratio for long-term alcohol cessation was 1.29 (95% CI, 0.44–3.77). After meta-analytic adjustment for smoking status and duration of smoking cessation, the calculated odds ratio for long-term cessation was 0.74 (95% CI, 0.56–0.98). The strengths and limitations of this study are described in Section 2.2.1.]

An outpatient-based case–control study in Aichi Cancer Center Hospital in Japan included men and women who completed a first-visit outpatient survey in 1988–1993 (Takezaki et al., 1996). Among the 43 775 men and women who completed the survey, 266 (aged 20–79 years) were diagnosed with oral, oropharyngeal, or hypopharyngeal cancer within 1 year after completing the survey and were identified through hospital records. The controls (n = 36 527 men and women) were selected from all first-visit outpatients aged 20–79 years who completed the questionnaire and were confirmed to be cancer-free within 1 year after completing the survey. Among this population, compared with almost-never drinking, the odds ratio for never quitting was 1.2 (95% CI, 0.9–1.6). Across all four categories of duration of alcohol cessation, there was a higher risk for cessation (OR, 2.4; 95% CI, 1.1–5.1 for 0–4 years of cessation; OR, 1.7; 95% CI, 0.6–4.8 for 5–14 years of cessation; and OR, 3.4; 95% CI, 1.2–9.9 for ≥ 15 years of cessation). [There was no evidence of a lower risk for cessation compared with continuing consumption overall (calculated OR, 2.00; 95% CI, 1.14–3.51) or for any strata of duration of cessation (calculated OR, 2.00; 95% CI, 0.91–4.39 for 0–4 years of cessation; OR, 1.42; 95% CI, 0.49–4.08 for 5–14 years of cessation; and OR, 2.83; 95% CI, 0.97–8.30 for ≥ 15 years of cessation. The strengths of this study are that the number of controls was large and that the alcohol consumption data were collected before diagnosis. The limitations of this study are that it is unclear what smoking categories were controlled for and that the associations were not adjusted for the amount of alcohol consumed.]

In a hospital-based case–control study in Taiwan (China) (Huang et al., 2017) (described in Section 2.2.1), 811 cases of head and neck cancer (SCC of the oral cavity, oropharynx, hypopharynx, and larynx), and 940 controls were included in the analysis. Compared with never and occasional drinking, the odds ratio for former-regular drinking was 1.14 (95% CI, 0.80–1.62) and for current-regular drinking was 1.81 (95% CI, 1.41–2.34). [Compared with continuing consumption, cessation was associated with

a lower risk of head and neck cancer (calculated OR, 0.63; 95% CI, 0.44–0.90).] Compared with current-regular drinking, the odds ratio for < 5 years of cessation was 0.76 (95% CI, 0.46–1.26), for 5–9.9 years of cessation was 0.79 (95% CI, 0.42–1.50), and for > 10 years of cessation was 0.46 (95% CI, 0.27–0.79). The odds ratio for > 10 years of cessation was lower in the light or moderate-drinking stratum (OR, 0.31; 95% CI, 0.14–0.65) than in the heavy-drinking stratum (OR, 0.75; 95% CI, 0.30–1.87). [The strengths and limitations of this study are described in Section 2.2.1.]

2.2.6 Colorectal cancer

Colorectal cancer refers to malignant tumours of the colon, rectum, anus, and anal canal (ICD-10 codes C18–C21) (Wild et al., 2020). Worldwide, colorectal cancer is the third most commonly diagnosed cancer (Morgan et al., 2023). Globally in 2020, the age-standardized (world population) incidence and mortality rates for colorectal cancer were 19.5 per 100 000 and 9.0 per 100 000, respectively (Ferlay et al., 2020).

In addition to alcohol consumption, risk of colorectal cancer is associated with dietary factors including consumption of processed meats, as well as low physical activity, excess body fatness, and tobacco smoking (Wild et al., 2020). Most studies included age, sex, tobacco smoking, and body mass index (BMI) among the adjustment variables.

(a) Cohort studies

The associations of reduction and cessation of alcoholic beverage consumption with risk of colon cancer, rectal cancer, and/or colorectal cancer were assessed in pooled analyses of cohort studies in the USA (Wei et al., 2004; Hur et al., 2021) and in the large cohort study in the Republic of Korea (Yoo et al., 2022). Reduction of alcohol consumption and risk of colorectal cancer was assessed in two other cohort studies in Europe (Mayén et al., 2022; Chen et al., 2023). Duration of cessation and risk of colon and rectal cancer mortality were assessed in a cohort study in Japan (Ozasa et al., 2007); in an earlier analysis of that study, associations of cessation with colon and rectal cancer incidence and mortality also were assessed (Wakai et al., 2005). Cessation only and risk of colon cancer, rectal cancer, and/or colorectal cancer were assessed in six other individual cohort studies in China (Im et al., 2021a), Japan (Nakaya et al., 2005), the Republic of Korea (Cho et al., 2015), and the USA (Klatsky et al., 1988; Su and Arab, 2004; Breslow et al., 2011) (Table 2.23; Supplementary Table S2.24, web only; available from https://publications.iarc.who.int/638).

The associations of change in alcohol consumption between early adulthood (ages 18–22 years) and mid-adulthood with risk of colorectal cancer were assessed in a pooled analysis of data from the Nurses' Health Study (baseline 1988 and follow-up until June 2014), Nurses' Health Study II (baseline 1989 and follow-up until June 2015), and the Health Professionals Follow-up Study (baseline 1988 and follow-up until January 2014) (Hur et al., 2021). Among 191 543 men and women included in the analysis, 2624 cases of colorectal cancer were identified during the follow-up time (up to 26 years) through self-report or linkage in a tumour or death registry, and, when available, subsequent medical or pathology records were reviewed. Compared with stable none consumption (i.e. < 1 g per day in early adulthood or in mid-adulthood), the hazard ratios were 1.11 (95% CI, 1.00–1.23) for stable low consumption (i.e. < 15 g per day), 1.39 (95% CI, 0.91–2.13) for stable high consumption (≥ 15 g per day), and 1.39 (95% CI, 1.01–1.92) for reduction from high to low consumption. [Compared with continuing stable high consumption, there was no association between reduction from high consumption in early adulthood to low consumption in mid-adulthood and risk of colorectal cancer

Table 2.23 Cohort studies of reduction, duration of cessation, and cessation of alcoholic beverage consumption and risk of colorectal cancer, colon cancer, and rectal cancer

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Klatsky et al. (1988) Northern California (USA) 1978–1984	Analysis included n = 106 203 men and women who received health examinations from 1978 to 1984; follow-up until December 1984 (up to 6 yr); cancer cases ascertained through hospital discharge records and linkage with the California State Resource for Cancer Epidemiology	Health examination questionnaire Drinking status: never was no drinking ever or almost never; ex-drinking was no consumption in the past year; current was categorized by quantity and frequency of consumption	Colon (adapted from ICD-8 code 153)	Drinking status			Sex, age, race, BMI, coffee consumption, total serum cholesterol, education, smoking (never, former, current < 1 pack/day, ≥ 1 pack/day)	No data reported about age Limited follow-up time No adjustment for amount of alcohol consumed Results for rectal cancer not shown here because there were 4 cases in the ex-drinking category
				Never	30	1.0 (ref)		
				Ex	6	0.84 (0.34–2.08)		
				Current				
				< 1 drink/day	98	1.16 (0.75–1.79)		
				1–2 drinks/day	49	1.59 (0.95–2.64)		
				≥ 3 drinks/day	20	1.71 (0.92–3.19)		
Su and Arab (2004) USA National Health and Nutrition Examination Survey I: National Health Epidemiologic Follow-up Study 1982 or 1984 to 1993	Analysis included n = 10 418 men and women (mean age, 58.5 yr for men and 56.1 yr for women) with complete alcohol information on 1982 or 1984 (baseline) survey; follow-up through July 1993 (up to 11 yr); cancer cases and deaths ascertained by self-report on follow-up surveys and linkage with National Death Index	Interviewer-administered questionnaire Drinking pattern: abstain was no drinking in 12 months before baseline and 5 yr earlier; casual was < 3.5 drinks/week at both times; initiate was no drinking 5 yr earlier but drinking at baseline; quit was drinking 5 yr earlier but not at baseline; drinking was > 3.5 drinks/week at both times	Colon (incidence and deaths) (ICD-9 code 153)	Drinking pattern			Age, race, sex, education, BMI, intake of poultry, non-poultry meat, seafood, multivitamin use, history of colon polyps, and smoking status (current or not current)	No adjustment for amount of alcohol consumed
				Abstain	55	1.0 (ref)		
				Casual	10	1.14 (0.58–2.22)		
				Initiate	23	1.50 (0.89–2.53)		
				Quit	7	1.10 (0.50–2.41)		
				Drinking	16	1.80 (1.00–3.23)		

Table 2.23 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Nakaya et al. (2005) Japan 1990–1997	Analysis included n = 21 201 men aged 40–64 yr who lived in 14 municipalities in Miyagi Prefecture; follow-up time from June 1990 through 1997 (up to 7.6 yr); cancer cases ascertained by cancer registry linkage	Self-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	Colon (no ICD codes reported)	Drinking status			Age, smoking (never, past, and categories for current number of cigarettes per day), education, daily orange juice and other fruit juice intake, and spinach, carrot, pumpkin, and tomato intake	Limited follow-up time No adjustment for amount of alcohol consumed or BMI Results for rectal cancer not shown here because there were 3 cases in the ex-drinking category
				Never	11	1.0 (ref)		
				Ex	10	1.6 (0.7–3.8)		
				Current	85	1.7 (0.9–3.3)		
Ozasa et al. (2007); Wakai et al. (2005) Japan Japan Collaborative Cohort Study for Evaluation of Cancer Risk 1988–2003 (mortality) 1988–1997 (incidence)	Mortality analysis (Ozasa et al., 2007) included n = 46 178 men aged 40–79 yr living in 1 of 45 areas of Japan; follow-up time from 1988–1990 through 2003 (except in 3 areas, where follow-up was through 1999) for cancer mortality; cause of death ascertained by linkage to a cancer registry and death certificate review (Tamakoshi et al., 2007)	Self-administered questionnaire Drinking status mortality analysis: non, ex, and current drinking status were self-reported at baseline, but categories of rare or none, drinking, and ex-drinking were not defined Duration of cessation: self-reported	Colon (C18) and rectum (C19–C20)	Colon	Deaths		Mortality: age and area of residence Incidence: age, area, education, family history of colorectal cancer, BMI, smoking status (never, ex, current), walking time, sedentary work, intake of green leafy vegetables, and intake of beef	Mortality analysis: results for duration of cessation and colon and rectal cancer mortality among women not shown here because there were 4 deaths from colon cancer and 2 deaths from rectal cancer in the ex-drinking category
				Drinking status/ duration of cessation	Men			
				Rare/none	36	1.0 (ref)		
				Drinking	148	1.16 (0.80–1.68)		
				Ex-drinking	19	1.57 (0.90–2.75)		
				< 5 yr	6	2.36 (0.97–5.74)		
				5–15 yr	4	1.29 (0.45–3.70)		
				≥ 15 yr	3	1.30 (0.39–4.32)		
				Rectum				
				Drinking status/duration of cessation				
				Rare/none	25	1.0 (ref)		
				Drinking	120	1.33 (0.86–2.06)		
				Ex-drinking	15	1.89 (0.99–3.60)		

Table 2.23 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Ozasa et al. (2007); Wakai et al. (2005) (cont.)	Incidence analysis (Wakai et al., 2005) included n = 23 708 men and n = 34 028 women aged 40–79 yr followed up from 1988–1990 through 1997 (except in 1 area, where follow-up was through 1994); cancer cases ascertained by linkage with population cancer registries supplemented by death certificate review	Drinking status incidence analysis: no definitions were reported for categories of drinking status		< 5 yr	6	3.46 (1.37–8.70)		No adjustment for amount of alcohol consumed, smoking, or BMI Incidence analysis: results for drinking status and rectal cancer incidence among women not shown here because there was 1 case in the ex-drinking category Limited follow-up time No adjustment for amount of alcohol consumed
				5–15 yr	2	0.85 (0.19–3.67)		
				≥ 15 yr	2	1.17 (0.27–5.06)		
				Drinking status	Incidence			
				Colon	Men			
				Non	24	1.0 (ref)		
				Ex	19	2.01 (1.09–3.68)		
				Current	177	1.97 (1.28–3.03)		
				Rectum				
				Non	30	1.0 (ref)		
				Ex	14	1.25 (0.66–2.38)		
				Current	106	1.01 (0.67–1.52)		
				Colon	Women			
				Non	149	1.0 (ref)		
				Ex	6	1.56 (0.68–3.60)		
				Current	43	1.03 (0.72–1.45)		
Breslow et al. (2011) USA National Health Interview Survey 1988–2006	Analysis included n = 138 590 men and n = 184 764 women aged ≥ 18 yr with complete alcohol intake data in the 1988, 1990, 1991, or 1997–2004 National Health Interview Survey who did not die within the quarter of their interview;	In-home interviews Drinking status: never was no alcohol in the year before baseline and < 12 drinks during the lifetime;	Colorectal cancer deaths (National Center for Health Statistics ICD-9 and ICD-10 bridge code 23)		Deaths		Race or ethnicity, education, region, marital status, smoking status and tertiles of current smoking intensity,	Results were similar after excluding deaths in the first 2 yr of follow-up time and when restricted to the first 10 yr of follow-up time
				Drinking status	All			
				Never	229	1.0 (ref)		
				Former	152	1.25 (0.97–1.60)		
				Lifetime infrequent	162	1.06 (0.86–1.32)		
				Current				
				Light	163	0.86 (0.67–1.10)		
				Moderate	102	1.04 (0.78–1.39)		
				Heavier	42	1.01 (0.70–1.47)		

Table 2.23 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Breslow et al. (2011) (cont.)	follow-up time from 1988 through 2006 (mean, 8.4 yr; range, 2–18 yr); cancer deaths ascertained by linkage with National Death Index	former was ≥ 12 drinks during the lifetime and ≥ 12 drinks in any previous year but not the year before baseline; current was categorized by drinks/week (light, < 3; moderate, > 3–7 for women and 3–14 for men; heavier, > 7 for women and > 14 for men)			Men		BMI, and sex in combined sex analyses	No adjustment for amount of alcohol consumed
				Never	41	1.0 (ref)		
				Former	90	1.48 (0.95–2.30)		
				Lifetime infrequent	52	1.24 (0.77–1.98)		
				Current				
				Light	84	1.05 (0.66–1.67)		
				Moderate	75	1.22 (0.78–1.91)		
				Heavier	25	1.08 (0.60–1.96)		
					Women			
				Never	188	1.0 (ref)		
				Former	62	1.08 (0.76–1.52)		
				Lifetime infrequent	110	0.98 (0.76–1.27)		
				Current				
				Light	79	0.74 (0.53–1.03)		
				Moderate	27	0.99 (0.59–1.68)		
				Heavier	17	1.05 (0.61–1.80)		
Cho et al. (2015) Republic of Korea Korean Multicenter Cancer Cohort 1993–2011	Analysis included *n* = 7488 men aged ≥ 20 yr; followed up from enrolment through 2011 (median, 11.2 yr); cancer cases ascertained by linkage with the Korean Central Cancer Registry or death certificate database	Interviewer-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	Colo-rectum (no ICD codes reported)	Drinking status	Men		BMI, moderate physical activity, and cigarette smoking status (never, former, current)	Results for women not shown here because there were 3 cases in the former drinking category No adjustment for amount of alcohol consumed
				Never	22	1.0 (ref)		
				Former	10	0.92 (0.43–1.96)		
				Current	79	1.70 (1.05–2.76)		
				Missing	1	2.08 (0.28–15.71)		

Table 2.23 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Hur et al. (2021); Wei et al. (2004) USA Change analysis: Hur et al. (2021) NHS 1988–2014 NHSII 1989–2015 HPFS 1988–2014 Current amount and past status analysis: Wei et al. (2004) NHS 1980–2000 HPFS 1986–2000	Change in intake analysis: NHS: n = 62 292 women aged 30–55 yr at enrolment in 1976; analysis from 1988 through June 2014 NHSII: n = 92 858 women aged 25–42 yr at enrolment in 1989; analysis from 1989 through June 2015 HPFS: n = 36 393 men aged 40–75 yr at enrolment in 1986; analysis from 1988 through January 2014 Total follow-up time (up to 26 yr); cancer cases ascertained by self-report or tumour or death registry linkage were confirmed by medical or pathology record review (if possible)	Self-administered questionnaires: Change in intake: alcohol intake in early adulthood (ages 18–22 yr) was recalled by participants in 1988–1989; alcohol intake in mid-adulthood (i.e. in 1986 in NHS and HPFS, and in 1989 and 1991 in NHSII; updated every 4 yr thereafter); none was defined as < 1 g/day, low was < 15 g/day, and high was ≥ 15 g/day Current amount and past status: self-administered semiquantitative FFQ assessed average intake at baseline (in 1980 in NHS women and in 1986 in HPFS)	Colon (ICD-9 code 153) and rectum (ICD-9 code 154)	Change in alcohol intake from early to mid-adulthood	NHS/ NHSII/ HPFS		Change in intake: age, race, height, BMI in early and mid-adulthood, pack-years of smoking before age 30 yr and in mid-adulthood, physical activity at ages 18–22 yr and in mid-adulthood; mid-adulthood menopausal status and menopausal hormone use (NHS and NHSII), family history of colorectal cancer, personal history of diabetes, regular use of aspirin and nonsteroidal anti-inflam-matory drugs,	In both studies (Hur et al., 2021 and Wei et al., 2004) associations were reported separately for each cohort. Because of the small number of cases within a cohort or some strata of past or consistently high consumption, only the pooled results are shown here
				Colorectum				
				None/none	532	1.0 (ref)		
				Low/low	1544	1.11 (1.00–1.23)		
				High/low	44	1.39 (1.01–1.92)		
				Low/high	478	1.32 (1.14–1.53)		
				High/high	26	1.39 (0.91–2.13)		
				Current amount (g/day)/past status	NHS/ HPFS			
				Colon				
				0	237	1.0 (ref)		
				< 10	430	0.97 (0.82–1.14)		
				10–19	204	1.04 (0.85–1.26)		
				≥ 20	180	1.27 (1.03–1.56)		
				Past	88	1.02 (0.79–1.32)		
						P_{trend} = 0.003		
				Rectum				
				0	67	1.0 (ref)		
				< 10	134	1.04 (0.77–1.40)		
				10–19	63	1.07 (0.75–1.55)		
				≥ 20	52	1.26 (0.85–1.87)		
				Past	23	0.93 (0.56–1.54)		
						P_{trend} = 0.20		

Table 2.23 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Hur et al. (2021); Wei et al. (2004) (cont.)	Current and past analysis: NHS: *n* = 87 733 women; analysis from 1980 through May 2000 HPFS: *n* = 46 632 men; analysis from 1986 through January 2000						multivitamin, intake of total energy, red meat and processed meat, dietary fibre, total folate, and total calcium, AHEI-2010 score without alcohol, and lower endoscopy within past 10 yr Current amount and past status: age, family history of cancer, BMI, physical activity, height, pack-years of smoking before age 30 yr, endoscopy, sex, intake of beef, processed meat, pork, lamb, folate, and calcium	

Table 2.23 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Im et al. (2021a) China China Kadoorie Biobank 2004–2016	Analysis included n = 209 237 men and n = 300 900 women aged 30–79 yr; follow-up time from 2004 through 2016 (median, 10 yr); cancer cases ascertained by linkage with cancer registries and the national health insurance databases	Interviewer-administered questionnaire Drinking status: abstain was no drinking in the past year or in most weeks prior; ex-regular was drinking < weekly in the past year but drinking ≥ weekly prior; occasional was drinking < weekly in the past year and prior; current regular was drinking in most weeks in the past year	Colon (ICD-10 code C18) and rectum (ICD-10 codes C19–C20)	Drinking status			Age, study area, education, income, smoking (never, occasional, and for ever smoked, 3 categories of cigarettes per day in men and 2 in women), BMI, physical activity, fruit intake, and family history of cancer	Floating standard errors were used to estimate the CIs; abstention was the reference category No adjustment for amount of alcohol consumed
				Colorectum	Men			
				Abstain	306	1.00 (0.89–1.13)		
				Ex-regular	203	1.27 (1.10–1.46)		
				Occasional	443	0.95 (0.86–1.05)		
				Current regular	575	1.20 (1.10–1.31)		
					Women			
				Abstain	1018	1.00 (0.92–1.08)		
				Ex-regular	17	0.92 (0.57–1.50)		
				Occasional	453	0.96 (0.87–1.06)		
				Current regular	41	1.10 (0.81–1.51)		
				Colon	Men			
				Abstain	180	1.00 (0.86–1.17)		
				Ex-regular	118	1.28 (1.06–1.53)		
				Occasional	255	0.93 (0.81–1.05)		
				Current regular	303	1.11 (0.98–1.25)		
					Women			
				Abstain	600	1.00 (0.90–1.11)		
				Ex-regular	8	0.70 (0.35–1.42)		
				Occasional	265	0.93 (0.82–1.05)		
				Current regular	28	1.21 (0.83–1.76)		
				Rectum	Men			
				Abstain	185	1.00 (0.86–1.16)		
				Ex-regular	122	1.22 (1.02–1.46)		
				Occasional	261	0.93 (0.82–1.06)		
				Current regular	378	1.26 (1.13–1.40)		
					Women			
				Abstain	587	1.00 (0.90–1.11)		
				Ex-regular	11	0.96 (0.53–1.76)		
				Occasional	265	1.02 (0.90–1.16)		
				Current regular	20	0.95 (0.61–1.48)		

Table 2.23 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Yoo et al. (2022) Republic of Korea NHIS 2009–2018	Analysis included *n* = 4 513 746 men and women aged ≥ 40 yr with drinking status data from 2 consecutive (2009 and 2011) biennial NHIS health screenings; without a personal history of cancer or cardiovascular disease before 2011, or cancer or cardiovascular diagnosis or death 1 yr after the baseline (2011), and complete information; follow-up time through 2018 (median, 6.4 yr); cancer cases ascertained through the NHIS billing system	Self-administered questionnaires in 2009 and 2011 Alcohol intake in 2009 and 2011: for each survey, alcohol intake was first classified by amount of ethanol consumed: none, mild (< 15 g/day), moderate (15–29.9 g/day), and heavy (≥ 30 g/day); then associations for each level of consumption in 2011 were assessed stratified on level of consumption in 2009; the reference group for each stratum was the stable group at each level of consumption (e.g. 2009/2011 none/none)	Colorectum (ICD-10 codes C18–C20 excluding appendix, ICD-10 code C18.1)	Alcohol intake in 2009/2011	41 102 total		Age, sex, socioeconomic position, smoking status, physical activity, comorbidities (hypertension, diabetes, dyslipidaemia, chronic kidney disease, and chronic obstructive pulmonary disease), and Charlson Comorbidity Index	Excluded the first year of follow-up time No information about alcohol consumption before the first wave of reporting Limited follow-up time
				None/none		1.0 (ref)		
				None/mild		0.96 (0.92–1.01)		
				None/moderate		1.01 (0.92–1.12)		
				None/heavy		1.02 (0.92–1.14)		
				Mild/none		1.08 (1.03–1.12)		
				Mild/mild		1.0 (ref)		
				Mild/moderate		0.97 (0.91–1.04)		
				Mild/heavy		0.94 (0.86–1.03)		
				Moderate/none		1.09 (0.99–1.20)		
				Moderate/mild		1.12 (1.06–1.19)		
				Moderate/moderate		1.0 (ref)		
				Moderate/heavy		0.96 (0.89–1.04)		
				Heavy/none		1.31 (1.17–1.46)		
				Heavy/mild		1.12 (1.03–1.23)		
				Heavy/moderate		1.04 (0.96–1.13)		
				Heavy/heavy		1.0 (ref)		

Table 2.23 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Mayén et al. (2022) Denmark, Italy, France, Germany, Greece, the Netherlands, Norway, Spain, Sweden, and the United Kingdom European Prospective Investigation into Cancer and Nutrition 1992–2013	Analysis included n = 191 180 men and women who were resurveyed ~7.1 yr after baseline in 1992–2000 and followed up for cancer incidence; cancer cases ascertained by linkage with cancer registries, or self-report with confirmation by linkage with health insurance or pathology records	Self-administered questionnaires at baseline and follow-up Absolute change from baseline to follow-up: difference between intake reported at follow-up and intake reported at baseline	Colon and rectum (ICD-O-3 codes C18–C20)	Absolute change from baseline to follow-up			Composite variable of smoking status and intensity, education, BMI, and stratified by centre	Reference group is no change in consumption between baseline and follow-up assessment Absolute change analysis excluded first 3 yr after follow-up assessment Average follow-up time among the 10 countries was not reported
				Decrease 12 g/day	1530	0.86 (0.78–0.95)		
Chen et al. (2023) Norway Norwegian Women and Cancer Study 1996–2018	Analysis included n = 66 233 women aged 41–76 yr who completed follow-up questionnaires in 1996–2004 (Q1) and in 2002–2014 (Q2); followed up from time of Q2 until December 2018 (median, 14.2 yr); cancer cases ascertained by linkage with Cancer Registry of Norway	Self-administered questionnaires Each lifestyle factor was assigned a score ranging from 0 to 4, with higher scores indicating a healthier lifestyle: alcohol HLI score was 4 = none, 3 = > 0–< 5 g/day, 2 = 5–< 10 g/day, 1 = 10–< 20 g/day, and 0 = > 20 g/day	Colorectum (ICD-10 codes C18–C20)	Change in alcohol HLI score between Q1 and Q2			Education, height, HLI score at Q1 (continuous), calendar year at Q2 (continuous), single-factor HLI score changes, and single-factor HLI scores at Q1	Among the 66 233 women in the analysis, missing data from Q1, Q2, or both were imputed for 21 830 women
				1-unit increase (i.e. reduction in alcohol consumption)	839	0.97 (0.86–1.08)		

AHEI, Alternative Healthy Eating Index; BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; HLI, healthy lifestyle index; HPFS, Health Professionals Follow-up Study; ICD, International Classification of Diseases; NHIS, National Health Insurance Service; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; Q1, questionnaire 1; Q2, questionnaire 2; ref, reference; yr, year or years.

(calculated HR, 1.00; 95% CI, 0.60–1.68). The strength of this study is the continuous updating of mid-adulthood consumption. The limitations of this study are the possibility of recall errors in retrospective data collection and the lack of adjustment for the duration of smoking cessation.] In an earlier pooled analysis of data from the Nurses' Health Study (*n* = 87 733 women followed up from 1986 to 2000) and the Health Professionals Follow-up Study (*n* = 46 632 men followed up from 1980 to 2000), the associations of cessation with risk of colon cancer (*n* = 1139 cases) and rectal cancer (*n* = 339 cases) were assessed (Wei et al., 2004). Compared with 0 g of ethanol per day, the relative risks for past drinking were 1.02 (95% CI, 0.79–1.32) for colon cancer and 0.93 (95% CI, 0.56–1.54) for rectal cancer. [Compared with any amount of continuing consumption, the calculated relative risk for cessation was 0.96 (95% CI, 0.72–1.26) for colon cancer and 0.84 (95% CI, 0.49–1.45) for rectal cancer. The strength of this study is the large pooled analysis. The limitation of this study is that the associations were not adjusted for the amount of alcohol consumed.]

In the study of Yoo et al. (2022) (described in Section 2.2.3), among the men and women included in the analysis, 41 102 cases of colorectal cancer were identified during the follow-up time. In analyses of alcohol reduction, compared with stable moderate consumption, the hazard ratio for reduction from moderate consumption in 2009 to mild consumption in 2011 was 1.12 (95% CI, 1.06–1.19); compared with stable heavy consumption, the hazard ratio for reduction from heavy to mild consumption was 1.12 (95% CI, 1.03–1.23) and for reduction from heavy to moderate consumption was 1.04 (95% CI, 0.96–1.13). Compared with stable mild, stable moderate, and stable heavy consumption, the hazard ratios for cessation from each level of consumption in 2009 to none in 2011 were 1.08 (95% CI, 1.03–1.12), 1.09 (95% CI, 0.99–1.20), and 1.31 (95% CI, 1.17–1.46), respectively. [The strengths and limitation of this study are described in Section 2.2.3.]

The association of absolute change in alcohol consumption with risk of colorectal cancer was investigated in an analysis of data from 10 countries in the EPIC study, which originally included 521 323 men and women aged 25–70 years recruited in 1992–2000, resurveyed 7.1 years later, on average, and followed up for cancer incidence until 2008–2013 (Mayén et al., 2022). Among 191 180 men and women included in the alcohol analysis, 1530 cases of colorectal cancer were identified during the follow-up through linkage with cancer registries or self-report with confirmation by linkage with health insurance data or pathology reports. In the absolute change analysis, a reduction in alcohol consumption from baseline to follow-up was inversely associated with risk of colorectal cancer (HR, 0.86; 95% CI, 0.78–0.95 for each 12 g per day decrease in consumption). [The strengths of this study are that it was a large multicentre study and that the absolute change analysis excluded the first 3 years after follow-up assessment. The limitations of this study are that the average follow-up time for cancer outcomes was not reported and that no between-country or between-centre heterogeneity was reported.]

Chen et al. (2023) assessed change in alcohol intake and cancer risk including colorectal cancer and breast cancer (see Section 2.2.8) in the Norwegian Women and Cancer Study. Among about 172 000 women enrolled in the study in 1991–2007, 66 233 women aged 41–76 years completed two follow-up questionnaires in 1996–2004 and in 2002–2014 (range, 2–11 years apart; mean, 7.0 years apart). During the follow-up from completion of the second questionnaire until December 2018 (median, 14.2 years), 839 cases of colorectal cancer were identified through linkage with the Cancer Registry of Norway. For each questionnaire, women were assigned a healthy lifestyle index (HLI) score for several lifestyle factors. For

alcohol consumption specifically, the HLI score was based on grams of ethanol consumed per day: 4 = 0 g per day; 3 = > 0–< 5 g per day; 2 = 5–< 10 g per day; 1 = 10–< 20 g per day; and 0 = > 20 g per day. The hazard ratio for a reduction in alcohol consumption corresponding to a 1-unit increase in the alcohol HLI score between the first and second measurements was 0.97 (95% CI, 0.86–1.08). [The strengths of this study are the long follow-up time and the adjustment for the first measure and the change between the first and second measures of other risk factors. The limitations of this study are that the response rate across follow-up surveys was low, that for a high proportion of women (*n* = 21 830 women) lifestyle or covariate data were missing from the first questionnaire, the second questionnaire, or both, and multiple imputation was used to derive these data, that for the lifestyle-related cancer incidence outcome a sensitivity analysis showed similar results after excluding women for whom data about lifestyle factors were imputed and after excluding the first 2 years of follow-up time, but results for colorectal cancer (or breast cancer; Section 2.2.9) were not reported separately, and that the proportional hazards assumption was tested but no results were reported.]

The JACC study was described in Section 2.2.4. In the JACC study that assessed the association of alcohol consumption with risk of cause-specific mortality, 219 colon cancer deaths and 164 rectal cancer deaths were identified during the follow-up time among 46 178 men aged 40–79 years (Ozasa et al., 2007; Tamakoshi et al., 2007). Among women, results for colon cancer and rectal cancer are not shown because there were four deaths from colon cancer and two deaths from rectal cancer in the ex-drinking category. Among men, compared with rare/none, the hazard ratio for current drinking was 1.16 (95% CI, 0.80–1.68) for colon cancer mortality and 1.33 (95% CI, 0.86–2.06) for rectal cancer mortality. The hazard ratio for ex-drinking was 1.57 (95% CI, 0.90–2.75) for colon cancer mortality and 1.89 (95% CI, 0.99–3.60) for rectal cancer mortality. [Compared with continuing consumption, the calculated hazard ratio for cessation was 1.35 (95% CI, 0.82–2.24) for colon cancer and 1.42 (95% CI, 0.80–2.52) for rectal cancer.] In analyses for duration of cessation, compared with rare/none, the hazard ratio was > 1 for long-term cessation (> 15 years) for colon cancer mortality (HR, 1.30; 95% CI, 0.39–4.32) and for rectal cancer mortality (HR, 1.17; 95% CI, 0.27–5.06). [Compared with continuing consumption, there was no evidence of a lower risk of colon cancer mortality for any category of duration of cessation including long-term cessation (calculated HR, 1.12; 95% CI, 0.33–3.76). For rectal cancer mortality, the calculated hazard ratio for 5–10 years of cessation was 0.64 (95% CI, 0.14–2.83) and for > 15 years of cessation was 0.88 (95% CI, 0.20–3.84). The strengths and limitations of this study are described in Section 2.2.4. In addition, there were few deaths from colon or rectal cancer among men in each category of duration of cessation (*n* range, 2–6).] In an earlier analysis of colon and rectal cancer incidence in the JACC study that included 23 708 men and 34 028 women, colon cancer cases (*n* = 220 men, *n* = 198 women) and rectal cancer cases (*n* = 150 men, *n* = 61 women) were identified through tumour registry linkage (supplemented by death certificate review) during the follow-up time until 1997 (except in one area, where follow-up ended in 1994; mean follow-up time, 7.6 years) (Wakai et al., 2005). Because there was only 1 case of rectal cancer among women in the ex-drinking category, the rectal cancer results for women are not shown. Compared with non-drinking, ex-drinking was associated with a higher risk of colon cancer among men (incidence rate ratio [IRR], 2.01; 95% CI, 1.09–3.68), as was current drinking (IRR, 1.97; 95% CI, 1.28–3.03). Among women, the incidence rate ratio for ex-drinking was 1.56 (95% CI, 0.68–3.60) and for current drinking was 1.03 (95% CI, 0.72–1.45). Among men, the incidence rate ratios for rectal cancer

were also > 1 for former drinking (IRR, 1.25; 95% CI, 0.66–2.38) and for current drinking (IRR, 1.01; 95% CI, 0.67–1.52). After excluding the first 2 years of follow-up time, for colon cancer, among men the incidence rate ratio for ex-drinking was 2.07 and for current drinking was 1.94, whereas among women the incidence rate ratio for ex-drinking was 1.64 and for current drinking was 1.01; for rectal cancer, among men the incidence rate ratio for ex-drinking was 1.46 and for current drinking was 0.95. [Compared with continuing consumption, there was no evidence of a reduced risk of colon cancer for cessation among men (calculated IRR, 1.02; 95% CI, 0.63–1.67) or among women (calculated IRR 1.51; 95% CI, 0.63–3.63) or of rectal cancer among men (calculated IRR, 1.24; 95% CI, 0.70–2.18). The strength of this study is that the results were similar when the first 2 years of follow-up time were excluded. The limitations of this study are that no definitions were reported for any categories of drinking status, that the follow-up time was limited, that the associations were not adjusted for the amount of alcohol consumed or BMI, that among women there were few cases in the ex-drinking category (*n* = 6), and that there was no test of the proportional hazards assumption.]

A cohort study conducted in northern California (USA) included 106 203 men and women from the two largest racial groups who received health examinations in a prepaid health plan in 1978–1984 (Klatsky et al., 1988). Participants were followed up for cancer incidence until December 1984 (up to 6 years), during which 203 cases of colon cancer and 66 cases of rectal cancer were identified through hospital discharge records and linkage with the California State Resource for Cancer Epidemiology. Results for rectal cancer are not shown here because there were 4 cases in the ex-drinking category. Compared with never drinking, the relative risk of colon cancer for each category of current drinks per day was > 1 (range, 1.16–1.79), whereas the relative risk for ex-drinking was 0.84 (95% CI, 0.34–2.08). [Compared with any amount of continuing consumption, the calculated relative risk for cessation was 0.60 (95% CI, 0.23–1.55). The strength of this study is that a sensitivity analysis was conducted that excluded colon cancer cases diagnosed within 6 months after examination (RR, 0.67; 95% CI, 0.23–1.98 for ex-drinking). The limitations of this study are that the follow-up time was limited (up to 6 years), that the associations were not adjusted for the amount of alcohol consumed, and that there was no test of the proportional hazards assumption.]

Su and Arab (2004) assessed the association between drinking pattern and risk of colorectal cancer using data from the National Health and Nutrition Examination Survey I Epidemiologic Follow-Up Study in the USA. Among 10 418 men and women aged 25–74 years who completed a questionnaire in 1982–1984, 111 cancer cases and deaths were ascertained by self-report on follow-up surveys and linkage with the National Death Index during the follow-up time until July 1993 (up to 11 years). Compared with abstention, there was a higher risk of colon cancer associated with [current] drinking (HR, 1.80; 95% CI, 1.00–3.23), whereas the hazard ratio for quitting was 1.10 (95% CI, 0.50–2.41). [The calculated hazard ratio for cessation compared with any amount of continuing consumption was 0.74 (95% CI, 0.32–1.68). The strength of this study is that the associations were assessed for recalled drinking pattern. The limitations of this study are that the associations were not adjusted for the amount of alcohol consumed, that there were few cases in the ex-drinking category (*n* = 7), and that there was no test of the proportional hazards assumption.]

Nakaya et al. (2005) assessed alcohol cessation and risk of colon and rectal cancer among 21 201 men aged 40–64 years from 14 municipalities enrolled in Miyagi Cohort 2 (described in Section 2.2.4). For the analysis for colon

and rectal cancer, follow-up time was from enrolment in 1990 until December 1997 (up to 7.6 years), during which 106 cases of colon cancer and 67 cases of rectal cancer were identified by cancer registry linkage. Because there were 3 cases of rectal cancer in the ex-drinking category, results for rectal cancer are not shown here. Compared with never drinking, the relative risk for ex-drinking was 1.6 (95% CI, 0.7–3.8) and for current drinking was 1.7 (95% CI, 0.9–3.3). [Compared with continuing consumption, the calculated relative risk for cessation was 0.94 (95% CI, 0.48–1.86). The strength of this study is that in an analysis of risk of all cancers, a sensitivity analysis excluding all cancer cases diagnosed during the first 3 years of follow-up time showed a positive association with alcohol consumption. The limitations of this study are that no definitions were reported for any category of drinking status, that no ICD codes were reported, that the follow-up time was limited (up to 7.6 years), that the associations were not adjusted for the amount of alcohol consumed or BMI, that the sensitivity analysis that excluded cancer cases diagnosed during the first 3 years of follow-up time did not report results for colon cancer specifically, and that there was no test of the proportional hazards assumption.]

The association between drinking status and risk of death from colorectal cancer (and breast cancer; see Section 2.2.8) was assessed in a prospective study from the National Health Interview Survey in the USA (Breslow et al., 2011). The analysis included 138 590 men and 184 764 women aged ≥ 18 years with complete alcohol consumption data in the 1988, 1990, 1991, or 1997–2004 National Health Interview Surveys. During the follow-up from 1988 until 2006 (mean, 8.4 years; range, 2–18 years), 367 colorectal cancer deaths among men and 483 among women were ascertained through linkage with the National Death Index. Among men and women combined, compared with never drinking, there were no clear patterns of association between categories of current drinking and colorectal cancer mortality, and the relative risk for former drinking was 1.25 (95% CI, 0.97–1.60); the relative risk for former drinking was 1.48 (95% CI, 0.95–2.30) among men and 1.08 (95% CI, 0.76–1.52) among women. [Cessation was associated with a higher risk of death from colorectal cancer compared with continuing consumption among men and women combined (calculated RR, 1.34; 95% 1.06–1.69); associations were similar among men only (calculated RR, 1.30; 95% CI, 0.93–1.82) and among women only (calculated RR, 1.31; 95% CI, 0.92–1.88). The strengths of this study are that the categories of drinking status were clearly defined, that the proportional hazards assumption was met, and that sensitivity analyses excluding participants who died within 2 years of their baseline interview and restriction of follow-up of each survey to 10 years to reduce misclassification over follow-up produced similar results. The limitations of this study are that the outcome was mortality, that the follow-up time was limited for some in the cohort (range, 2–18 years; mean, 8.4 years), and that the associations were not adjusted for the amount of alcohol consumed.]

The association of alcohol consumption and cessation with risk of colorectal cancer was assessed in the Korean Multi-center Cancer Cohort (Cho et al., 2015). Among 19 252 participants enrolled in the study in 1993–2005, 7488 men and 11 034 women aged ≥ 20 years were included in the analysis. During the follow-up from enrolment until 2011 (median, 11.2 years), 220 cases of colorectal cancer (n = 112 men, n = 108 women) were identified through linkage with the Korean Central Cancer Registry or the Statistics Korea death certificate database. Because there were 3 cases of colorectal cancer among women in the ex-drinking category, results for women are not shown. Among men, compared with never drinking, there was a higher risk for current drinking (HR, 1.70; 95% CI, 1.05–2.76) but not for former drinking

(HR, 0.92; 95% CI, 0.43–1.96). [Compared with continuing consumption, cessation was associated with a lower risk (calculated HR, 0.54; 95% CI, 0.27–1.07). The strength of this study is the long follow-up time. The limitations of this study are that the associations were not adjusted for the amount of alcohol consumed and that there was no sensitivity analysis excluding at least the first year of follow-up time and no test of the proportional hazards assumption.]

(b) Case–control studies

The associations of duration of cessation and cessation of alcoholic beverage consumption with risk of colon cancer, rectal cancer, and/or colorectal cancer were assessed in a case–control study in Hong Kong Special Administrative Region (China) (Ho et al., 2004). Five other case–control studies, in China, Italy, the Republic of Korea, and the USA, assessed cessation and risk (Le Marchand et al., 1997; Tavani et al., 1998; Ji et al., 2002; Wei et al., 2009; Lee et al., 2019) (Supplementary Table S2.24, web only; available from https://publications.iarc.who.int/638; Table 2.25).

In a hospital-based case–control study in Hong Kong Special Administrative Region (China) (Ho et al., 2004), men and women aged 20–85 years with colorectal adenocarcinoma newly diagnosed from April 1998 to March 2000 and matched controls were ascertained from three public hospitals. Included in the analysis were 452 cases of colon cancer, 357 cases of rectal cancer, and 13 cases of both colon and rectal cancer, and 926 inpatient controls matched on sex and age (± 5 years) who had no dietary restrictions. Compared with never drinking, current drinking was associated with a higher risk of colorectal cancer (OR, 1.42; 95% CI, 1.09–1.85), but there was no association for former drinking (OR, 1.00; 95% CI, 0.77–1.32). Results were similar for colon cancer and for rectal cancer. [Compared with continuing consumption, cessation was associated with a lower risk of colorectal cancer (calculated OR, 0.70; 95% CI, 0.52–0.96), colon cancer (calculated OR, 0.64; 95% CI, 0.44–0.92), and, to a lesser extent, rectal cancer (calculated OR, 0.79; 95% CI, 0.53–1.17).] Compared with current drinking, the odds ratio for < 66 months of cessation was 1.37 (95% CI, 0.91–2.06), whereas the odds ratio for long-term cessation (> 180 months) was 0.52 (95% CI, 0.31–0.86). Long-term cessation was associated also with a lower risk of colon cancer (OR, 0.50; 95% CI, 0.31–0.86). In a sensitivity analysis of colorectal cancer, with the shortest duration of cessation as the reference group, the odds ratio for long-term cessation (OR, 0.44; 95% CI, 0.24–0.82) was only slightly attenuated after adjustment for the amount of alcohol consumed (OR, 0.50; 95% CI, 0.28–0.96) or frequency of consumption (OR, 0.48; 95% CI, 0.26–0.90). [The strength of this study is the large number of ex-drinkers. The limitations are that there was limited information about selection of hospital-based controls, including the exclusion of controls on a special diet, that no ICD codes were reported, that the primary results were adjusted for smoking status (ever or not) but not for detailed smoking history, amount of alcohol consumed (for the primary analysis), or BMI, and that the results for duration of cessation for rectal cancer raised some concern, because the sum of the number of cases of rectal cancer in the categories of duration of cessation (i.e. n = 92) is greater than the total number of cases in the ex-drinking category (n = 84), and therefore are not shown.]

In a population-based case–control study conducted in Hawaii (USA), cases were identified using a rapid reporting system and included men and women aged < 84 years diagnosed in 1987–1991 with histologically confirmed adenocarcinoma of the large bowel (n = 364 right colon, n = 464 left colon, and n = 350 rectum) (Le Marchand et al., 1997). The controls were identified from a list of Oahu residents who had participated in a Department of Health survey and were individually matched 1:1 on sex,

Table 2.25 Case–control studies of duration of cessation and cessation of alcoholic beverage consumption and risk of colorectal cancer, colon cancer, and rectal cancer

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Le Marchand et al. (1997) Oahu, Hawaii, USA 1987–1991	Men and women aged ≤ 84 yr with histologically confirmed right colon (n = 364), left colon (n = 464), or rectal (n = 350) adenocarcinoma; Oahu residents; identified through the Hawaii Tumor Registry rapid reporting system; 66% participation rate	Population-base controls matched 1:1 on sex, ethnicity, and age (± 2.5 yr); identified from list of Oahu residents who had participated in a Department of Health survey; 71% participation rate	Interviewer-administered questionnaire Drinking status: never was not defined; past was drinking ≥ once per week for ≥ 6 weeks but not at diagnosis date or date of interview; current was drinking up to diagnosis date for cases or interview date for controls	Right colon	Men (197 pairs)		Age, family history of colorectal cancer, pack-years of smoking, lifetime physical activity, BMI 5 yr ago, intake of eggs, dietary fibre, calcium, and total energy	No adjustment for amount of alcohol consumed
				Never		1.0 (ref)		
				Past		2.6 (1.4–5.2)		
				Current		1.8 (1.0–3.4)		
					Women (167 pairs)			
				Never		1.0 (ref)		
				Past		3.1 (1.0–9.4)		
				Current		2.5 (0.9–7.0)		
				Left colon	Men (270 pairs)			
				Never		1.0 (ref)		
				Past		1.7 (0.8–3.3)		
				Current		1.1 (0.7–2.0)		
					Women (194 pairs)			
				Never		1.0 (ref)		
				Past		1.3 (0.5–3.4)		
				Current		1.0 (0.5–2.3)		
				Rectum	Men (221 pairs)			
				Never		1.0 (ref)		
				Past		1.4 (0.8–2.4)		
				Current		1.1 (0.6–2.0)		
					Women (129 pairs)			
				Never		1.0 (ref)		
				Past		1.5 (0.6–4.1)		
				Current		1.0 (0.3–3.0)		

Table 2.25 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Tavani et al. (1998) Italy 1991–1996	Men and women aged 24–74 yr with histologically confirmed colon cancer (*n* = 1225; ICD-10 codes C18.0–C18.7) or rectal cancer (*n* = 728; ICD-10 codes C19–C20); admitted to the major teaching and general hospitals in 6 areas of Italy; > 96% participation rate	Hospital-based controls (*n* = 4154 men and women) aged 20–74 yr; admitted to the same hospitals for non-neoplastic diseases unrelated to alcohol consumption or tobacco use, or had long-term changes in diet; > 96% participation rate	Interviewer-administered questionnaire Drinking status/current amount: never was lifelong non-drinking or drinking < 1 g/day; occasional was 1–3 drinks/month, and ex-drinking was quit ≥ 1 yr before the interview; current was based on amount consumed	Colon			Centre, sex, age, education, physical activity, smoking status, family history of colorectal cancer, intake of β-carotene, vitamin C, and total energy	Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption No adjustment for amount of alcohol consumed or BMI
				Never	248	1.0 (ref)		
				Ex	89	1.20 (0.90–1.61)		
				Current (g/day)				
				1–11.82	169	1.17 (0.93–1.48)		
				> 11.82–22.66	190	1.29 (1.03–1.62)		
				> 22.66–34.36	188	1.20 (0.94–1.51)		
				> 34.36–51.82	172	1.07 (0.84–1.37)		
				> 51.82	169	1.01 (0.78–1.31)		
						P_{trend} = 0.001		
				Rectum				
				Never	147	1.0 (ref)		
				Ex	51	1.07 (0.74–1.54)		
				Current (g/day)				
				1–11.82	87	1.10 (0.82–1.47)		
				> 11.82–22.66	132	1.48 (1.13–1.94)		
				> 22.66–34.36	114	1.21 (0.91–1.61)		
				> 34.36–51.82	97	0.94 (0.69–1.27)		
				> 51.82	100	0.90 (0.65–1.23)		
						P_{trend} = 0.657		
				Colorectum				
				Never	395	1.0 (ref)		
				Ex	140	1.15 (0.90–1.47)		
				Current (g/day)				
				1–11.82	256	1.15 (0.94–1.40)		
				> 11.82–22.66	322	1.35 (1.12–1.63)		
				> 22.66–34.36	302	1.20 (0.99–1.46)		
				> 34.36–51.82	269	1.02 (0.83–1.26)		
				> 51.82	269	0.95 (0.77–1.19)		
						P_{trend} = 0.196		

Table 2.25 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Ji et al. (2002) Shanghai, China 1990–1992	Men and women aged 30–74 yr with pathologically or clinically confirmed colon cancer (*n* = 462 men, *n* = 469 women; ICD-9 codes 153.0–153.9) or rectal cancer (*n* = 463 men, *n* = 411 women; ICD-9 codes 154.0–154.9); identified from a rapid reporting system of the Shanghai Cancer Registry; participation rate 92% for colon cancer and 91% for rectal cancer	Population-based controls (*n* = 851 men, *n* = 701 women) randomly selected from among Shanghai residents based on personal identification cards; frequency-matched on sex and age (± 5 yr); for each case, 2 potential controls were selected; for 16% of cases, the second control was interviewed	Interviewer-administered questionnaire Drinking status: an alcohol "drinker" consumed ≥ 1 drink/week for ≥ 6 months; specific definitions were not reported for non-drinking, ex-drinking, and current drinking	Drinking status			Age, income, and cigarette smoking	BMI, years of education, diet, and history of colorectal polyps did not confound associations and therefore were not included in the model No adjustment for amount of alcohol consumed Unclear what categories of smoking were controlled for Results for rectal cancer among women not shown here because there were 4 cases in the ex-drinking category
				Colon	Men			
				Non	248	1.0 (ref)		
				Ex	41	2.3 (1.4–3.7)		
				Current	173	1.0 (0.8–1.3)		
				Rectum				
				Non	255	1.0 (ref)		
				Ex	34	1.1 (0.9–1.4)		
				Current	174	0.6 (0.4–1.0)		
				Colon	Women			
				Non	448	1.0 (ref)		
				Ex	6	1.4 (0.4–4.3)		
				Current	15	0.7 (0.4–1.3)		

Table 2.25 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Ho et al. (2004) Hong Kong Special Administrative Region (China) 1998–2000	Men and women aged 20–85 yr with histologically confirmed colon (n = 452) or rectal (n = 357) adenocarcinoma; identified from 3 public hospitals; 82.2% participation rate	Hospital-based controls (n = 926 men and women); matched on sex and age (± 5 yr); inpatients identified from the same departments as the cases admitted for acute non-gastrointestinal and non-malignant surgical conditions and with no dietary restrictions; 95.5% participation rate	Interviewer-administered questionnaire Drinking status: self-reported status immediately before cancer diagnosis for cases and hospital admission for controls, but categories were not defined Duration of cessation: definition was not reported	Drinking status	Colorectum		Sex, age, geographical distribution, marital status, education, physical activity, analgesic intake, family history of colorectal cancer, smoking habits (ever or not), and selected nutrient and food group intake (2 yr before reference date)	Limited information about selection of hospital-based controls No adjustment for detailed smoking history or BMI Because the sum of the number of rectal cancer cases for categories of duration of cessation (i.e. n = 92) was greater than the total number of cases in the ex-drinking category (n = 84), results for duration of cessation for rectal cancer not shown here
				Never	385	1.0 (ref)		
				Ex	186	1.0 (0.77–1.32)		
				Current	247	1.42 (1.09–1.85)		
						P_{trend} = 0.012		
				Duration of cessation				
				Current	247	1.0 (ref)		
				< 66 months	79	1.37 (0.91–2.06)		
				66–180 months	40	0.66 (0.42–1.06)		
				> 180 months	34	0.52 (0.31–0.86)		
				Never	385	0.72 (0.55–0.94)		
						P_{trend} = 0.002		
				Drinking status	Colon			
				Never	219	1.0 (ref)		
				Ex	97	0.95 (0.68–1.31)		
				Current	133	1.49 (1.08–2.04)		
						P_{trend} = 0.02		
				Duration of cessation				
				Current	133	1.0 (ref)		
				< 66 months	37	1.13 (0.69–1.87)		
				66–180 months	21	0.62 (0.35–1.11)		
				> 180 months	19	0.50 (0.31–0.86)		
				Never	219	0.68 (0.49–0.95)		
				Drinking status	Rectum			
				Never	161	1.0 (ref)		
				Ex	84	1.06 (0.74–1.51)		
				Current	111	1.34 (0.95–1.88)		
						P_{trend} = 0.10		

Table 2.25 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Wei et al. (2009) China 2002–2008	Men and women with sporadic colon cancer ($n = 348$) or rectal cancer ($n = 358$); identified from 6 hospitals in Guangzhou; 85%–~95% participation rate	Population-based controls ($n = 723$) randomly selected from among 10 000 Guangzhou City residents; matched on age (± 5 yr) and sex; ~85% participation rate	Interview-administered questionnaire Drinking status: non was never drinking ≥ once per week for ≥ 1 yr; former was drinking ≥ once per week for ≥ 1 yr but quit for ≥ 1 yr; current was the remainder, who drank ≥ once per week for ≥ 1 yr	Drinking status			Age, sex, smoking status (non, former, current), family history of cancer, and BMI	Cases were from 6 hospitals in Guangzhou, whereas controls were population-based No ICD codes were reported The age distribution, but not the range, was reported No adjustment for amount of alcohol consumed or detailed smoking history
				Colorectum				
				Non	307	1.0 (ref)		
				Former	26	2.30 (1.27–4.17)		
				Current	373	8.61 (6.15–12.05)		
						$P_{trend} < 0.0001$		
				Colon	348 total			
				Non		1.0 (ref)		
				Former		2.51 (1.24–5.07)		
				Current		7.60 (5.13–11.25)		
				Rectum:	358 total			
				Non		1.0 (ref)		
				Former		1.71 (0.80–3.65)		
				Current		7.52 (5.13–11.01)		
Lee et al. (2019) Republic of Korea 2010–2013	Men and women with histologically confirmed proximal colon ($n = 126$ men, $n = 61$ women; ICD-10 codes C18.0–C18.4), distal colon ($n = 179$ men, $n = 113$ women; ICD-10 codes C18.5–C18.7), or rectal ($n = 321$ men, $n = 125$ women; ICD-10 codes C19–C20) cancer;	Hospital-based controls ($n = 1878$ men, $n = 897$ women) attending a health screening programme at the same institution as the cases; frequency-matched (3 controls per case) on sex and age (± 5 yr); participation rate not reported	Interviewer-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	Drinking status			Age, education, family history of colorectal cancer, history of diabetes, BMI, regular physical activity, pack-years of smoking, total energy intake, calcium intake, folate intake, and red meat and processed meat intake	Limited information about selection of hospital-based controls The age distribution, but not the range, was reported No adjustment for amount of alcohol consumed or duration of smoking cessation [The ICD-10 codes for rectal cancer were erroneously reported in the paper as C19–C29.]
				Colorectum	Men			
				Never	107	1.0 (ref)		
				Ex	103	1.62 (1.11–2.37)		
				Current	416	1.05 (0.78–1.40)		
				Proximal colon				
				Never	19	1.0 (ref)		
				Ex	22	2.10 (1.07–4.14)		
				Current	85	1.25 (0.73–2.15)		
				Distal colon				
				Never	31	1.0 (ref)		
				Ex	26	1.36 (0.75–2.47)		
				Current	122	1.04 (0.67–1.62)		
				Rectum				
				Never	57	1.0 (ref)		
				Ex	55	1.63 (1.02–2.59)		
				Current	209	0.99 (0.69–1.42)		

Table 2.25 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Lee et al. (2019) (cont.)	recruited from the National Cancer Center; 73% participation rate			Colorectum	Women			Results for proximal colon cancer among women not shown here because there were 3 cases in the ex-drinking category
				Never	173	1.0 (ref)		
				Ex	26	2.54 (1.39–4.66)		
				Current	100	1.31 (0.93–1.84)		
				Distal colon				
				Never	67	1.0 (ref)		
				Ex	11	2.73 (1.24–6.01)		
				Current	35	1.19 (0.74–1.93)		
				Rectum				
				Never	73	1.0 (ref)		
				Ex	12	2.68 (1.25–5.76)		
				Current	40	1.18 (0.75–1.87)		

BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; ref, reference; yr, year or years.

ethnicity, and age (± 2.5 years). Among men and among women, compared with never drinking, there was a higher odds of right colon cancer for past drinking (OR, 2.6 for men; OR, 3.1 for women) and current drinking (OR, 1.8 for men; OR, 2.5 for women). [Compared with continuing consumption, the calculated odds ratio for cessation and right colon cancer was 1.44 (95% CI, 0.59–3.54) among men and 1.24 (95% CI, 0.27–5.66) among women.] Associations were similar for left colon cancer and for rectal cancer. [Compared with continuing consumption, the calculated odds ratios for cessation and left colon and rectal cancer ranged from 1.27 to 1.55. The strengths of this study are the population-based cases and controls. The limitations of this study are that the numbers of matched pairs in each category of never, past, and current drinking were not reported and that the associations were adjusted for pack-years of smoking but not for duration of smoking cessation or the amount of alcohol consumed.]

Tavani et al. (1998) conducted a hospital-based case–control study between 1991 and 1996 in six areas of Italy. The cases were men and women aged 24–74 years who were admitted to the major teaching and general hospitals with incident, histologically confirmed colon cancer (n = 1225) or rectal cancer (n = 728). The controls (n = 4154 men and women aged 20–74 years) were admitted to the same hospital as the cases for non-neoplastic diseases unrelated to alcohol consumption or tobacco use and did not have long-term dietary changes. Compared with never drinking, the odds ratio for former drinking was 1.20 (95% CI, 0.90–1.61) for colon cancer, 1.07 (95% CI, 0.74–1.54) for rectal cancer, and 1.15 (95% CI, 0.90–1.47) for colorectal cancer. Across categories of current amount of consumption, there was no clear pattern of association with any cancer site. [The calculated odds ratios for cessation compared with continuing consumption were 1.03 (95% CI, 0.79–1.35) for colon cancer, 0.93 (95% CI, 0.66–1.31) for rectal cancer, and 0.99 (95% CI, 0.79–1.25) for colorectal cancer. The strengths of this study are that there were > 50 cases in each ex-drinking category and the selection of hospital-based controls with conditions unrelated to alcohol consumption or tobacco use. The limitation of this study is that the associations were not adjusted for the amount of alcohol consumed or BMI.]

In a population-based case–control study in China (Ji et al., 2002), the cases were men and women, aged 30–74 years newly diagnosed between October 1990 and July 1992 with pathologically or clinically confirmed colon cancer (n = 462 men, n = 469 women) or rectal cancer (n = 463 men, n = 411 women) who had been identified through a rapid reporting system of the Shanghai Cancer Registry. The controls were 1552 men and women randomly selected from the Shanghai Resident Registry who were frequency-matched to cases on age and sex. Because there were 4 cases of rectal cancer among women in the ex-drinking category, results for rectal cancer among women are not shown. Among men, compared with non-drinking, there was no association between current drinking and risk of colon cancer (OR, 1.0; 95% CI, 0.8–1.3), but ex-drinking was associated with a higher risk (OR, 2.3; 95% CI, 1.4–3.7). Current drinking was associated with a lower risk of rectal cancer (OR, 0.6; 95% CI, 0.4–1.0), but there was no association for ex-drinking (OR, 1.1; 95% CI, 0.9–1.4). [Compared with continuing consumption, cessation was associated with a higher risk of colon cancer (calculated OR, 2.30; 95% CI, 1.40–3.77) and rectal cancer (calculated OR, 1.83; 95% CI, 1.15–2.93).] Among women, compared with non-drinking, the odds ratio for colon cancer for ex-drinking was 1.4 (95% CI, 0.4–4.3) and for current drinking was 0.7 (95% CI, 0.4–1.3). [Compared with continuing consumption, cessation was associated with a 2-fold higher risk of colon cancer among women (calculated OR, 2.00; 95% CI, 0.54–7.44). The strength of this study is that it was population-based. The limitations

of this study are that none of the categories of drinking status were defined, that it is unclear which smoking categories were controlled for, and that the associations were not adjusted for the amount of alcohol consumed.]

In a mixed hospital-based and population-based case–control study in China (Wei et al., 2009), the cases (*n* = 348 colon, *n* = 358 rectum) were men and women with sporadic colorectal cancer who were recruited from six hospitals in Guangzhou City between July 2002 and December 2008. Population-based controls (*n* = 723) were randomly selected from among 10 000 residents of Guangzhou City during the same time period and matched to cases on sex and age (± 5 years). Compared with non-drinking, the odds ratio for colorectal cancer and current drinking (OR, 8.61; 95% CI, 6.15–12.05) was higher than that for former drinking (OR, 2.30; 95% CI, 1.27–4.17). For colon cancer and rectal cancer separately, similar odds ratios were observed. [Compared with continuing consumption, cessation was associated with a lower risk of colorectal cancer (calculated OR, 0.27; 95% CI, 0.13–0.53), colon cancer (calculated OR, 0.33; 95% CI, 0.15–0.74), and rectal cancer (calculated OR, 0.23; 95% CI, 0.10–0.53). The strengths of this study are that it restricted cases to sporadic colorectal cancer and that all categories of drinking status were well described. The limitations of this study are that the cases were hospital-based and the controls were population-based, that no information was reported about histological or clinical confirmation of colorectal cancer, that no ICD codes were reported, that the numbers of colon cancer cases and rectal cancer cases within categories of drinking status were not reported, that there was limited information about selection of hospital-based controls, that the age distribution, but not the range, was reported, and that the associations were adjusted for smoking status but not for detailed smoking history or the amount of alcohol consumed.]

In a hospital-based study in the Republic of Korea (Lee et al., 2019), cases included men and women with histologically confirmed cancers of the proximal colon (*n* = 126 men, *n* = 61 women), distal colon (*n* = 179 men, *n* = 113 women), or rectum (*n* = 321 men, *n* = 125 women) who were recruited from the National Cancer Center between August 2010 and August 2013. The controls were men (*n* = 1878) and women (*n* = 897) who came for a health screening and were frequency-matched to cases (3 controls per case) on sex and 5-year age intervals. Among men, compared with never drinking, ex-drinking was associated with higher risks of colorectal, proximal and distal colon, and rectal cancer (OR range, 1.36–2.10), whereas for current drinking, the odds ratios ranged from 0.99 to 1.25. [Compared with continuing consumption, cessation was associated with a higher risk of colorectal cancer (calculated HR, 1.54; 95% CI, 1.08–2.20), proximal colon cancer (calculated OR, 1.68), distal colon cancer (calculated OR, 1.31), and rectal cancer (calculated OR, 1.65).] Among women, compared with never drinking, ex-drinking was also associated with a higher risk of colorectal cancer (OR, 2.54; 95% CI, 1.39–4.66), distal colon cancer (OR, 2.73), and rectal cancer (OR, 2.68); results for proximal colon cancer are not shown here because there were 3 cases in the ex-drinking category. For current drinking, the odds ratios ranged from 1.18 to 1.31. [Compared with continuing consumption, cessation was associated with a higher risk of colorectal cancer (calculated OR, 1.94; 95% CI, 1.03–3.64), distal colon cancer (OR, 2.29), and rectal cancer (OR, 2.27). The strengths of this study are that it was large and had a detailed analysis by colorectal cancer subsites. The limitations of this study are that there was limited information about selection of hospital-based controls, that definitions were not reported for categories of drinking status, that the reference time period for alcohol consumption and cancer diagnosis is unclear, that the age distribution, but not the range, was

reported, and that the associations were adjusted for pack-years of smoking but not for duration of smoking cessation or the amount of alcohol consumed.]

2.2.7 Liver cancer

Liver cancer (ICD-O-3 topography code C22) is the sixth most frequently occurring cancer in the world, but the most common cause of cancer deaths (Ferlay et al., 2020). Globally in 2020, the age-standardized (world population) incidence and mortality rates for liver cancer were 9.5 per 100 000 and 8.7 per 100 000, respectively (Ferlay et al., 2020). In most parts of the world, hepatocellular carcinoma (ICD-O-3 morphology codes 8170–8175) is the most common histological type of liver cancer (70–85%), followed by intrahepatic cholangiocarcinoma (10–15%). The major risk factors for hepatocellular carcinoma include chronic HBV and HCV infection, consumption of foods contaminated with aflatoxin B_1 (AFB_1), alcohol consumption, the related metabolic conditions of metabolic syndrome, obesity, type 2 diabetes, and non-alcoholic fatty liver disease (McGlynn et al., 2021), and tobacco smoking (IARC, 2012a). The relative contribution of the major risk factors varies by area of the world. In most countries in Asia and Africa with historically high rates of liver cancer, HBV and AFB_1 have been the dominant risk factors. The exceptions are Egypt and Japan, where HCV is the dominant risk factor. In North America and Europe, HCV and alcohol consumption are the dominant risk factors. Recently, non-alcoholic fatty liver disease has played an increasingly important role in hepatocellular carcinoma risk.

The majority of hepatocellular carcinomas arise in livers with pre-existing liver damage, which starts with mild fibrosis. Fibrosis progresses to compensated cirrhosis (i.e. asymptomatic cirrhosis), then to decompensated cirrhosis (i.e. cirrhosis complicated by ascites, jaundice, variceal haemorrhage, or hepatic encephalopathy), and finally to hepatocellular carcinoma. Whether an intervention can prevent hepatocellular carcinoma depends on the severity of the underlying liver damage at the time of the intervention.

(a) Cohort studies

(i) General population studies

Among the five general population cohort studies, the associations of reduction and cessation of alcoholic beverage consumption with risk of liver cancer were assessed in one study (Yoo et al., 2022), the duration of cessation and cessation were assessed in a cohort study of liver cancer incidence (Goodman et al., 1995) and in another cohort study of liver cancer mortality (Ozasa et al., 2007), and cessation only was assessed in two other cohort studies (Nakaya et al., 2005; Im et al., 2021b). All five studies were conducted among populations in Asia, and none of the studies assessed associations with hepatocellular carcinoma specifically (Table 2.26; Supplementary Table S2.27, web only; available from https://publications.iarc.who.int/638).

In the study of Yoo et al. (2022) (described in Section 2.2.3), among the men and women included in the analysis, 15 333 cases of liver cancer were identified during the follow-up time. In analyses of alcohol reduction, compared with stable moderate consumption, the hazard ratio was 1.10 (95% CI, 1.00–1.21) for reduction from moderate consumption in 2009 to mild consumption in 2011. Compared with stable heavy consumption, the hazard ratio for reduction from heavy to mild consumption was 1.11 (95% CI, 0.96–1.28) and for reduction from heavy to moderate consumption was 1.11 (95% CI, 0.99–1.26). Compared with stable mild, stable moderate, and stable heavy consumption, the hazard ratios for cessation from each level of consumption in 2009 to none in 2011 were 0.99 (95% CI, 0.92–1.06), 1.25 (95% CI, 1.10–1.43), and 1.39 (95% CI, 1.20–1.62), respectively. [The strengths and limitations of this study

Table 2.26 Cohort studies of reduction, duration of cessation, and cessation of alcoholic beverage consumption and risk of liver cancer

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
General populations								
Goodman et al. (1995) Japan Life Span Study of Hiroshima and Nagasaki 1980–1989	Analysis included men who were Nagasaki and Hiroshima atomic bomb survivors and completed the 1978 questionnaire; followed up from 1980 (men) through 1989 (mean, 8.6 yr); cancer cases ascertained by tumour registry linkage supplemented with death certificate review	Self-administered questionnaire Drinking status: never was no consumption ever; current and ex were self-reported but were not defined further Duration of cessation: definition was not reported	Liver (ICD-O code 155.0)	Drinking status			Sex, city, age at the time of bombings, attained age, and radiation dose to the liver	No data were reported about HBV or HCV No adjustment for amount of alcohol consumed or smoking
				Never	25	1.0 (ref)		
				Current	100	0.98 (0.63–1.52)		
				Ex-drinking	25	2.33 (1.34–4.07)		
				Duration of cessation				
				≤ 10 yr	12	7.87 (3.89–16.0)		
				11–15 yr	8	2.08 (0.93–4.67)		
				≥ 16 yr	4	0.96 (0.33–2.77)		
Nakaya et al. (2005) Japan 1990–1997	Analysis included n = 21 201 men aged 40–64 yr who lived in 14 municipalities in Miyagi Prefecture; follow-up time from June 1990 through 1997 (up to 7.6 yr); cancer cases ascertained by registry linkage	Self-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	Liver (no ICD codes reported)	Drinking status			Age, smoking (never, past, and 3 categories of current number of cigarettes per day), education, daily orange juice and other fruit juice intake, and spinach, carrot, pumpkin, and tomato intake	No data were reported about HBV or HCV No adjustment for amount of alcohol consumed
				Never	3	1.0 (ref)		
				Ex-drinking	10	6.6 (1.8–24.2)		
				Current	35	2.7 (0.8–8.9)		

Table 2.26 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Ozasa et al. (2007) Japan Japan Collaborative Cohort Study for Evaluation of Cancer Risk 1988–2003	Analysis included *n* = 46 178 men and *n* = 63 600 women aged 40–79 yr, living in 1 of 45 areas of Japan, who were cancer-free; follow-up time from 1988 through 2003 (except in 3 areas, where follow-up was through 1999) (Tamakoshi et al., 2007); cause of death ascertained by death certificate review (Ogimoto et al., 2004)	Self-administered questionnaire (Ogimoto et al., 2004) Drinking status: no definitions were reported for categories of drinking status Duration of cessation: self-reported	Liver and intrahepatic bile duct (ICD-10 code C22)		Deaths		Age and area of study	No data were reported about HBV or HCV No adjustment for amount of alcohol consumed or smoking
				Drinking status	Men			
				Rare/none	79	1.0 (ref)		
				Drinking	271	0.89 (0.69–1.15)		
				Ex-drinking	79	3.16 (2.32–4.31)		
					Women			
				Rare/none	141	1.0 (ref)		
				Drinking	36	0.83 (0.57–1.21)		
				Ex-drinking	10	2.89 (1.51–5.53)		
				Duration of cessation	Men			
				Rare/none	79	1.0 (ref)		
				< 5 yr	19	3.79 (2.24–6.42)		
				5–15 yr	26	4.56 (2.83–7.33)		
				≥ 15 yr	10	2.43 (1.23–4.79)		
					Women			
				Rare/none	141	1.0 (ref)		
				< 5 yr	1	1.58 (0.22–11.40)		
				5–15 yr	5	7.53 (3.04–18.70)		
				≥ 15 yr	1	1.92 (0.26–13.80)		

Table 2.26 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Im et al. (2021b) China China Kadoorie Biobank 2004–2016	Analysis included *n* = 201 039 men and *n* = 291 604 women aged 30–79 yr recruited from 10 areas of China during 2004–2008; follow-up time from 2004 through 2016 (median, 10 yr); 3% HBsAg+; cancer cases ascertained by linkage with cancer registries and the national health insurance databases	Interviewer-administered questionnaire Drinking status: abstain was no drinking in the past year or in most weeks prior; ex-regular was drinking < weekly in the past year but drinking ≥ weekly prior; occasional was drinking < weekly in the past year and prior; current regular was drinking in most weeks in the past year	Liver and intrahepatic bile duct (ICD-10 code C22)	Drinking status	Men		Education, household income, smoking (never, occasional, and for ever smoked, 3 categories of cigarettes per day in men and 2 in women), BMI, and physical activity	Floating standard errors were used to estimate the CIs; abstention was the reference category No data were reported about HCV No adjustment for amount of alcohol consumed
				Abstain	365	1.00 (0.90–1.12)		
				Ex-regular	203	1.24 (1.08–1.43)		
				Occasional	477	0.86 (0.78–0.94)		
				Current regular	547	1.07 (0.98–1.17)		
					Women			
				Abstain	679	1.00 (0.90–1.11)		
				Ex-regular	13	1.04 (0.59–1.81)		
				Occasional	227	0.78 (0.68–0.90)		
				Current regular	20	0.84 (0.54–1.31)		
Yoo et al. (2022) Republic of Korea NHIS 2009–2018	Analysis included *n* = 4 513 746 men and women aged ≥ 40 yr with drinking status data from 2 consecutive (2009 and 2011) biennial NHIS health screenings; follow-up time through 2018 (median, 6.4 yr); cancer cases ascertained through the NHIS billing system	Self-administered questionnaires in 2009 and 2011 Alcohol intake in 2009 and 2011: for each survey, alcohol intake was first classified by amount of ethanol consumed: none, mild (< 15 g/day), moderate (15–29.9 g/day), and heavy (≥ 30 g/day); then associations for each level of consumption in 2011 were stratified on level of consumption in 2009;	Liver and intrahepatic bile duct (ICD-10 code C22)	Alcohol intake in 2009/2011	15 333 total		Age, sex, socioeconomic position, smoking status, physical activity, comorbidities (hypertension, diabetes, dyslipidaemia, chronic kidney disease, and chronic obstructive pulmonary disease), and Charlson Comorbidity Index	Excluded the first year of follow-up time No information about alcohol consumption before the first wave of reporting Limited follow-up time No data were reported about HBV or HCV
				None/none		1.0 (ref)		
				None/mild		1.12 (1.04–1.21)		
				None/moderate		1.26 (1.09–1.46)		
				None/heavy		1.15 (1.00–1.33)		
				Mild/none		0.99 (0.92–1.06)		
				Mild/mild		1.0 (ref)		
				Mild/moderate		1.03 (0.93–1.14)		
				Mild/heavy		0.91 (0.80–1.03)		

Table 2.26 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Yoo et al. (2022) (cont.)		the reference group for each stratum was the stable group at each level of consumption (e.g. 2009/2011 none/ none)		Moderate/none		1.25 (1.10–1.43)		
				Moderate/mild		1.10 (1.00–1.21)		
				Moderate/moderate		1.0 (ref)		
				Moderate/heavy		0.89 (0.80–0.99)		
				Heavy/none		1.39 (1.20–1.62)		
				Heavy/mild		1.11 (0.96–1.28)		
				Heavy/moderate		1.11 (0.99–1.26)		
				Heavy/heavy		1.0 (ref)		
Special populations with underlying liver disease not confined to alcohol-related cirrhosis								
Kato et al. (1992) Japan 1987–1990	Analysis included men and women aged ≥ 16 yr with decompensated cirrhosis (*n* = 70 liver cancer cases and *n* = 815 non-cases); followed up through record linkage from August 1987 through August 1990 (up to 3 yr); cancer cases ascertained by cancer registry linkage	Self-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	Liver (no ICD-O codes reported)	Drinking status	Cirrhosis group		Sex and age	Study population limited to individuals who needed financial assistance Some participants were tested for HBV Limited follow-up time No adjustment for amount of alcohol consumed or smoking
				Never	46	1.0 (ref)		
				Past	19	0.58 (0.32–1.04)		
				Occasional	4	0.43 (0.15–1.24)		
				Current	5	0.41 (0.16–1.06)		

Table 2.26 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Tsukuma et al. (1993) Japan 1987–1991	Analysis included n = 917 men and women aged 40–69 yr with chronic hepatitis (n = 677) or compensated cirrhosis (n = 240); followed up at a clinic in Osaka from May 1987 through September 1991 (mean, 35.7 months); cancer cases ascertained through clinical diagnosis (some histologically confirmed); 8.7% HBsAg+, 47.2% HCV+	Interviewer-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	HCC (no ICD codes reported)	Drinking status	54 total		Age, sex, stage of disease, AFP levels, hepatitis virus markers, and smoking status (current, ex, non)	Limited follow-up time No adjustment for amount of alcohol consumed
				Non-drinking		1.0 (ref)		
				Current ≥ 80 g/day		1.15 (0.35–3.78)		
				Current < 80 g/day		1.10 (0.39–3.07)		
				Former ≥ 80 g/day		1.66 (0.69–3.96)		
				Former < 80 g/day		1.46 (0.56–3.79)		
				Occasional		0.77 (0.20–2.99)		
Tanaka et al. (2008) Japan 1985–1995	Analysis included n = 96 men and women aged 40–69 yr with cirrhosis who were inpatients or outpatients at 1 hospital; followed up from enrolment in 1985–1987 through 1995 (mean, 5.3 yr); most participants HBV+ or HCV+; cancer cases ascertained clinically (Tanaka et al., 1998)	Interviewer-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	HCC (no ICD code reported)	Drinking status			Sex, age, years since cirrhosis diagnosis, department, hospitalization status, serum albumin, AST, AFP, HBsAg, anti-HCV, and smoking	Limited follow-up time No adjustment for amount of alcohol consumed Unclear what categories of smoking were controlled for
				Never	16	1.0 (ref)		
				Past	17	0.59 (0.20–1.73)		
				Current				
				< 2.4 drinks/day	1	0.06 (0.01–0.57)		
				≥ 2.4 drinks/day	3	0.17 (0.02–1.42)		

Table 2.26 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Special populations with underlying liver disease confined to alcohol-related cirrhosis								
Rodríguez et al. (2021) Spain 1992–2019	Analysis included n = 727 men and women aged 35–80 yr with alcohol-related cirrhosis (n = 480 with prior decompensated cirrhosis; n = 247 with compensated cirrhosis) participating in an HCC screening programme; cancer cases ascertained clinically per study protocol	Interviewer-administered questionnaire Drinking status: abstinent was no alcohol consumption within 3 months before study enrolment and maintaining abstinence during follow-up time	HCC (no ICD code reported)	Drinking status	All		Age, sex, anti-HBc, anti-AST, platelets, Child–Pugh score, and AFP	In a competing risk analysis, there was a higher risk of death for non-abstinent compared with abstinent among all participants and among those with prior decom-pensated cirrhosis No adjust-ment for amount of alcohol consumed
				Non-abstinent	52	1.0 (ref)		
				Abstinent	52	0.80 (0.53–1.19)		
					With prior decompensated cirrhosis			
				Non-abstinent	32	1.0 (ref)	Age, sex, AST, platelets, Child–Pugh score, and tobacco use status	
				Abstinent	46	0.95 (0.59–1.52)		
					No prior decompensated cirrhosis			
				Non-abstinent	20	1.0 (ref)	Albumin and prothrombin activity	
				Abstinent	6	0.35 (0.13–0.94)		

AFP, α-fetoprotein; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; HBc, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD, International Classification of Diseases; NHIS, National Health Insurance Service; ref, reference; yr, year or years.

are described in Section 2.2.3. For liver cancer, another limitation is that no data on HBV or HCV were reported.]

Goodman et al. (1995) assessed duration of cessation and cessation in relation to risk of liver cancer in the Life Span Study, which originally included about 120 000 men and women who were exposed or unexposed to atomic bomb radiation and were residents of Hiroshima and Nagasaki (Japan) in 1950. The alcohol analysis included data from 36 133 men and women who returned the 1978 survey. Among women, associations were not reported for ex-drinking and current drinking separately; therefore, results for cessation and duration of cessation were reported only for men. During the follow-up from 1980 until the end of 1989 (mean, 8.6 years), 156 incident cases of liver cancer among the men included in the analysis were identified through linkage with population-based cancer registries, which was supplemented by death certificate review. Compared with never drinking, the relative risk for current drinking was 0.98 (95% CI, 0.63–1.52) and for ex-drinking was 2.33 (95% CI, 1.34–4.07). The higher risk associated with ex-drinking decreased with longer duration of cessation; relative risks were 7.87 (95% CI, 3.89–16.0) for ≤ 10 years of cessation and 0.96 (95% CI, 0.33–2.77) for ≥ 16 years of cessation. [Compared with continuing consumption, cessation was associated with a higher risk of liver cancer (calculated RR, 2.38; 95% CI, 1.53–3.70). Calculated relative risks decreased across categories of longer duration of cessation but remained ≥ 1 (calculated RRs were 8.03; 95% CI, 4.39–14.70 for ≤ 10 years of cessation and 0.98; 95% CI, 0.36–2.70 for ≥ 16 years of cessation). The strength of this study is that in a sensitivity analysis, the results were similar after excluding the first 2 years of follow-up time. The limitations of this study are that participants' age range was not reported, that the number of men and women was not reported separately, that the associations were not adjusted for smoking or the amount of alcohol consumed, that the follow-up time was limited (mean, 8.6 years), that no data were reported about HBV or HCV, although HCV testing was only implemented in the early 1990s, and that among men there were few cases in the 11–15 years of cessation category (n = 8) and the ≥ 16 years of cessation category (n = 4).]

The JACC study was described in Section 2.2.4. In the JACC study that assessed the association of alcohol consumption with risk of cause-specific mortality, 690 liver cancer deaths (n = 463 men, and n = 227 women) were identified during the follow-up time until 2003 (except in three areas, where follow-up was until 1999) (Ozasa et al., 2007; Tamakoshi et al., 2007). Compared with rare/none, the hazard ratio for drinking was 0.89 (95% CI, 0.69–1.15) among men and 0.83 (95% CI, 0.57–1.21) among women. Ex-drinking was associated with a higher risk of death from liver cancer among both men (HR, 3.16; 95% CI, 2.32–4.31) and women (HR, 2.89; 95% CI, 1.51–5.53). [Cessation was associated with higher liver cancer mortality compared with continuing consumption among both men (calculated HR, 3.55; 95% CI, 2.76–4.57) and women (calculated HR, 3.48; 95% CI, 1.71–7.10).] Compared with rare/none, there was a higher risk of death from liver cancer in all categories of duration of cessation among men (HR 3.79; 95% CI, 2.24–6.42 for < 5 years of cessation and 2.43; 95% CI, 1.23–4.79 for > 15 years of cessation). [Compared with continuing consumption, the risk of death from liver cancer remained higher for all categories of duration of cessation (calculated HR 4.26; 95% CI, 2.63–6.88 for < 5 years of cessation and 2.73; 95% CI, 1.43–5.23 for > 15 years of cessation).] Among women, compared with rare/none, the risk of death from liver cancer was higher across all categories of duration of cessation (HR, 1.58; 95% CI, 0.22–11.40 for < 5 years and HR, 1.92; 95% CI, 0.26–13.80 for > 15 years of cessation). There were too few deaths from liver cancer among women who reported former drinking (n = 7) to

assess associations for categories of duration of cessation compared with continuing consumption. [The strengths and limitations of this study are described in Section 2.2.4. For liver cancer, an additional limitation is that no data were reported about HBV or HCV.]

Nakaya et al. (2005) assessed the association between alcohol cessation and risk of liver cancer among 21 201 men aged 40–64 years from 14 municipalities enrolled in Miyagi Cohort 2 (described in Section 2.2.4). For the analysis for liver cancer, follow-up time was from enrolment in 1990 until 1997, during which 48 cases of liver cancer were identified by cancer registry linkage. Compared with never drinking, the relative risk for current drinking was 2.7 (95% CI, 0.8–8.9) and for ex-drinking was 6.6 (95% CI, 1.8–24.2). [Compared with continuing consumption, cessation was associated with a higher risk of liver cancer (calculated RR, 2.44; 95% CI, 1.20–4.99). The strength of this study is that in an analysis of risk of all cancers, a sensitivity analysis excluding all cancer cases diagnosed during the first 3 years of follow-up time showed a positive association with alcohol consumption. The limitations of this study are that no definitions were reported for any categories of drinking status, that no data were reported about HBV or HCV, that no ICD codes were reported, so it is unlikely that the analysis was restricted to hepatocellular carcinoma, that the associations were not adjusted for the amount of alcohol consumed, that the follow-up time was limited (up to 7.6 years), that there were few cases in the never-drinking category (n = 3) and the ex-drinking category (n = 10), and that the sensitivity analysis that excluded cancer cases diagnosed during the first 3 years of follow-up time did not report results for liver cancer specifically.]

The China Kadoorie Biobank was described in Section 2.2.1. A separate report of the China Kadoorie Biobank that was focused specifically on liver cancer included 201 039 men and 291 604 women, among whom 2531 cases of liver cancer (n = 1592 men, n = 939 women) were identified during the follow-up time (Im et al., 2021b). Compared with abstaining, the hazard ratio for current-regular drinking was 1.07 (95% CI, 0.98–1.17) among men and 0.84 (95% CI, 0.54–1.31) among women. Compared with abstaining, the hazard ratio for ex-drinking was 1.24 (95% CI, 1.08–1.43) among men and 1.04 (95% CI, 0.59–1.81) among women. In a sensitivity analysis that excluded the first 3 years of follow-up time among men, the hazard ratio for ex-drinking compared with abstaining was 1.18 (95% CI, 0.98–1.42). [Compared with continuing consumption, the calculated hazard ratio for cessation was 1.16 (95% CI, 0.98–1.37) among men and 1.24 (95% CI, 0.61–2.53) among women. The strengths of this study are that it was very large and had a population-based cohort, that a sensitivity analysis was conducted excluding the first 3 years of follow-up time, and that a test of the proportional hazards assumption showed no evidence of departure from proportionality. The limitations of this study are that the data on HCV were not reported and that no adjustment was made for the amount of alcohol consumed.]

(ii) Special population studies among individuals with underlying liver disease not confined to alcohol-related cirrhosis

Cessation of alcoholic beverage consumption and risk of liver cancer was assessed in three cohort studies (all in Japan) of individuals with underlying liver disease that was not confined to alcohol-related cirrhosis (Kato et al., 1992; Tsukuma et al., 1993; Tanaka et al., 2008) (Table 2.26; Supplementary Table S2.27, web only; available from https://publications.iarc.who.int/638).

Kato et al. (1992) conducted a follow-up study of 1068 individuals with decompensated cirrhosis and 248 individuals with post-transfusion hepatitis who were part of an original cohort of 2235 residents of Aichi Prefecture aged ≥ 16 years by 31 March 1987 that was assembled by the local

government to subsidize the medical expenses of individuals in need of financial support. Drinking history was obtained with a questionnaire mailed in August 1987, and liver cancer cases diagnosed until August 1990 were identified by linkage to the Aichi Cancer Registry. Only 3 cases of liver cancer were identified among individuals with post-transfusion hepatitis; therefore, associations with alcohol consumption were not reported for this group. Among the individuals with decompensated cirrhosis, alcohol data were available for 70 cases and 815 non-cases. In the group with decompensated cirrhosis, compared with never drinking, the relative risk for current drinking was 0.41 (95% CI, 0.16–1.06) and the relative risk for former drinking was 0.58 (95% CI, 0.32–1.04). [The calculated relative risk for cessation compared with continuing consumption was 1.41 (95% CI, 0.49–4.05). The strength of this study is that the cancer cases were ascertained through the population-based cancer registry. The limitations of this study are that the cohort included only individuals who needed financial assistance, so it may not be representative of the underlying population, that no definitions were reported for any categories of drinking status, that it is unclear whether cases were limited to hepatocellular carcinoma because ICD codes were not reported, that only some of the participants were tested for HBV (HCV testing was not yet available when the study was conducted), that the follow-up time was limited (up to 3 years) and the total period of follow-up time was unclear because participants had to re-enrol in the cohort on an annual basis in order to not be lost to follow-up, and that the associations were not adjusted for smoking or the amount of alcohol consumed.]

Tsukuma et al. (1993) conducted a study that included 917 men and women aged 40–69 years with either chronic hepatitis ($n = 677$) or compensated cirrhosis ($n = 240$) who were outpatients at a hospital in Osaka. Participants were enrolled from May 1987 to March 1991, and during follow-up until September 1991 (mean follow-up time, 35.7 months), 54 cases of hepatocellular carcinoma were identified through clinical diagnosis; individuals who were diagnosed with hepatocellular carcinoma within 3 months of study enrolment were excluded from the analysis. Compared with non-drinking, the hazard ratio for current drinking of < 80 g per day was 1.10 (95% CI, 0.39–3.07) and for current drinking of ≥ 80 g per day (heavy) was 1.15 (95% CI, 0.35–3.78). Compared with non-drinking, the hazard ratio for former drinking of < 80 g per day was 1.46 (95% CI, 0.56–3.79) and for former drinking of ≥ 80 g per day was 1.66 (95% CI, 0.69–3.96). [The calculated hazard ratio for cessation compared with continuing consumption was 1.40 (95% CI, 0.51–3.84).] In a subgroup analysis restricted to the compensated cirrhosis group, compared with non-drinking the hazard ratio for former drinking of ≥ 80 g per day was 3.75 ($P = 0.04$) and for current drinking of ≥ 80 g per day was 1.32 ($P = 0.75$). The data were not shown for chronic hepatitis. [The strengths of this study are that the participants were tested for HBV and HCV and that hepatocellular carcinoma was determined clinically and histologically. The limitations of this study are that no participation rate was provided and no definitions were reported for any categories of drinking status, that the distribution of cases by drinking status was not reported, that the follow-up time was limited (35.7 months), and that the associations were not adjusted for the amount of alcohol consumed.]

Another cohort study in Japan included 96 prevalent and incident inpatients and outpatients with cirrhosis (men and women), the majority of whom were positive for HBV or HCV, who were seen at one hospital in Fukuoka in 1985–1987 and followed up until 1995 (mean follow-up time, 5.3 years) (Tanaka et al., 1998). Individuals with biliary cirrhosis or cirrhosis due to autoimmune hepatitis, parasitosis, congestive heart failure, or metabolic disorders were excluded. Among 41 cases of hepatocellular carcinoma clinically

diagnosed or verified via medical records during the follow-up time, 37 were included in the analysis. The association between alcohol cessation and risk of liver cancer was reported in Tanaka et al. (2008). Compared with never drinking, the relative risk for current drinking of < 2.4 drinks per day was 0.06 (95% CI, 0.01–0.57) and for current drinking of ≥ 2.4 drinks per day was 0.17 (95% CI, 0.02–1.42). The relative risk for former compared with never drinking was 0.59 (95% CI, 0.20–1.73). [Compared with any amount of continuing consumption, the calculated relative risk for cessation was 6.00 (95% CI, 0.97–37.09). The strengths of this study are that complete follow-up information was available for all members of the cohort and that all participants were tested for HBV and some were also tested for HCV. The limitations of this study are that the cohort included individuals with both incident and prevalent cirrhosis, that reasons for excluding certain types of cirrhosis were not specified, that the follow-up time was limited (mean, 5.3 years), that it is unclear what categories of smoking were controlled for, that the associations were not adjusted for the amount of alcohol consumed, that there was no sensitivity analysis excluding at least the first year of follow-up time and no test of the proportional hazards assumption, and that there were few cases in the current-drinking categories (n = 4 total).]

(iii) Special population studies among individuals with underlying liver disease confined to alcohol-related cirrhosis

The associations of cessation of alcoholic beverage consumption with risk of liver cancer were assessed in hepatocellular carcinoma surveillance in Spain (Rodríguez et al., 2021) (Table 2.26; Supplementary Table S2.27, web only; available from https://publications.iarc.who.int/638). The study included men and women (n = 743) aged 35–80 years with alcohol-related compensated cirrhosis (n = 247) and decompensated cirrhosis (n = 480) who were enrolled in 1992–2004. During follow-up until 30 July 2019 (median, 54 months), 104 cases of hepatocellular carcinoma were ascertained through clinical diagnosis among the 727 men and women included in the analysis. (n = 16 participants diagnosed with hepatocellular carcinoma within 12 months of enrolment were excluded from analysis). Among all participants, the hazard ratio for abstinence during the follow-up time compared with non-abstinence was 0.80 (95% CI, 0.53–1.19). In stratified analysis, among participants with previous decompensated cirrhosis, the hazard ratio for abstinence was 0.95 (95% CI, 0.59–1.52), whereas among participants with compensated cirrhosis, the hazard ratio was 0.35 (95% CI, 0.13–0.94). A competing risk analysis found a higher risk of death among non-abstinent individuals in the analysis of all participants (P < 0.001) and in the analysis restricted to the decompensated group (P < 0.001) but not the compensated group (P = 0.31). [The strengths of this study are that the cirrhosis compensation status of all participants was determined, that cases of hepatocellular carcinoma were clinically diagnosed, that the analysis excluded all cases diagnosed during the first year of follow-up time, that competing risk analyses were conducted, and that the abstinence category included participants who maintained abstinence during the follow-up time. The limitations of this study are that the reasons for stopping follow-up due to development of severe cirrhosis or severe comorbidity were not provided, that the associations were not adjusted for the amount of alcohol consumed, that in the analysis of participants with compensated cirrhosis, there were few cases of hepatocellular carcinoma in the abstinence category (n = 6), and that there was no test of the proportional hazards assumption.]

(b) Case–control studies

The associations of duration of cessation and cessation of alcoholic beverage consumption with risk of hepatocellular carcinoma were assessed in

two case–control studies in Italy (Donato et al., 2002; Franceschi et al., 2006). Cessation only was assessed in a hospital-based case–control study in Japan (Sakamoto et al., 2006) (Supplementary Table S2.27, web only; available from https://publications.iarc.who.int/638; Table 2.28).

Donato et al. (2002) assessed duration of cessation and cessation and risk of histologically or clinically confirmed hepatocellular carcinoma in a hospital-based case–control study in Italy. The cases (n = 380 men, n = 84 women) were aged 40–75 years and ascertained from admissions to two hospitals in Brescia, Italy, between January 1995 and April 2000. The controls (n = 824) were selected from among inpatients not hospitalized due to an injury and with conditions unrelated to liver disease or any cancer and were frequency-matched to cases on age, sex, hospital, and date of hospital admission. Compared with never drinking, there was a higher odds of liver cancer for current drinking among men (OR, 2.7; 95% CI, 1.1–6.8) but not among women (OR, 0.9; 95% CI, 0.3–2.3). Among both men and women, there was a higher odds of liver cancer for former drinking compared with never drinking (OR, 8.5; 95% CI, 3.3–22.3 among men and OR, 2.8; 95% CI, 1.0–7.9 among women). [Compared with current drinking, cases were more likely than controls to report former drinking among both men (calculated OR, 3.15; 95% CI, 2.25–4.41) and women (calculated OR, 3.11; 95% CI, 1.08–8.94).] Among men, compared with current drinking, the odds ratios decreased with longer duration of cessation but remained > 1 (OR, 5.0; 95% CI, 2.9–8.6 for 1–5 years of cessation and OR, 1.4; 95% CI, 0.6–3.1 for > 15 years of cessation). Among women, compared with current drinking, the odds ratios for duration of alcohol cessation were 3.0 (95% CI, 0.6–15.2) for 1–5 years of cessation, 1.9 (95% CI, 0.2–19.2) for 11–15 years of cessation, and 8.6 (95% CI, 1.3–56.0) for > 15 years of cessation. [The strengths of this study are that the control group was well described, that HBV and HCV status was assessed, and that definitions for categories of current and former drinking were reported. The limitations of this study are that the control group excluded individuals with liver disease, so it may not be representative of the underlying population, that there were few women with hepatocellular carcinoma in the 11–15 years of cessation category (n = 3) and > 15 years of cessation category (n = 7), and that the associations were not adjusted for smoking or the amount of alcohol consumed.]

Franceschi et al. (2006) conducted a hospital-based case–control study that included 229 histologically or clinically confirmed cases of hepatocellular carcinoma and 431 hospital-matched controls aged < 85 years admitted to hospitals in two regions of Italy between January 1999 and July 2002. Compared with never drinking, the odds ratio for current drinking was 0.84 (95% CI, 0.39–1.83) and for former drinking was 3.98 (95% CI, 1.74–9.09). In an analysis of duration of alcohol cessation, the odds ratio for < 5 years of cessation was 6.34 (95% CI, 1.92–21.04) and for ≥ 5 years of cessation was 2.56 (95% CI, 0.96–6.82). [Compared with continuing consumption, cessation was associated with a higher risk (calculated OR, 4.74; 95% CI, 2.69–8.36). The strengths of this study are that all cases of hepatocellular carcinoma were histologically or clinically diagnosed, that HBV and HCV status was assessed, and that selection of hospital-based controls included patients with conditions thought to be unrelated to smoking, alcohol consumption, or hepatitis virus infection. The limitations of this study are that the control group excluded individuals with certain underlying medical conditions, so it may not be representative of the underlying population, that the timing of questionnaire administration to the controls was not specified, that the cases and controls were not matched on date of hospital admission, and that the associations were not adjusted for smoking or the amount of alcohol consumed.]

Table 2.28 Case–control studies of duration of cessation and cessation of alcoholic beverage consumption and risk of liver cancer

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Donato et al. (2002) Italy 1995–2000	Men (n = 380) and women (n = 84) aged 40–< 76 yr with histologically or clinically confirmed HCC; ascertained from 2 main hospitals in Brescia, Italy; high proportion tested HBV+ and HCV+; 93.5% participation rate	Hospital-based controls (n = 686 men, n = 138 women) aged 40–< 76 yr; born in Italy, admitted to same hospitals as cases but with no hepatic disease; frequency-matched on age (± 5 yr), sex, and date and hospital of admission during which HBV and HCV testing was performed; 96.1% participation rate	Interviewer-administered questionnaire Drinking status: never was not defined; current was drinking at time of interview; former was abstaining ≥ 1 yr before assessment Duration of cessation: difference between self-reported date of abstinence and interview date	Drinking status	Men		Age, residence, HBsAg, and HCV RNA	Limited information about selection of hospital-based controls No adjustment for amount of alcohol consumed or smoking
				Never	8	1.0 (ref)		
				Former	151	8.5 (3.3–22.3)		
				Current	221	2.7 (1.1–6.8)		
				Duration of cessation				
				0 yr [current]	221	1.0 (ref)		
				1–5 yr	66	5.0 (2.9–8.6)		
				6–10 yr	51	4.0 (2.2–7.4)		
				11–15 yr	14	1.6 (0.6–4.5)		
				> 15 yr	20	1.4 (0.6–3.1)		
				Drinking status	Women			
				Never	24	1.0 (ref)		
				Former	31	2.8 (1.0–7.9)		
				Current	29	0.9 (0.3–2.3)		
				Duration of cessation				
				0 yr [current]	29	1.0 (ref)		
				1–5 yr	9	3.0 (0.6–15.2)		
				6–10 yr	12	2.7 (0.5–13.6)		
				11–15 yr	3	1.9 (0.2–19.2)		
				> 15 yr	7	8.6 (1.3–56.0)		

Table 2.28 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Franceschi et al. (2006) Italy 1999–2002	Men and women (n = 229) aged 43–84 yr; histologically, cytologically, or other clinically confirmed HCC cases; ascertained from 7 hospitals in Italy; tested for HBV and HCV (HCV highly prevalent); 99% participation rate	Hospital-based controls (n = 431 men and women) frequency-matched on age (≥ 40–< 85 yr) and sex; admitted to the same hospitals as cases with conditions unrelated to alcohol consumption or tobacco or had any comorbid condition that resulted in lifestyle changes; 99% participation rate	Questionnaire Drinking status: never was lifetime abstention; former was abstaining for ≥ 12 months before completing the questionnaire Duration of cessation: definition was not reported	Drinking status	All		Age, sex, hospital, education, HBV, and HCV	Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol consumption No adjustment for amount of alcohol consumed or smoking
				Never	20	1.0 (ref)		
				Former	118	3.98 (1.74–9.09)		
				Current	91	0.84 (0.39–1.83)		
				Duration of cessation				
				Never	20	1.0 (ref)		
				< 5 yr	46	6.34 (1.92–21.04)		
				≥ 5 yr	72	2.56 (0.96–6.82)		
Sakamoto et al. (2006) Japan 2001–2004	Men and women (n = 209) aged 40–79 yr with clinically diagnosed HCC; ascertained from 2 hospitals in Saga City, Japan; tested for HBV and HCV; 92% participation rate	Hospital-based controls: Control group 1: n = 275 (men and women); outpatients at same hospitals as cases (73% response) Control group 2: n = 381 (men and women), inpatients or outpatients with chronic liver disease at same hospitals as cases and enrolled in another study; 96% participation rate	Interview-administered questionnaire Drinking status: never was lifetime abstention or had consumed alcohol < once per week for < 1 yr; former was quit alcohol consumption ≥ 1 yr before the interview; current was any other status	Drinking status	Control group 1		Age, sex, smoking status (never, former, current), HBsAg, and anti-HCV	Limited information about selection of hospital-based controls No adjustment for amount of alcohol consumed
				Never	78	1.0 (ref)		
				Former	50	5.3 (1.6–18.6)		
				Current	81	2.9 (1.2–7.4)		
					Control group 2			
				Never	78	1.0 (ref)		
				Former	50	1.3 (0.7–2.2)		
				Current	81	1.8 (1.0–3.0)		

CI, confidence interval; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ref, reference; yr, year or years.

Sakamoto et al. (2006) conducted a hospital-based case–control study that enrolled 209 histologically or clinically confirmed cases of hepatocellular carcinoma, aged 40–79 years, from two hospitals in Saga City (Japan) between 2001 and 2004, and two control groups. Control group 1 was composed of 275 outpatients who were consecutively seen at the hospital clinics and control group 2 was composed of 381 inpatients and outpatients with chronic liver disease (CLD), except biliary cirrhosis, autoimmune hepatitis, or liver disease related to parasitosis, congestive heart failure, or metabolic disorders. Compared with the outpatient controls, the cases were more likely to report current drinking (OR, 2.9; 95% CI, 1.2–7.4) or former drinking (OR, 5.3; 95% CI, 1.6–18.6) than never drinking. Compared with the CLD controls, the odds ratio was 1.8 (95% CI, 1.0–3.0) for current drinking and 1.3 (95% CI, 0.7–2.2) for former drinking. [Compared with continuing consumption, the calculated odds ratio for cessation was 1.83 (95% CI, 0.52–6.41) in analyses with outpatient controls and 0.72 (95% CI, 0.39–1.34) in analyses of CLD controls. The strengths of this study are that all cases of hepatocellular carcinoma were histologically or clinically diagnosed and that HBV and HCV status were assessed. The limitations of this study are that reasons for excluding some liver diseases from the CLD control group were not reported and the exclusion may have resulted in a non-representative control group, that the CLD control group was composed of both inpatients and outpatients, that the percentage of inpatients versus outpatients in the CLD control group was not reported, and that the associations were not adjusted for the amount of alcohol consumed.]

2.2.8 Female breast cancer

Breast cancer (ICD-10 code C50) is the cancer most commonly diagnosed among women globally (Arnold et al., 2022). Globally in 2020, the age-standardized (world population) incidence and mortality rates for female breast cancer were 47.8 per 100 000 and 13.6 per 100 000, respectively (Ferlay et al., 2020). The majority of breast cancers (> 80%) are of ductal histology. Breast cancer can also be classified by molecular subtype, including the presence (+) or absence (–) of estrogen receptors (ERs) and progesterone receptors (PRs).

Alcoholic beverage consumption is an established risk factor for breast cancer (IARC, 2012a), and there is evidence that the association is stronger for postmenopausal women compared with premenopausal women, and for ER+ breast cancer compared with ER– breast cancer (WCRF/AICR, 2018). Other established risk factors for breast cancer include family history of breast cancer and other types of cancer, radiation exposure (particularly during puberty), menopausal hormone therapy, excess body fatness, and hormone-related life events, such as early age at menarche, older age at menopause, and first pregnancy at age ≥ 30 years.

(a) Cohort studies

There are 11 cohort studies of reduction, duration of cessation, and/or cessation of alcoholic beverage consumption and female breast cancer incidence or mortality, which included data from seven countries and were conducted from 1959 to 2018 (Table 2.29; Supplementary Table S2.30, web only; available from https://publications.iarc.who.int/638). The associations between reduction and breast cancer incidence were assessed in four cohort studies (Dam et al., 2016; Botteri et al., 2021; Yoo et al., 2022; Chen et al., 2023). The associations between cessation and breast cancer incidence overall were assessed in six cohort studies (Simon et al., 1991; Baglietto et al., 2005; Li et al., 2009; White et al., 2017; Im et al., 2021a; Yoo et al., 2022); in a seventh study, associations were also reported by breast cancer histology and by hormone receptor status (Li et al., 2010), and in an eighth study, the outcome was breast cancer mortality (Breslow et al., 2011).

Table 2.29 Cohort studies of reduction, duration of cessation, and cessation of alcoholic beverage consumption and risk of female breast cancer

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Simon et al. (1991) USA Tecumseh Community Health Survey from 1959 for up to 28 yr follow-up	Analysis included *n* = 1954 women aged ≥ 21 yr from a small town in Michigan; follow-up time from 1959–1960 for up to 28 yr; cancer cases ascertained by self-report or death certificate and confirmed by medical record review	Interviewer-administered questionnaire Drinking status: never was consumed 0 g of ethanol per week at baseline and during lifetime; ex was consumed 0 g of ethanol per week at baseline but drinking previously; current was consumed > 0 g of ethanol per week at baseline	Breast (no ICD codes reported)	Drinking status Never Ex Current 0–< 1 drink/day 1–< 2 drinks/day ≥ 2 drinks/day	87 total	 1.0 (ref) 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, BMI, subscapular and triceps skin-fold measure-ments, education level, cigarette use, family history of breast cancer, age at menarche, mother's age at first live birth, and parity	10.4% of the cohort were in the ex-drinking category; given that there were 87 total cases, there were probably few cases in the ex-drinking category No adjustment for amount of alcohol consumed
Baglietto et al. (2005) Australia Melbourne Collaborative Cohort Study 1990–2003	Analysis included *n* = 17 447 women, residents of Melbourne aged 40–69 yr; followed up from recruitment in 1990–1994 through 2003 (average, 10.1 yr); cancer cases ascertained by cancer registry linkage	Interviewer-administered questionnaire Drinking status: abstainers never consumed ≥ 12 alcoholic drinks in a year; ex was ever consumed ≥ 12 alcoholic drinks in a year but did not consume alcohol at baseline; current was ≥ 1 g/day at baseline	Histolog-ically con-firmed invasive breast cancer	Drinking status Abstain Ex Current 1–19 g/day 20–39 g/day ≥ 40 g/day	 171 16 286 43 21	 1.0 (ref) 1.03 (0.62–1.73) 1.12 (0.93–1.36) 0.87 (0.62–1.22) 1.41 (0.90–2.23)	Total energy intake, folate intake, with age as time scale in the adjusted analyses	Neither education, BMI, age at menarche, HRT use, parity, nor use of multivita-mins confounded associations No adjust-ment for amount of alcohol consumed

Table 2.29 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Li et al. (2009) USA Kaiser Permanente Medical Care Program 1978–2004	Analysis included n = 70 033 women (mean age, 40.6 yr) who completed a health examination; follow-up time from 1978–1985 through 2004 (mean, 16 yr); cancer cases ascertained by cancer registry linkage	Self-administered questionnaire Drinking status: never was no drinking within the past year, and never or almost was never before the past year; ex was no drinking during past year but prior drinking; current was any amount of consumption during the past year	Breast (no ICD code reported)	Drinking status Never Ex Current < 1 drink/month > 1 drink/month – < 1 drink/day 1–2 drinks/day ≥ 3 drinks/day	 442 82 761 896 466 147	 1.0 (ref) 1.2 (1.0–1.5) 1.1 (1.0–1.3) 1.1 (1.0–1.2) 1.2 (1.1–1.4) 1.4 (1.1–1.7)	Age, ethnicity, education, BMI, marital status, history of any breast surgery, mother or sister with breast cancer, and parity	No adjustment for amount of alcohol consumed
Li et al. (2010) USA Women's Health Initiative Observational Study 1993–2005	Analysis included n = 87 724 postmenopausal women aged 50–79 yr; follow-up time from 1993–1998 through September 2005; cancer cases ascertained in yearly follow-up questionnaires and confirmed by medical record review	Self-administered questionnaire Drinking status: never was consuming < 12 drinks during lifetime; former was consuming ≥ 12 drinks but quit at time of questionnaire; current was consuming ≥ 12 drinks during lifetime and drinking at time of questionnaire	Breast (ICD-O code 8500 ductal; ICD-O codes 8520, 8522 lobular); 88% with data about ER and PR status	Drinking status Never Former Current Never Former Current Never Former Current Never Former Current	All 279 485 2180 Ductal 185 314 1306 Lobular 50 106 564 ER+PR+ 162 290 1351	 1.0 (ref) 0.98 (0.83–1.15) 1.08 (0.94–1.25) 1.0 (ref) 0.94 (0.77–1.15) 0.99 (0.83–1.18) 1.0 (ref) 1.25 (0.86–1.82) 1.50 (1.08–2.09) 1.0 (ref) 0.96 (0.78–1.19) 1.07 (0.89–1.28)	Age, race, ethnicity, education, BMI, HRT use, smoking, Gail model 5-yr risk, first-degree family history of breast cancer, parity, number of mammograms in past 5 yr	No adjustment for amount of alcohol consumed

Table 2.29 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Li et al. (2010) (cont.)					ER+PR−			
				Never	34	1.0 (ref)		
				Former	57	0.92 (0.57–1.49)		
				Current	282	1.11 (0.74–1.69)		
					ER−PR−			
				Never	46	1.0 (ref)		
				Former	74	1.11 (0.73–1.70)		
				Current	239	0.94 (0.64–1.37)		
Breslow et al. (2011) USA National Health Interview Survey 1988–2006	Analysis included n = 184 764 women aged ≥ 18 yr with complete alcohol intake data in the 1988, 1990, 1991, or 1997–2004 National Health Interview Survey who did not die within the quarter of their interview; follow-up time from 1988 through 2006 (mean, 8.4 yr; range, 2–18 yr); cancer deaths ascertained by linkage with National Death Index	In-home interviews Drinking status: never was no alcohol in the year before baseline and < 12 drinks during the lifetime; former was ≥ 12 drinks during the lifetime and ≥ 12 drinks in any previous year but not the year before baseline; current was categorized by drinks/week (light, < 3; moderate, > 3–7 for women and 3–14 for men; heavier, > 7 for women and > 14 for men)	Breast cancer deaths (National Center for Health Statistics ICD-9 and ICD-10 bridge code 29)	Drinking status	Deaths		Race or ethnicity, education, region, marital status, smoking status and tertiles of current smoking intensity, BMI, and sex in combined sex analyses	Results were similar after excluding deaths in the first 2 yr of follow-up time and when restricted to the first 10 yr of follow-up time No adjustment for amount of alcohol consumed
				Never	228	1.0 (ref)		
				Former	98	1.26 (0.93–1.70)		
				Lifetime infrequent	146	0.90 (0.70–1.17)		
				Current				
				Light	128	0.75 (0.57–0.98)		
				Moderate	46	1.02 (0.66–1.57)		
				Heavier	31	1.09 (0.68–1.76)		
						P_{trend} = 043		

Table 2.29 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Dam et al. (2016) Denmark Diet, Cancer, and Health Study 1993–2012	Analysis included *n* = 21 523 postmenopausal women aged 50–64 yr who participated in 2 waves of data collection (1993–1998 and 1999–2003); follow-up time from 1998–2003 through 2012 (average, 11 yr); cancer cases ascertained by cancer registry linkage	Self-administered questionnaire Drinking status: FFQ-assessed consumption over the past year was reported at each wave of data collection	Breast (ICD-10 code C50)	Change in alcohol intake from 1993–1998 to 1999–2003			Age, education, BMI, smoking, Mediterranean diet score, parity and number of births, and HRT use	Change in alcohol intake modelled using cubic splines Did not separately assess cessation Adjustment for baseline data
				< 7 to < 7 drinks/week	496	1.0 (ref)		
				< 7 to 7–13 drinks/week	90	1.38 (1.10–1.73)		
				< 7 to ≥ 14 drinks/week	32	1.16 (0.81–1.67)		
				7–13 to < 7 drinks/week	66	0.88 (0.64–1.20)		
				7–13 to 7–13 drinks/week	99	1.0 (ref)		
				7–13 to ≥ 14 drinks/week	69	1.18 (0.87–1.62)		
				≥ 14 to < 7 drinks/week	26	1.23 (0.81–1.88)		
				≥ 14 to 7–13 drinks/week	40	1.16 (0.81–1.66)		
				≥ 14 to ≥ 14 drinks/week	136	1.0 (ref)		
White et al. (2017) Puerto Rico and USA Sister Study 2003–2014	Analysis included *n* = 50 884 women aged 35–74 yr with a sister who had been diagnosed with breast cancer; follow-up time from 2003–2009 through June 2014 (mean, 6.4 yr); cancers cases were self-reported and verified by medical record review among 80% of cases	Telephone questionnaire Drinking status: never was not defined; former was no alcohol consumption during the 12 months before baseline; current was categorized by number of drinks per day	Breast (no ICD code reported)	Drinking status			Age, race or ethnicity, education, age at menarche, age at first birth, parity, hormonal contraceptive use, pack-years of smoking, HRT use, age at menopause, menopausal status, BMI	Associations for years since regular drinking were similar to those for duration of cessation No adjustment for amount of alcohol consumed Limited follow-up time
				Never	65	1.0 (ref)		
				Former	277	1.04 (0.79–1.37)		
				Current				
				< 1 drink/day	1219	1.06 (0.82–1.36)		
				1–1.9 drinks/day	170	1.10 (0.82–1.48)		
				≥ 2 drinks/day	110	1.22 (0.89–1.68)		
				Duration of cessation				
				≤ 5 yr	89	1.0 (ref)		
				6–14 yr	43	0.72 (0.49–1.04)		
				≥ 15 yr	139	1.03 (0.79–1.36)		

Table 2.29 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Im et al. (2021a) China China Kadoorie Biobank 2004–2016	Analysis included *n* = 300 900 women aged 30–79 yr; follow-up time from 2004 through 2016 (median, 10 yr); cancer cases ascertained by linkage with cancer registries and the national health insurance databases	Interviewer-administered questionnaire Drinking status: abstain was no drinking in the past year or in most weeks prior; ex-regular was drinking < weekly in the past year but drinking ≥ weekly prior; occasional was drinking < weekly in the past year and prior; current regular was drinking in most weeks in the past year	Breast (ICD-10 code C50)	Drinking status			Age, study area, education, income, smoking (never, occasional, and for ever smoked, 2 categories of cigarettes per day), BMI, physical activity, fruit intake, and family history of cancer	Floating standard errors were used to estimate the CIs; abstention was the reference category No adjustment for amount of alcohol consumed
				Abstain	1280	1.00 (0.93–1.08)		
				Ex-regular	19	1.46 (0.79–1.95)		
				Occasional	934	1.12 (1.05–1.20)		
				Current regular	56	1.16 (0.89–1.52)		
Botteri et al. (2021) Sweden Swedish Women's Lifestyle and Health Cohort Study 1991–2012	Analysis included *n* = 29 930 women aged 30–49 yr randomly selected from Uppsala Health Care Region; follow-up from time of second questionnaire (2003) through 2012 (median, 9.5 yr); cancer cases ascertained by linkage with cancer registry	Self-administered questionnaire Drinking status: assessed number of units of each type of alcoholic beverage consumed per week or month, which was recalculated into daily intake in grams	Breast (ICD-7 code 170)	Change in alcohol intake 1991/1992 to 2003	685 total		Age, menopausal status, education, and changes in weight, physical activity, and smoking	Subcohort of full cohort of 49 259 women; ~28% of original cohort did not return second questionnaire and were excluded
				Stable > 12 g/day		1.0 (ref)		
				Stable < 12 g/day		0.73 (0.49–1.10)		
				Decrease to ≤ 12 g/day		1.27 (0.71–2.29)		
				Increase to ≥ 12 g/day		0.81 (0.52–1.26)		

Table 2.29 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Yoo et al. (2022) Republic of Korea NHIS 2009–2018	Analysis included $n = 2\ 189\ 574$ women aged ≥ 40 yr with drinking status data from 2 consecutive (2009 and 2011) biennial NHIS health screenings; follow-up time through 2018 (median, 6.4 yr); cancer cases ascertained through the NHIS billing system	Self-administered questionnaires in 2009 and 2011 Alcohol intake in 2009 and 2011: for each survey, alcohol intake was first classified by amount of ethanol consumed: none, mild (< 15 g/day), moderate (15–29.9 g/day), and heavy (≥ 30 g/day); then associations for each level of consumption in 2011 were assessed, stratified on level of consumption in 2009; the reference group for each stratum was the stable group at each level of consumption (e.g. 2009/2011 none/none)	Breast (ICD-10 code C50)	Alcohol intake in 2009/2011	20 532 total		Age, sex, socio-economic position, smoking status, physical activity, comorbidities (hypertension, diabetes, dyslipidaemia, chronic kidney disease, and chronic obstructive pulmonary disease), and Charlson Comorbidity Index	Excluded the first year of follow-up time No information about alcohol consumption before the first wave of reporting Limited follow-up time Associations not shown by hormone receptor status
				None/none		1.0 (ref)		
				None/mild		0.97 (0.91–1.04)		
				None/moderate		0.83 (0.63–1.10)		
				None/heavy		1.07 (0.69–1.67)		
				Mild/none		0.94 (0.88–0.99)		
				Mild/mild		1.0 (ref)		
				Mild/moderate		0.83 (0.66–1.03)		
				Mild/heavy		0.69 (0.45–1.06)		
				Moderate/none		0.92 (0.74–1.16)		
				Moderate/mild		1.02 (0.87–1.19)		
				Moderate/moderate		1.0 (ref)		
				Moderate/heavy		1.15 (0.77–1.71)		
				Heavy/none		0.76 (0.49–1.17)		
				Heavy/mild		0.95 (0.68–1.32)		
				Heavy/moderate		0.64 (0.43–0.97)		
				Heavy/heavy		1.0 (ref)		

Table 2.29 (continued)

Reference Study location Name of cohort Period	Cohort description	Alcohol exposure assessment and definitions	Organ site (ICD codes)	Exposure categories	No. of cases or deaths	Relative risk (95% CI)	Adjustment factors	Comments
Chen et al. (2023) Norway Norwegian Women and Cancer Study 1996–2018	Analysis included *n* = 66 233 women aged 41–76 yr who completed follow-up questionnaires in 1996–2004 (Q1) and in 2002–2014 (Q2); followed up from time of Q2 until December 2018 (median, 14.2 yr); cancer cases ascertained by linkage with Cancer Registry of Norway	Self-administered questionnaires Each lifestyle factor was assigned a score ranging from 0 to 4, with higher scores indicating a healthier lifestyle: alcohol HLI score was 4 = none, 3 = > 0–< 5 g/day, 2 = 5–< 10 g/day, 1 = 10–< 20 g/day, and 0 = > 20 g/day	Breast (ICD-10 code C50)	Change in alcohol HLI score between Q1 and Q2			Education (years), height (cm), single-factor HLI score changes and single-factor HLI scores at Q1, calendar year at Q2 (continuous), age at menarche (years), menopausal status, breastfeeding, HRT use, oral contraceptive use, parity, and breast cancer in first-degree relatives	Among the 66 233 women in the analysis, missing data from Q1, Q2, or both were imputed for 21 830 women
				1-unit increase (i.e. reduction in alcohol consumption)	2384	0.94 (0.88–1.00)		

BMI, body mass index; CI, confidence interval; ER, estrogen receptor; FFQ, food frequency questionnaire; HLI, healthy lifestyle index; HRT, hormone replacement therapy; ICD, International Classification of Diseases; NHIS, National Health Insurance Service; PR, progesterone receptor; Q1, questionnaire 1; Q2, questionnaire 2; ref, reference; yr, year or years.

Duration of cessation was assessed in the study of White et al. (2017); however, the data were not available to compare categories of duration of cessation with continuing consumption.

The study of Dam et al. (2016) was a cohort study of 21 523 postmenopausal women aged 50–64 years who completed two surveys about 5 years apart. For each survey, alcohol consumption was categorized as: < 7 drinks per week, 7–13 drinks per week, and ≥ 14 drinks per week. Incident cancer cases during the follow-up time between the date of the second survey (1998–2003) and 31 December 2012 (mean, 11 years) were ascertained through the Danish Cancer Register. Among the women included in the analysis, 1054 cases of breast cancer were identified. Compared with stable consumption of ≥ 14 drinks per week, the hazard ratios for reduction to 7–13 drinks per week was 1.16 (95% CI, 0.81–1.66), and for reduction to < 7 drinks per week, the hazard ratio was 1.23 (95% CI, 0.81–1.88). Compared with stable consumption of 7–13 drinks per week, the hazard ratio for reduction to < 7 drinks per week was 0.88 (95% CI, 0.64–1.20). [The strengths of this study are that the analysis was stratified on consumption reported at the first survey and that the results in the sensitivity analysis excluding the first 3 years of follow-up time were consistent with the main results. The limitations of this study are that there was no information about history of alcohol consumption before the first survey and that the associations were adjusted for categories of smoking status and amount of use but not for duration of smoking cessation.]

Botteri et al. (2021) investigated an approximately 10-year change in alcohol consumption in relation to risk of breast cancer using data from the Swedish Women's Lifestyle and Health Cohort Study. Among 29 930 women aged 40–61 years followed up from 2003 until 2012 (median follow-up, 9.5 years), 685 incident cases of breast cancer were identified through linkage with the Swedish Cancer Registry. Consumption was categorized as ≤ 12 g of ethanol per day or > 12 g of ethanol per day. Change in consumption between surveys was then classified as stable in these categories or as increased or decreased. Compared with stable consumption of > 12 g of ethanol per day, the hazard ratio for decreasing consumption to ≤ 12 g of ethanol per day was 1.27 (95% CI, 0.71–2.29). [The strengths of this study are that the results were stratified on consumption in the first wave and adjusted for changes in other lifestyle risk factors, including changes in weight, physical activity, and smoking, and that no violation of the proportional hazards assumption was detected. The limitations of this study are that the number of cases in each category was not shown and that the follow-up time was limited.]

In the study of Yoo et al. (2022) (described in Section 2.2.3), among the 2 189 574 women aged ≥ 40 years included in the analysis, 20 532 cases of breast cancer were identified during the follow-up time. Compared with stable moderate consumption, there was no association with reduction from moderate consumption in 2009 to mild consumption in 2011 (HR, 1.02; 95% CI, 0.87–1.19). Compared with stable heavy consumption, a reduction from heavy to moderate consumption was associated with a lower risk of breast cancer (HR, 0.64; 95% CI, 0.43–0.97), but a reduction from heavy to mild consumption was not (HR, 0.95; 95% CI, 0.68–1.32). Compared with stable mild, stable moderate, and stable heavy consumption, the hazard ratios for cessation from each level of consumption in 2009 to none in 2011 were 0.94 (95% CI, 0.88–0.99), 0.92 (95% CI, 0.74–1.16), and 0.76 (95% CI, 0.49–1.17), respectively. [The strengths and limitation of this study are described in Section 2.2.3.]

In the study of Chen et al. (2023) (described in Section 2.2.6), among the 66 233 women aged 41–76 years included in the analysis, 2384 cases of breast cancer were identified during the follow-up time. A reduction in alcohol consumption corresponding to a 1-unit increase in the

alcohol HLI score between the first and second measurements was associated with a lower risk of breast cancer (HR, 0.94; 95% CI, 0.88–1.00). [The strengths and limitation of this study are described in Section 2.2.6.]

Simon et al. (1991) conducted a cohort study of 1954 women aged ≥ 21 years who enrolled in the Tecumseh Community Health Survey in the USA. This cohort was followed up from 1959–1960 for up to 28 years, during which 87 cases of breast cancer were identified from questionnaires or death certificates and confirmed by medical record review. Compared with never drinking, the relative risks of breast cancer were 0.93 (95% CI, 0.40–2.18) for ex-drinking and 1.12 (95% CI, 0.25–5.01) for consumption of ≥ 2 drinks per day at baseline. [Compared with continuing consumption that included all amounts of consumption, the calculated relative risk associated with cessation was 0.83 (95% CI, 0.32–2.16). The strength of this study is the long follow-up time. The limitations of this study are that the number of cases by category of consumption was not reported but because there were 87 total cases and 10.4% of the cohort reported ex-drinking, there were probably a few cases in the ex-drinking category, that the associations were not adjusted for the amount of alcohol consumed, and that there was no sensitivity analysis excluding at least the first year of follow-up time and no test of the proportional hazards assumption.]

Baglietto et al. (2005) assessed the association between alcohol cessation and risk of breast cancer in 17 447 Anglo-Australian women in Melbourne (Australia) who were aged 40–69 years at recruitment. Lifetime history of alcohol consumption was assessed at baseline. During the follow-up from 1990 until 2003 (mean, 10.1 years), 537 cases of breast cancer were identified by linkage with the Victorian Cancer Registry. Compared with abstention, the hazard ratio for cessation was 1.03 (95% CI, 0.62–1.73) and for current consumption of ≥ 40 g of ethanol per day was 1.41 (95% CI, 0.90–2.23). [Compared with any amount of continuing consumption, the calculated hazard ratio for cessation was 0.93 (95% CI, 0.57–1.54). The strength of this study is that the categories of drinking status were well defined. The limitations of this study are that the associations for alcohol cessation were not adjusted for the amount of alcohol consumed and that there was no sensitivity analysis excluding at least the first year of follow-up time and no test of the proportional hazards assumption.]

Among 70 033 women (mean baseline age, 40.6 years) who enrolled in a large health-care system in California (USA) and completed a questionnaire during a health examination, 2829 cases of breast cancer were identified through the health-care programme's cancer registry during an average follow-up time of 16 years (Li et al., 2009). Compared with abstention, the relative risk for alcohol cessation was 1.2 (95% CI, 1.0–1.5) and for current drinking of ≥ 3 drinks per day was 1.4 (95% CI, 1.1–1.7). [Compared with continuing consumption, there was no association between cessation and risk of breast cancer (calculated RR, 1.08; 95% CI, 0.89–1.30). The strengths of this study are the large cohort and the well-defined categories of drinking status. The limitations of this study are that the associations for alcohol cessation were not adjusted for the amount of alcohol consumed and that there was no sensitivity analysis excluding at least the first year of follow-up time and no test of the proportional hazards assumption.]

In a cohort study of 87 724 postmenopausal women aged 50–79 years who participated in the Women's Health Initiative Observational Study in the USA (Li et al., 2010), alcohol consumption was self-reported at baseline in 1993–1998. During the follow-up time (up to 12 years) until 15 September 2005, 2944 cases of invasive breast cancer (n = 2549 with ER and PR status data) were identified from self-reported annual questionnaires and confirmed by medical record review. Compared with never drinking, former drinking was not associated with overall risk of breast

cancer (HR, 0.98; 95% CI, 0.83–1.15). The hazard ratios for the association of former drinking with histological and molecular subtypes of breast cancer were 0.94 (95% CI, 0.77–1.15) for ductal carcinoma, 1.25 (95% CI, 0.86–1.82) for lobular carcinoma, 0.96 (95% CI, 0.78–1.19) for ER+PR+ cancer, 0.92 (95% CI, 0.57–1.49) for ER+PR– cancer, and 1.11 (95% CI, 0.73–1.70) for ER–PR– cancer. [Compared with continuing consumption, the hazard ratios for breast cancer overall and for most subtypes of the disease and alcohol cessation were < 1, but all confidence intervals included 1 (calculated HRs, 0.91; 95% CI, 0.81–1.02 for overall, 0.95; 95% CI, 0.82–1.09 for ductal carcinoma, 0.83; 95% CI, 0.66–1.06 for lobular carcinoma, 0.90; 95% CI, 0.77–1.04 for ER+PR+ cancer, 0.83; 95% CI, 0.59–1.16 for ER+PR– cancer, and 1.18; 95% CI, 0.88–1.58 for ER–PR– cancer). The strengths of this study are the large cohort and minimal loss to follow-up, the well-defined categories of drinking status, and that no violation of the proportional hazards assumption was detected. The limitation of this study is that the associations for alcohol cessation were not adjusted for the amount of alcohol consumed.]

In the study of Breslow et al. (2011) (described in Section 2.2.6), 677 breast cancer deaths were identified during the follow-up time among 184 764 women aged ≥ 18 years. Compared with never-drinking, the relative risk of death from breast cancer for former drinking was 1.26 (95% CI, 0.93–1.70). Current drinking of ≤ 3 drinks per week was associated with a lower risk of death from breast cancer (RR, 0.75; CI, 0.57–0.98), whereas there was no association for current drinking of > 7 drinks per week (RR, 1.09; 95% CI, 0.68–1.76). [Cessation was associated with a higher risk of death from breast cancer compared with any amount of continuing consumption (calculated RR, 1.52; 95% CI, 1.12–2.05). The strengths and limitation of this study are described in Section 2.2.6.]

White et al. (2017) assessed the associations of duration of cessation and cessation with risk of breast cancer using data from the Sister Study, a large cohort study of women aged 35–74 years in the USA with at least one sister previously diagnosed with breast cancer. During follow-up from 2003–2009 until June 2014 (mean, 6.4 years), 1843 invasive breast cancers cases were identified from self-reported diagnoses validated by medical records among the 50 884 women included in the analysis. Compared with never drinking, the hazard ratio for breast cancer for alcohol cessation was 1.04 (95% CI, 0.79–1.37) and for current drinking of ≥ 2 drinks per day was 1.22 (95% CI, 0.89–1.68). [The calculated hazard ratio for alcohol cessation compared with any amount of continuing consumption was 0.97 (95% CI, 0.85–1.11).] Compared with ≤ 5 years of cessation, the hazard ratio for 6–14 years of cessation was 0.72 (95% CI, 0.49–1.04) and for ≥ 15 years of cessation was 1.03 (95% CI, 0.78–1.36). [The strengths of this study are the large cohort and that no violation of the proportional hazards assumption was detected. The limitations of this study are that the data were not available to compare cancer risk for categories of duration of cessation with continuing consumption, that the associations were not adjusted for the amount of alcohol consumed, that the average follow-up time was limited (6.4 years), and that results stratified by molecular subtype were not reported.]

In the study of Im et al. (2021a) (described in Section 2.2.1), 2289 incident cases of breast cancer were identified during the follow-up time among 300 900 women aged 30–79 years. Compared with abstaining, the hazard ratio was 1.24 (95% CI, 0.79–1.95) for ex-regular drinking and 1.16 (95% CI, 0.89–1.52) for current-regular drinking. [Compared with continuing consumption, the calculated hazard ratio for cessation was 1.07 (95% CI, 0.63–1.81). The strengths and limitations of this study are described in Section 2.2.1.]

(b) Case–control studies

The association between cessation of alcoholic beverage consumption and risk of breast cancer overall was assessed in nine case–control studies (Byers and Funch, 1982; Rosenberg et al., 1982; Holmberg et al., 1995; Royo-Bordonada et al., 1997; Tung et al., 1999; Männistö et al., 2000; Kawase et al., 2009; Zhang and Holman, 2011; Qian et al., 2014). In a 10th case–control study, results were also reported by histology and hormone receptor status (Li et al., 2003). Among all 10 case–control studies, which were conducted from 1957 to 2013, data were collected from women in 13 countries (Supplementary Table S2.30, web only; available from https://publications.iarc.who.int/638; Table 2.31). There were no case–control studies of duration of cessation and risk of breast cancer.

The study of Rosenberg et al. (1982) was a hospital-based case–control study conducted from July 1976 to July 1980 in Canada, Israel, and the USA as part of a drug surveillance programme. The study enrolled 1152 cases of breast cancer and 2 control groups from the same hospitals as the cases (n = 519 controls with other types of cancer, and n = 2702 controls without malignancies) among women aged 30–69 years. Ex-drinking was associated with a higher risk of breast cancer compared with never drinking in analyses that used controls without malignancies (OR, 1.6; 95% CI, 1.1–2.4), but in analyses with other cancer patients as controls, the odds ratio for ex-drinking was 1.3 (95% CI, 0.7–2.3). Compared with never drinking, current drinking ≥ 4 days per week was associated with a higher risk of breast cancer in the analyses with non-cancer controls (OR, 2.5; 95% CI, 1.9–3.4) and in the analysis with cancer controls (OR, 2.0; 95% 1.3–2.0). [The calculated odds ratios for cessation compared with any amount of continuing consumption were 0.79 (95% CI, 0.55–1.12) in the analysis with non-cancer controls and 0.67 (95% CI, 0.40–1.15) in the analysis with cancer controls. The strengths of this study are that it was a multicountry study, that hospital-based controls with conditions thought to be unrelated to alcohol consumption were selected, and that the categories of drinking status were well defined. The limitation of this study is that the associations were not adjusted for the amount of alcohol consumed.]

Byers and Funch (1982) conducted a hospital-based case–control study in the USA from 1957 to 1965 that included 1314 women with breast cancer and 770 women without breast cancer who were aged 30–69 years. Compared with never drinking, the odds ratio for alcohol cessation was 0.59 (P = 0.16) and for current consumption of ≥ 26 drinks per month was 1.13 (P = 0.35). [Compared with any amount of continuing consumption, the calculated odds ratio for cessation was 0.53 (95% CI, 0.26–1.09). The strength of this study is that the alcohol consumption data were collected at hospital admission and before diagnosis in most cases. The limitations of this study are that there was limited information about selection of hospital-based controls and that the associations were adjusted for age only and not for the amount of alcohol consumed or other potential confounders.]

In a population-based case–control study nested within a screening programme in Sweden, cases and controls were selected from among women aged 40–74 years who received a screening mammogram from March 1987 until December 1990 (Holmberg et al., 1995). Clinically or histologically confirmed cases of breast cancer (n = 276) were identified at the first screening or a subsequent screening, or independently of the screening programme. The controls (n = 452) were women who were found to not have breast cancer during the study period, and were frequency-matched to cases on month of diagnosis, age (± 5 years), and county of residence. Among women aged ≥ 50 years, compared with never drinking, the relative risk for the category "stopped drinking" was 1.6

Table 2.31 Case–control studies of cessation of alcoholic beverage consumption and risk of female breast cancer

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Rosenberg et al. (1982) Canada, Israel, and USA 1976–1980	Women (n = 1152), aged 30–69 yr with clinical or pathologically confirmed breast cancer at hospital admission; admitted to hospitals participating in a drug surveillance programme; 6% of patients or their physicians refused interview	Hospital-based controls: Control group 1: cancer controls (n = 519) with endometrial or ovarian cancer Control group 2: non-cancer controls (n = 2702) with other disorders; from the same hospitals as cases	Nurse-administered questionnaire Drinking status: current was drinking alcoholic beverages in year before admission; ex was last drinking ≥ 1 yr before admission; never was having never consumed alcohol	Drinking status vs cancer controls			Geographical area of admitting hospital, age, history of benign breast disease, late age at first pregnancy, late age at menopause, low parity, family history of breast cancer, socio-economic status, religion, education, cigarette smoking, and prior biopsy	Selection of hospital-based controls with conditions thought to be unrelated to alcohol consumption No adjustment for amount of alcohol consumed Participation rates not reported
				Never	188	1.0 (ref)		
				Ex	71	1.3 (0.7–2.3)		
				Current				
				≥ 4 days/week	198	2.0 (1.3–2.0)		
				< 4 days/week	689	1.5 (1.1–2.1)		
				vs non-cancer controls				
				Never	188	1.0 (ref)		
				Ex	71	1.6 (1.1–2.4)		
				Current				
				≥ 4 days/week	198	2.5 (1.9–3.4)		
				< 4 days/week	689	1.9 (1.5–2.4)		
Byers and Funch (1982) New York, USA 1957–1965	Women (n = 1314) aged 30–69 yr with primary diagnosis of breast cancer; admitted to Roswell Park Memorial Institute	Hospital-based controls (n = 770 women), aged 30–69 yr; non-cancer patients with conditions not affecting the breast, reproductive sites, or gastrointestinal tract	Interviewer-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	Drinking status			Age	Limited information about selection of hospital-based controls No adjustment for amount of alcohol consumed or other potential confounding factors Participation rates not reported
				Never	393	1.0 (ref)		
				Ex	17	0.59 (P = 0.16)		
				Current				
				< 3 drinks/month	247	1.11 (P = 0.45)		
				3–8 drinks/month	201	1.02 (P = 0.93)		
				9–25 drinks/month	140	1.09 (P = 0.62)		
				≥ 26 drinks/month	315	1.13 (P = 0.35)		

Table 2.31 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Holmberg et al. (1995) Sweden 1987–1990	Women (*n* = 276) aged 40–74 yr with clinically or pathologically confirmed breast cancer; recruited in a screening cohort; cases identified through surveillance of pathology laboratories and registers at the screening centres	Population-based controls (*n* = 452 women) frequency-matched on month of diagnosis of cases, age (± 5 yr), and county of residence; without breast cancer during the study period	Self-administered questionnaire Drinking status: never was no drinking before cancer diagnosis; stopped was no drinking for > 2 yr; current was drinking in the previous 2 yr	Drinking status	Age > 50 yr		Family history of breast cancer, parity, age at first birth, education level, and BMI	Results for women in the age < 50 yr subgroup not shown because few among the cases (*n* = 3) reported stopping drinking Results for all women combined not shown because the Working Group considered them unreliable because they were inconsistent with the age-stratified results No adjustment for amount of alcohol consumed
				Never	56	1.0 (ref)		
				Stopped	20	1.6 (1.0–2.6)		
				Current	146	1.8 (1.2–2.8)		

Table 2.31 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Royo-Bordonada et al. (1997) Subset of the EURAMIC study The Netherlands, Northern Ireland (United Kingdom), and Switzerland 1991–1992	Women (n = 213), aged 50–74 yr, postmenopausal; breast cancer diagnosis (ICD-9 code 174), histologically ductal, tumour size < 5 cm, axillary lymph node stage ≤ N3, and no metastases (M0); recruited from the surgical units of participating hospitals	Mixed hospital-based (2 centres) and population-based (1 centre) controls (n = 239 women), frequency-matched on age (± 5 yr) and centre	Interviewer-administered questionnaire Drinking status: no definitions were reported for categories of drinking status	Drinking status			Age, centre, BMI, smoking, parity, age at menopause, age at menarche, HRT use, family history of breast cancer, history of benign breast disease, and age at first childbirth	Two countries in the EURAMIC study did not contribute to this analysis; for Germany, no data on past alcohol consumption, and for Spain, few cases (n = 3) and 0 controls in the ex-drinking category Participants with a history of drug or alcohol abuse, major psychiatric disorders, modified dietary pattern within past year, and weight loss > 5 kg were excluded No adjustment for amount of alcohol consumed Response rates were not reported for cases and controls
				Never	44	1.0 (ref)		
				Ex	66	1.61 (0.90–2.90)		
				Current tertile 1	(all current n = 103)	0.87 (0.45–1.70)		
				Current tertile 2		0.90 (0.44–1.82)		
				Current tertile 3		0.99 (0.48–2.01)		

Table 2.31 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Tung et al. (1999) Japan 1990–1995	Women (n = 376; n = 190 premeno-pausal and n = 182 postmeno-pausal; mean age, 51.6 yr) with incident breast cancer, admitted to OMCC	Hospital-based controls (n = 430 women; n = 119 premenopau-sal and n = 282 postmenopau-sal) admitted to OMCC during same time period as cases; without any cancer or changes in weight, nutritional status, or physical activity related to illness	Self-administered questionnaire Drinking status: current was consumption within 1 yr of diagnosis; ex was quit ≥ 1 yr before diagnosis; non was having consumed alcohol rarely or never	Drinking status	All		Smoking habits and age; collected other risk factor data, including age at first delivery, age at menopause, body weight, height, and age at menarche	No adjustment for amount of alcohol consumed Response rates were not reported, but cases were 46.5% of the total patients with breast cancer (incident or prevalent), and 23.5% of controls were excluded on the basis of underlying conditions leading to changes in weight, nutritional status, and physical activity
				Non	233	1.0 (ref)		
				Ex	11	0.42 (0.19–0.95)		
				Current	130	0.86 (0.61–1.22)		
					Premenopausal			
				Non	100	1.0 (ref)		
				Ex	5	1.09 (0.22–5.36)		
				Current	85	0.73 (0.41–1.25)		
					Postmenopausal			
				Non	130	1.0 (ref)		
				Ex	6	0.43 (0.15–1.26)		
				Current	44	1.14 (0.68–1.88)		
Männistö et al. (2000) Finland 1990–1995	Women (n = 113 premenopausal and n = 188 postmeno-pausal) aged 25–75 yr, with clinical diagnosis of breast cancer at Kuopio University Hospital; response rate for cases not reported	Population-based controls (n = 443 women; n = 172 premeno-pausal and n = 271 postmeno-pausal), matched on area of resi-dence (rural or urban) and age (± 5 yr); with no other serious disease; over-all 72% partici-pation rate for controls	Self-administered questionnaire Drinking status: non-drinking was lifetime abstention; current and ex-drinking were not defined		Premenopausal		Age, area, age at menarche, age at first full-term pregnancy, oral contra-ceptive use, HRT use, family history of breast cancer, history of benign breast disease, education level, smoking, physical activity, BMI, and waist-to-hip ratio	No adjustment for amount of alcohol consumed
				Non-drinking	29	1.0 (ref)		
				Ex	5	1.4 (0.3–6.2)		
				Current				
				1–12 g/week	23	0.8 (0.4–1.9)		
				13–36 g/week	25	0.9 (0.4–1.9)		
				> 36 g/week	31	1.0 (0.4–2.2)		
					Postmenopausal			
				Non-drinking	105	1.0 (ref)		
				Ex	8	0.6 (0.2–1.7)		
				Current				
				1–12 g/week	27	0.9 (0.5–1.6)		
				13–36 g/week	20	0.6 (0.3–1.2)		
				> 36 g/week	28	0.8 (0.4–1.6)		

Table 2.31 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Li et al. (2003) USA 1997–1999	Women (n = 975) aged 65–79 yr with invasive ductal (n = 651) or lobular (n = 196) breast cancer (ICD-O codes 8520, 8522); identified from the regional population-based tumour registry; 80.6% of eligible cases participated	Population-based controls (n = 1007), frequency-matched; drawn from Health Care Financing Administration records; 73.8% of eligible individuals participated	Interviewer-administered questionnaire Drinking status: never was < 12 drinks and never ≥ 1 drinks/month for ≥ 6 months during the past 20 yr; former was consuming alcohol during the year before reference date and ≥ 12 drinks and ≥ 1 drinks/month for ≥ 6 months during the past 20 yr; current was ≥ 12 drinks during the past 20 yr, ≥ 1 drinks/ month for ≥ 6 months during the past 20 yr, and consuming alcohol during the year before reference date	Drinking status	Overall		Age, first-degree family history of breast cancer, and BMI	No adjustment for amount of alcohol consumed
				Never	459	1.0 (ref)		
				Former	70	1.1 (0.8–1.7)		
				Current	438	1.3 (1.0–1.6)		
					Ductal			
				Never	319	1.0 (ref)		
				Former	43	1.0 (0.6–1.5)		
				Current	289	1.2 (1.0–1.5)		
					Lobular			
				Never	77	1.0 (ref)		
				Former	16	1.5 (0.8–2.8)		
				Current	102	1.8 (1.3–2.6)		
					ER+			
				Never	370	1.0 (ref)		
				Former	57	1.1 (0.8–1.7)		
				Current	362	1.3 (1.1–1.6)		
					ER–			
				Never	53	1.0 (ref)		
				Former	8	1.1 (0.5–2.5)		
				Current	45	1.1 (0.7–1.8)		
					PR+			
				Never	300	1.0 (ref)		
				Former	47	1.2 (0.8–1.8)		
				Current	301	1.4 (1.1–1.7)		
					PR–			
				Never	122	1.0 (ref)		
				Former	18	1.0 (0.6–1.8)		
				Current	104	1.1 (0.8–1.5)		

Table 2.31 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Kawase et al. (2009) Japan 2001–2005	Women (n = 456, mean age 52.8 yr) with histologically confirmed breast cancer; diagnosed at ACCH	Hospital-based controls (n = 912) randomly selected and matched on age (± 3 yr) and menopausal status (1:2 case–control ratio)	Self-administered questionnaire Drinking status: never was not defined; former was quit ≥ 1 yr before the survey; current was drinking < 1 yr before the survey; current light was < 5 g/day, moderate was 5–< 15 g/day, and heavy was ≥ 15 g/day	Drinking status			Matching factors plus smoking status, BMI, regular exercise, family history of breast cancer, age at menarche, parity, HRT use, and mode of referral to hospital	Limited information about selection of hospital-based controls Alcohol consumption data were collected before cancer diagnosis No adjustment for amount of alcohol consumed 95% of women completed questionnaires; response rate not reported for cases and controls separately
				Never	286	1.0 (ref)		
				Former	8	1.17 (0.48–2.83)		
				Current				
				Light	73	0.92 (0.67–1.26)		
				Moderate	50	0.95 (0.65–1.39)		
				Heavy	36	1.33 (0.84–2.11)		
Zhang and Holman (2011) China 2004–2005	Women (n = 1009) aged 20–87 yr with histologically confirmed invasive ductal or in situ breast carcinoma; identified from 4 teaching hospitals in Zhejiang; 98.8% participation rate	Hospital-based outpatient controls (n = 1009 women) matched on outpatient clinic of case hospital and age (± 5 yr); response rate 98.7%	Interviewer-administered questionnaire Drinking status: reference period was 1 yr before diagnosis in cases or interview in controls; abstain, ex, and current drinking were not defined	Drinking status	All		Age, education, BMI, oral contraceptive use, HRT use, first-degree family history of breast cancer, total energy intake, folate intake, tea drinking, and menopausal status	Limited information about selection of hospital-based controls No adjustment for amount of alcohol consumed
				Abstain	660	1.0 (ref)		
				Ex	15	1.34 (0.56–3.22)		
				Current	334	0.63 (0.52–0.76)		
					Premenopausal			
				Abstain	416	1.0 (ref)		
				Ex	10	2.44 (0.71–8.39)		
				Current	246	0.66 (0.53–0.84)		
					Postmenopausal			
				Abstain	224	1.0 (ref)		
				Ex	5	0.68 (0.17–2.67)		
				Current	88	0.55 (0.38–0.78)		

Table 2.31 (continued)

Reference Study location Period	Characteristics of cases	Characteristics of controls	Alcohol exposure assessment and definitions	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Qian et al. (2014) Cameroon, Nigeria, and Uganda 1998–2013	Women (*n* = 2138; mean age, 47.5 yr; 54.5% premeno-pausal); invasive breast cancer; response rate > 90%	Community and clinic controls (*n* = 2589; mean age, 43.1 yr; 68.7% premeno-pausal); selected from randomly approa-ched households in communities the cases came from or sampled from outpatient clinics; hospital and community controls were combined; response rate > 90%	Interviewer-administered questionnaire Drinking status: alcohol consumption defined as consuming alcoholic beverages ≥ once per week for ≥ 6 months; never, past, and current not further defined	Drinking status	Total		Age at diagnosis, ethnicity, education, age at menarche, number of live births, age at first birth, menopausal status, family history of breast cancer, benign breast disease, hormonal contraceptive use, BMI, height, and study sites	No adjustment for amount of alcohol consumed
				Never	1730	1.0 (ref)		
				Past	193	1.54 (1.19–2.00)		
				Current	186	1.71 (1.30–2.23)		
					Nigeria			
				Never	1546	1.0 (ref)		
				Past	117	1.88 (1.33–2.67)		
				Current	68	1.70 (1.13–2.55)		
					Cameroon			
				Never	94	1.0 (ref)		
				Past	17	1.00 (0.45–2.23)		
				Current	80	2.17 (1.28–3.69)		
					Uganda			
				Never	90	1.0 (ref)		
				Past	59	0.99 (0.57–1.75)		
				Current	38	1.01 (0.55–1.85)		

ACCH, Aichi Cancer Center Hospital; BMI, body mass index; CI, confidence interval; ER, estrogen receptor; EURAMIC, European Study on Antioxidants, Myocardial Infarction and Cancer of the Breast; HRT, hormone replacement therapy; ICD, International Classification of Diseases; OMCC, Osaka Medical Center for Cancer and Cardiovascular Diseases; PR, progesterone receptor; ref, reference; yr, year or years.

(95% CI, 1.0–2.6) and for current drinking was 1.8 (95% CI, 1.2–2.8). [Compared with continuing consumption, the calculated relative risk for cessation was 0.89 (95% CI, 0.55–1.45). The strengths of this study are that the controls came from the same screening population as the cases and that cessation was defined as having stopped > 2 years before measurement. The limitations of this study are that the associations were also reported for women aged < 50 years but there were few cases in the cessation category (*n* = 3), and therefore they are not shown here (similarly, the Working Group considered the results for all women combined to be unreliable, and therefore they are not shown here) and that the associations were not adjusted for the amount of alcohol consumed.]

Royo-Bordonada et al. (1997) conducted a mixed hospital-based and population-based case–control study in 1991–1992 that included postmenopausal women aged 50–74 years in three European countries or regions (the Netherlands, Northern Ireland [United Kingdom], and Switzerland). The study included 213 cases and 239 controls frequency-matched to cases on 5-year age intervals and centre. Compared with never drinking, the odds ratios were 1.61 (95% CI, 0.90–2.90) for ex-drinking and 0.99 (95% CI, 0.48–2.01) for the highest tertile of current drinking. [Compared with any amount of continuing consumption, the calculated odds ratio for cessation was 1.76 (95% CI, 0.86–3.57). The strength of this study is that it was multicentric. The limitations of this study are that the amount of current drinking and the proportion of current drinking and ex-drinking varied markedly across centres and that the associations were not adjusted for the amount of alcohol consumed.]

A hospital-based case–control study conducted in Japan included 376 cases of breast cancer (mean age, 51.6 years) newly diagnosed in 1990–1995. The controls (*n* = 430; mean age, 54.5 years) were women admitted during the same time period as the cases (Tung et al., 1999). Compared with non-drinking, ex-drinking was associated with a lower overall risk of breast cancer (OR, 0.42; 95% CI, 0.19–0.95), whereas the odds ratio for current drinking was 0.86 (95% CI, 0.61–1.22). In the analysis by menopausal status, the odds ratios for ex-drinking were 0.43 (95% CI, 0.15–1.26) for postmenopausal breast cancer and 1.09 (95% CI, 0.22–5.36) for premenopausal breast cancer. [Compared with continuing consumption, the calculated odds ratios for the association between cessation and risk of breast cancer were 0.49 (95% CI, 0.21–1.12) for breast cancer overall, 0.38 (95% CI, 0.12–1.16) for postmenopausal breast cancer, and 1.49 (95% CI, 0.30–7.47) for premenopausal breast cancer. The strength of this study is that the categories of drinking status were well defined. The limitations of this study are that the analysis by menopausal status had few cases in the ex-drinking category for both premenopausal women (*n* = 5) and postmenopausal women (*n* = 6) and that the associations were not adjusted for the amount of alcohol consumed.]

A population-based case–control study conducted in Finland (Männistö et al., 2000) included women aged 25–75 years who were referred to the hospital for a breast examination between October 1990 and December 1995, among whom 301 were diagnosed with breast cancer. The controls (*n* = 443) were selected from the National Population Register and were individually matched with the cases on area of residence (rural or urban) and age (± 5 years). Compared with non-drinking, the odds ratios for ex-drinking were 1.4 (95% CI, 0.3–6.2) among premenopausal women and 0.6 (95% CI, 0.2–1.7) among postmenopausal women. The odds ratios for the groups with the highest amount of current drinking were 1.0 (95% CI, 0.4–2.2) among premenopausal women and 0.8 (95% CI, 0.4–1.6) among postmenopausal women. [Compared with any amount of continuing consumption, the calculated odds ratios for cessation were 1.59 (95%

CI, 0.38–6.70) for premenopausal breast cancer and 0.77 (95% CI, 0.26–2.29) for postmenopausal breast cancer. The strengths of this study are that it was population-based, that the associations were reported separately for premenopausal and postmenopausal breast cancer, and that alcohol consumption data for cases were collected before any diagnostic procedure. The limitations of this study are that the analysis by menopausal status had few cases in the ex-drinking category for both premenopausal women (n = 5) and post-menopausal women (n = 8), and that the associations were not adjusted for the amount of alcohol consumed.]

A population-based case–control study of postmenopausal women aged 65–79 years, was conducted within a large health-care system in the USA (Li et al., 2003). The cases (n = 975 cases) were women newly diagnosed with breast cancer from April 1997 to May 1999. The controls (n = 1007) were women from the same geographical area, selected from Health Care Financing Administration records, who were frequency-matched to cases on age. The association between former drinking compared with never drinking and risk was reported for breast cancer overall (OR, 1.1; 95% CI, 0.8–1.7), by histology (OR, 1.0; 95% CI, 0.6–1.5 for ductal carcinoma and OR, 1.5; 95% CI, 0.8–2.8 for lobular carcinoma), and by hormone receptor status (ER+ OR, 1.1; 95% CI, 0.8–1.7; ER– OR, 1.1; 95% CI, 0.5–2.5; PR+ OR, 1.2; 95% CI, 0.8–1.8; PR– OR, 1.0; 95% CI, 0.6–1.8). The odds ratio for current versus never drinking was 1.3 (95% CI, 1.0–1.6) for breast cancer overall. [The calculated odds ratios for cessation compared with continuing consumption were 0.85 (95% CI, 0.57–1.25) for breast cancer overall, 0.83 (95% CI, 0.53–1.31) for ductal carcinoma, 0.83 (95% CI, 0.43–1.61) for lobular carcinoma, 0.85 (95% CI, 0.58–1.23) for ER+ breast cancer, 1.0 (95% CI, 0.44–2.28) for ER– breast cancer, 0.86 (95% CI, 0.57–1.29) for PR+ breast cancer, and 0.91 (95% CI, 0.52–1.60) for PR– breast cancer. The strengths of this study are that it was population-based and that the associations were reported by histological and hormone receptor subtypes. The limitations of this study are that there were few ER– cases in the former-drinking category (n = 8) and that the associations were not adjusted for the amount of alcohol consumed.]

A second hospital-based case–control study conducted in Japan included 456 women (mean age, 52.8 years) with histologically confirmed breast cancer and 912 controls (2 controls per case) matched on age (± 3 years) and menopausal status (Kawase et al., 2009). Compared with never drinking, the odds ratio for former drinking was 1.17 (95% CI, 0.48–2.83) and for current heavy drinking was 1.33 (95% CI, 0.84–2.11). [Compared with any amount of continuing consumption, the calculated odds ratio for cessation was 1.17 (95% CI, 0.48–2.87). The strength of this study is that self-reported alcohol consumption data were collected before cancer diagnosis. The limitations of this study are that there was limited information about selection of hospital-based controls, that there were few cases in the former-drinking category (n = 8), and that the associations were not adjusted for the amount of alcohol consumed.]

A hospital-based case–control study conducted in China included 1009 cases, aged 20–87 years, diagnosed with breast cancer between July 2004 and September 2005, and 1009 outpatient controls from the same hospitals as the cases matched on age (± 5 years) (Zhang and Holman, 2011). Overall, compared with lifetime abstention, the odds ratio for ex-drinking was 1.34 (95% CI, 0.56–3.22) and for current drinking was 0.63 (95% CI, 0.52–0.76). The odds ratio for ex-drinking was 2.44 (95% CI, 0.71–8.39) for premenopausal breast cancer and 0.68 (95% CI, 0.17–2.67) for postmenopausal breast cancer. [The calculated odds ratio for cessation compared with continuing consumption was 2.13 (95% CI, 0.88–5.12) for breast cancer overall, 3.70 (95% CI, 1.07–12.75) for premenopausal breast cancer,

and 1.24 (95% CI, 0.31–4.97) for postmenopausal breast cancer. The strength of this study is that the associations were reported separately for premenopausal and postmenopausal breast cancer. The limitations of this study are that there was limited information about selection of hospital-based controls, that there were few women in the ex-drinking category among premenopausal controls (*n* = 4), postmenopausal cases (*n* = 5), and postmenopausal controls (*n* = 6), and that the associations were not adjusted for the amount of alcohol consumed.]

A mixed population-based and hospital-based multicentre case–control study in Cameroon, Nigeria, and Uganda, conducted between March 1998 and July 2013, included 2138 cases of breast cancer and 2589 controls aged ≥ 18 years (Qian et al., 2014). Overall, both past drinking (OR, 1.54; 95% CI, 1.19–2.00) and current drinking (OR, 1.71; 95% CI, 1.30–2.23) were associated with a higher risk of breast cancer compared with never drinking. In analyses stratified by country, past drinking was not associated with risk of breast cancer in Cameroon (OR, 1.00; 95% CI, 0.45–2.23) or in Uganda (OR, 0.99; 95% CI, 0.57–1.75), but it was associated with higher risk in Nigeria (OR, 1.88; 95% CI, 1.33–2.67). [The calculated odds ratios for cessation compared with continuing consumption were 0.90 (95% CI, 0.63–1.29) overall, 0.46 (95% CI, 0.20–1.08) in Cameroon, 0.98 (95% CI, 0.50–1.93) in Uganda, and 1.11 (95% CI, 0.65–1.87) in Nigeria. The strength of this study is that it included multiple countries in Africa. The limitations of this study are that population-based controls were available only for Nigeria and that the associations were not adjusted for the amount of alcohol consumed.]

(c) Meta-analyses

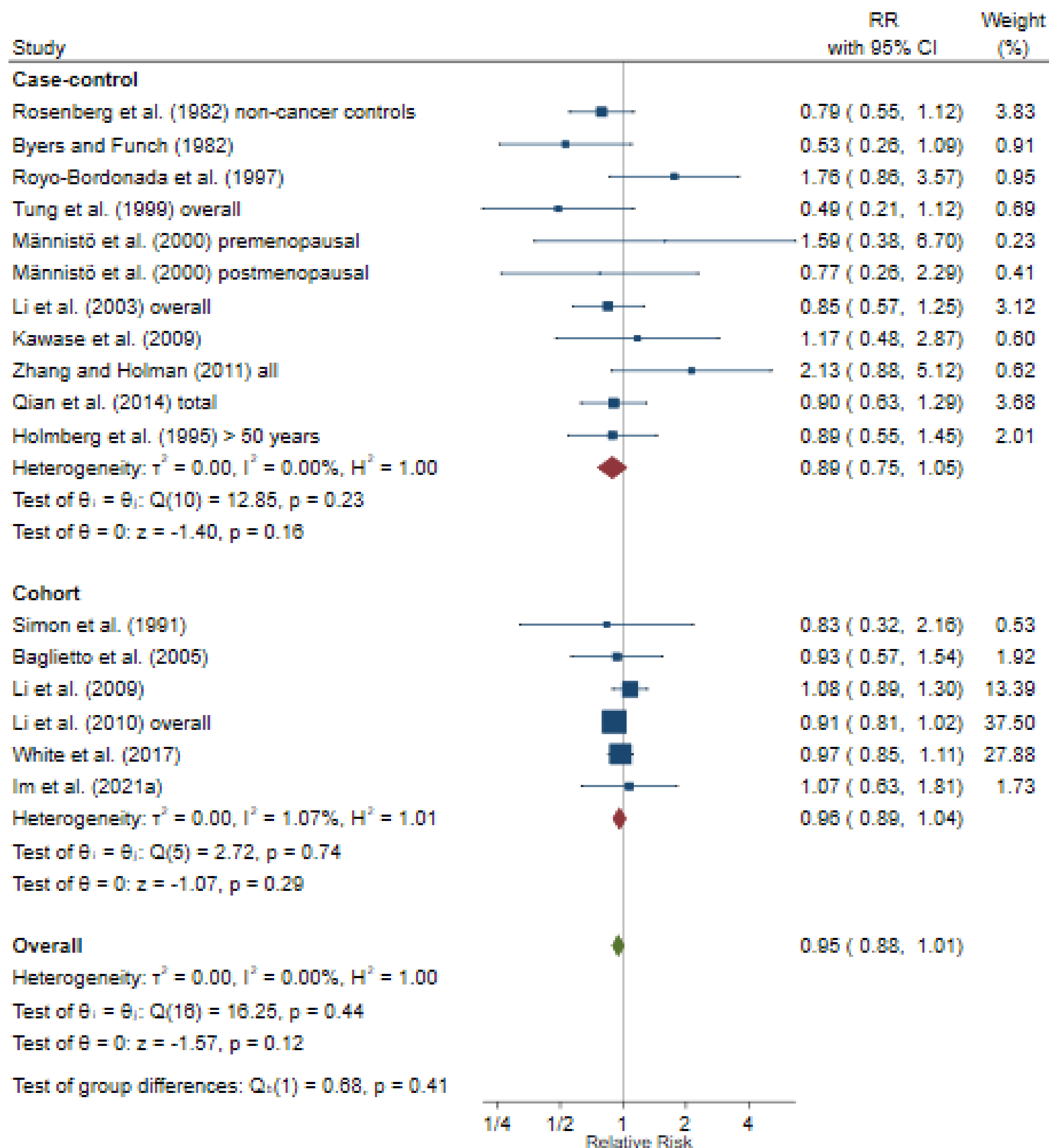
[Using a random-effects model and meta-analytic techniques, the Working Group assessed the association between cessation of alcoholic beverage consumption compared with continuing consumption and risk of breast cancer; the summary relative risks were 0.89 (95% CI, 0.75–1.05) for 10 case–control studies, 0.96 (95% CI, 0.89–1.04) for 6 cohort studies of cancer incidence (1 cohort study of cancer mortality was excluded), and 0.95 (95% CI, 0.88–1.01) for all studies combined (Fig. 2.1).]

2.2.9 Gene-by-environment interactions

Variants in three genes that encode alcohol-metabolizing enzymes (i.e. *ADH1B*, *ADH1C*, and *ALDH2*) play a role in alcohol-induced carcinogenesis in humans – particularly for cancers of the upper aerodigestive tract (for more details, please refer to IARC, 2012a). Moreover, these variants have synergistic effects with alcohol consumption. The Working Group identified three informative case–control studies that assessed the joint associations of variants and cessation of alcoholic beverage consumption with cancer risk; these included one study of oesophageal SCC (Yokoyama et al., 2002), one study of oral and pharyngeal cancer (Asakage et al., 2007), and one study of breast cancer (Kawase et al., 2009). Relevant results of these studies are described in Table 2.32. All three studies assessed cessation but not alcohol reduction, and none of the studies discussed in Sections 2.2.1–2.2.8 that assessed reduction and cancer risk examined interactions with alcohol-metabolizing genes.

[There are key methodological considerations among the three studies. First, none of the studies were specifically designed to assess effect modification of the association between alcohol cessation and cancer risk by genotype. Two of the three studies assessed cancer risk for all drinking and genotype strata compared with a single reference stratum of the lowest-risk genotype and continuing light consumption (Yokoyama et al., 2002) or never or rare to light consumption (Asakage et al., 2007). The third study assessed associations for three categories of continuing consumption and for cessation compared with abstention within strata of genotype (Kawase

Fig. 2.1 Meta-analysis of case–control studies, cohort studies, and all studies combined for the association between cessation of alcoholic beverage consumption compared with continuing consumption and risk of breast cancer



CI, confidence interval; REML, restricted maximum likelihood; RR, relative risk.
Computed by the *Handbook* 20A Working Group.

Table 2.32 Interactions of alcohol-metabolizing gene polymorphisms and cessation of alcoholic beverage consumption and risk of cancer

Reference Study location Study type Outcome	Study description (cases, controls, exposure definition)	Gene Alcohol exposure strata	Genotype			Comments
			OR (95% CI)	OR (95% CI)	OR (95% CI)	
Yokoyama et al. (2002) Japan Case–control Oesophageal SCC	Men (n = 234) aged 40–79 yr diagnosed with oesophageal SCC within 3 yr before study registration (September 2000 and December 2001) and treated at 1 of 4 hospitals in Kawasaki, Osaka, or Tokyo; 99% participation rate Controls (n = 634 men) received annual health check-ups at 2 Tokyo clinics from September 2000 to December 2001; 86% participation rate Self-administered questionnaire Drinking status: current consumption was categorized as light (1–8.9 units/week), moderate (9–17.9 units/week), or heavy (≥ 18 units/week), where 1 unit = 22 g of ethanol	*ADH1B*[a]	**1/*2 + *2/*2*	**1/*1*	Not applicable	13 cases in ex-drinking category For *ADH1B*, in ex-drinking: 11 cases with *1/*2 or *2/*2 genotype; 2 cases with *1/*1 genotype For *ADH1C*, in ex-drinking: 12 cases with *1/*2 or *2/*2 genotype; 1 case with *1/*1 genotype For *ALDH2*, in ex-drinking: 0 cases with *2/*2 genotype; 4 cases with *1/*1 genotype; 9 cases with *1/*2 genotype ORs adjusted for amount and duration of smoking, consumption of green–yellow vegetables, and age Significant linkage disequilibrium between *ADH1B* and *ADH1C* gene polymorphisms among controls (P < 0.0001) and cases (P < 0.0001)
		Never/rare	0.21 (0.06–0.68)	4.25 (0.41–43.82)	–	
		Light	1.0 (ref)	3.97 (1.01–15.63)	–	
		Moderate	4.09 (2.25–7.42)	33.30 (11.14–99.50)	–	
		Heavy	7.01 (3.77–13.04)	38.64 (13.27–112.55)	–	
		Ex-drinking	5.73 (2.03–16.20)	19.63 (1.65–233.20)	–	
		ADH1C[b]	**1/*1*	**1/*2 + *2/*2*	Not applicable	
		Never/rare	0.23 (0.08–0.68)	[no cases]	–	
		Light	1.0 (ref)	0.81 (0.17–3.99)	–	
		Moderate	3.66 (2.04–6.55)	13.32 (5.28–33.63)	–	
		Heavy	6.64 (3.66–12.05)	23.83 (7.67–74.06)	–	
		Ex-drinking	8.44 (2.94–24.25)	1.01 (0.09–11.93)	–	
		ALDH2[c]	**1/*1*	**1/*2*	**2/*2*	
		Never/rare	[no cases]	0.75 (0.14–4.11)	1.44 (0.22–9.54)	
		Light	1.0 (ref)	5.82 (1.59–21.38)	[no cases]	
		Moderate	5.58 (1.54–20.25)	55.84 (15.40–202.51)	–	
		Heavy	10.38 (2.85–37.84)	88.88 (23.97–329.57)	–	
		Ex-drinking	8.81 (1.53–50.76)	50.50 (9.18–277.95)	–	

Table 2.32 (continued)

Reference Study location Study type Outcome	Study description (cases, controls, exposure definition)	Gene Alcohol exposure strata	Genotype			Comments
			OR (95% CI)	OR (95% CI)	OR (95% CI)	
Asakage et al. (2007) Japan Case–control Oral cavity and pharyngeal SCC	Men (n = 96) aged 40–79 yr with primary oral or pharyngeal SCC within 3 yr before study registration (September 2000 and December 2003) and treated at 1 of 4 hospitals in Kawasaki, Osaka, or Tokyo Controls (n = 642 men) received annual health check-ups at 2 Tokyo clinics from September 2000 to December 2001; 86% participation rate Self-administered questionnaire Drinking status: never or rare to current light was < 9 units/week (1 unit = 22 g of ethanol); current moderate to heavy was ≥ 9 units/week; ex-drinking was not defined	*ADH1B*[a]	**1/*2 + *2/*2*	**1/*1*	Not applicable	ORs for hypopharynx and oral cavity/oropharynx also reported, but the CIs are very wide 6 oral cavity/oropharyngeal cancer cases and 5 hypopharyngeal cancer cases in ex-drinking category For *ADH1B*, in ex-drinking: 9 cases with *1/*2 or *2/*2 genotype; 2 cases with *1/*1 genotype For *ADH1C*, in ex-drinking: 1 case with *1/*2 or *2/*2 genotype; 10 cases with *1/*1 genotype For *ALDH2*, in ex-drinking: 0 cases with *2/*2 genotype; 4 cases with *1/*1 genotype; 7 cases with *1/*2 genotype ORs adjusted for strong alcoholic beverages, smoking, consumption of green–yellow vegetables, subcategory of alcohol consumption, and age Significant linkage disequilibrium between *ADH1B* and *ADH1C* gene polymorphisms among controls (P < 0.0001) and cases (P = 0.0002)
		Never or rare to light	1.0 (ref)	1.00 (0.10–10.22)	–	
		Moderate to heavy	4.75 (2.44–9.23)	26.40 (9.57–72.84)	–	
		Ex-drinking	16.60 (5.21–52.94)	111.28 (8.23–> 999)	–	
		ADH1C[b]	**1/*1*	**1/*2 + *2/*2*	Not applicable	
		Never or rare to light	1.0 (ref)	2.34 (0.58–9.48)	–	
		Moderate to heavy	5.64 (2.82–11.31)	17.93 (6.43–50.00)	–	
		Ex-drinking	35.89 (10.74–119.9)	4.81 (0.38–60.77)	–	
		ALDH2[c]	**1/*1*	**1/*2*	**2/*2*	
		Never or rare to light	1.0 (ref)	0.56 (0.20–1.59)	[no cases]	
		Moderate to heavy	2.29 (0.94–5.57)	8.26 (3.30–20.68)	–	
		Ex-drinking	5.41 (1.09–26.75)	32.39 (6.83–153.70)	–	

Table 2.32 (continued)

Reference Study location Study type Outcome	Study description (cases, controls, exposure definition)	Gene Alcohol exposure strata	Genotype OR (95% CI)	OR (95% CI)	OR (95% CI)	Comments
Kawase et al. (2009) Japan Case–control Breast cancer	Women (n = 456, mean age 52.8 yr) newly diagnosed with histologically confirmed breast cancer at ACCH from January 2001 to June 2005 Controls (n = 912) matched to cases (2:1) on age (± 3 yr) and menopausal status, randomly selected from ACCH Self-administered questionnaire Drinking status: never was self-reported; former was quit ≥ 1 yr before the survey; light was < 5 g/day, moderate was 5–< 15 g/day, and heavy was ≥ 15 g/day	*ADH1B*	**2/*2*	**1/*2*	**1/*1*	8 cases in former drinking category For *ADH1B*, in former drinking: 0 cases with *1/*1 genotype; 2 cases with *1/*2 genotype; 6 cases with *2/*2 genotype For *ALDH2*, in former drinking; 0 cases with *2/*2 genotype; 3 cases with *2/*1 genotype; 5 cases with *1/*1 genotype Adjusted for age, menopausal status, alcohol consumption, smoking status (never, former, current < 20 pack-years, current ≥ 20 pack-years), BMI, regular exercise, family history of breast cancer, age at menarche, parity, HRT use, and mode of referral to hospital
		Never	1.0 (ref)	1.0 (ref)	1.0 (ref)	
		Former	1.78 (0.59–5.34)	0.91 (0.16–5.11)	[no cases]	
		Light	0.93 (0.61–1.43)	0.85 (0.5–1.45)	0.82 (0.21–3.25)	
		Moderate	1.06 (0.66–1.72)	0.88 (0.45–1.71)	0.59 (0.09–3.93)	
		Heavy	1.61 (0.85–3.02)	1.12 (0.52–2.4)	1.7 (0.16–17.69)	
		P_{trend}	0.418	0.832	0.887	
		ALDH2	**1/*1*	**1/*2*	**2/*2*	
		Never	1.0 (ref)	1.0 (ref)	[no cases]	
		Former	1.03 (0.34–3.16)	1.94 (0.4–9.27)	–	
		Light	0.88 (0.57–1.36)	0.97 (0.57–1.67)	–	
		Moderate	0.98 (0.61–1.59)	0.85 (0.41–1.76)	–	
		Heavy	1.21 (0.7–2.11)	1.82 (0.52–6.36)	–	
		P_{trend}	0.887	0.892	–	

ACCH, Aichi Cancer Center Hospital; BMI, body mass index; CI, confidence interval; HRT, hormone replacement therapy; OR, odds ratio; ref, reference; SCC, squamous cell carcinoma; yr, year or years.

[a] *ADH1B* allele *1 = slow and *2 = rapid; *ADH1B*1/*1* high-risk genotype; *ADH1B* referred to by previous name (*ADH2*) in Yokoyama et al. (2002).

[b] *ADH1C* allele *1 = rapid and *2 = slow; *ADH1C*1/*1* high-risk genotype; *ADH1C* referred to by previous name (*ADH3*) in Yokoyama et al. (2002).

[c] *ALDH2* allele *1 = active and *2 = null; *ALDH2*1/*2* high-risk genotype.

et al., 2009). Second, the estimates of cessation were not directly compared with categories of continuing consumption. Given the very small numbers of cases in each alcohol cessation/genotype stratum, the Working Group did not recalculate associations to compare cessation with continuing consumption. Third, overall, none of the three studies had a sufficient number of cases in the alcohol-cessation stratum (range, 8–13) to provide reliable estimates for an association with cancer risk. When further stratified by genotype status, the number of cases within each alcohol cessation/genotype stratum was even smaller (range, 0–11). Because of the limited sample size and the need to adjust for potential confounding variables, odds ratios resulting from multivariable regression were imprecise. Finally, there was no control for the amount of alcohol consumed, which could confound associations.]

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3. MECHANISTIC DATA

3.1 Overview of the mechanisms of alcohol-induced carcinogenesis among humans

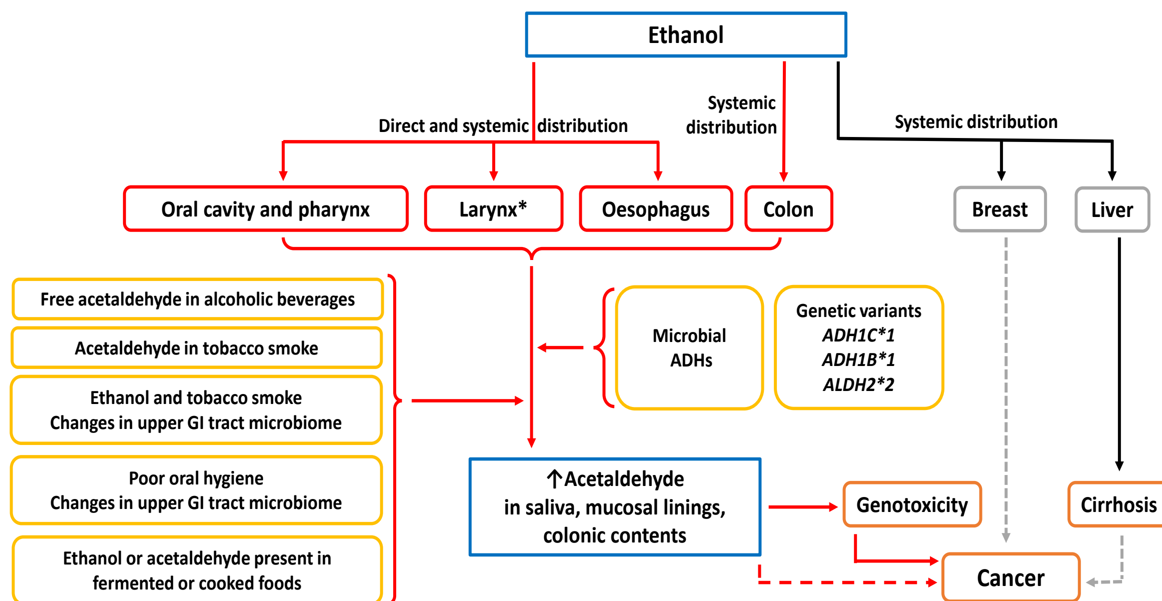
3.1.1 *Absorption, distribution, and metabolism of ethanol*

After a sip of an alcoholic beverage, ethanol is rapidly absorbed from the upper aerodigestive tract. Within 30 minutes of consumption, it is evenly distributed to the aqueous phase of the human body, including the saliva, sweat, gastric juices, colonic contents, blood, and urine. The bulk of ethanol elimination (~90%) takes place in the liver, where it is oxidized mainly by alcohol dehydrogenase (ADH) enzymes to acetaldehyde (Cederbaum, 2012; IARC, 2012). Oxidation of acetaldehyde to acetate by hepatic aldehyde dehydrogenase (ALDH) enzymes is so effective that among individuals with the active ALDH2 enzyme variant, acetaldehyde cannot be detected in the peripheral venous blood (DeMaster et al., 1983; Lindros, 1983). However, significantly elevated acetaldehyde concentrations may be detectable in the hepatic venous blood after alcohol ingestion, especially among individuals with alcohol use disorder (AUD) (DeMaster et al., 1983; Nuutinen et al., 1984). Acetate is oxidized in the peripheral tissues to carbon dioxide and water.

At high ethanol concentrations (> 10 mM), some ethanol is metabolized in the liver to acetaldehyde by the cytochrome P450-dependent ethanol-oxidizing system (cytochrome P450 2E1 [CYP2E1]) (Lieber, 1999; Cederbaum, 2012). Hepatic catalase is an insignificant (~2%) pathway for ethanol oxidation, as is excretion of unchanged ethanol in breath, sweat, or urine. Many microorganisms in the gastrointestinal tract can metabolize ethanol. In the oral cavity, oropharynx, and oesophagus, oxidation of ethanol is essentially mediated by the respective microbiomes, which may lead to high exposure of the local mucosa to acetaldehyde (Fig. 3.1). In addition, up to 10% of ingested ethanol is oxidized in the large intestine by the bacteriocolonic pathway (Salaspuro, 2003).

Chronic alcohol consumption increases the rate of ethanol elimination in both experimental animals and humans by attenuating the ethanol-induced change in the hepatic ratio of nicotinamide adenine dinucleotide, reduced form (NADH) to NAD and inducing the microsomal ethanol-oxidizing system CYP2E1 (Salaspuro and Kesänimi, 1973; Salaspuro et al., 1981; Lieber, 1999). The ethanol-induced CYP2E1 fades away within 8–15 days after the cessation of alcohol consumption (Oneta et al., 2002). The speed of ethanol-induced changes in the hepatic NADH/NAD ratio after cessation of or reduction in alcohol consumption is unknown.

Fig. 3.1 Major role of local acetaldehyde in alcohol-induced carcinogenesis



The red boxes indicate organs known to be exposed to high local acetaldehyde concentrations via saliva or colon contents. The red arrows indicate well-described mechanisms. The dotted red arrow indicates other mechanisms of carcinogenesis. The yellow boxes indicate additional factors that can increase local concentrations of acetaldehyde or duration of acetaldehyde exposure. The grey boxes indicate organs in which local levels of acetaldehyde are unlikely to be high. The dashed grey arrows indicate mechanisms of carcinogenesis that are currently unknown or hypothetical.
ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; GI, gastrointestinal.
* The magnitude of laryngeal exposure to acetaldehyde via saliva is unknown.
Prepared by the Working Group.

(a) Genetic polymorphisms

Several gene polymorphisms in the alcohol metabolic pathway modify the amount of ethanol or acetaldehyde to which an organ is exposed when an individual consumes alcohol. Genetic susceptibility has been demonstrated for ADH, polymorphic at the *ADH1B* and *ADH1C* loci, and for polymorphic variants of the gene that encodes mitochondrial ALDH2.

(i) ADH1B

ADH1B has three variants: *ADH1B*1*, *ADH1B*2*, and *ADH1B*3*. *ADH1B*1* is the most common allele among individuals of European ancestry, whereas *ADH1B*2* is frequent among individuals of East Asian ancestry (Eng et al., 2007; Li et al., 2007; Edenberg and McClintick, 2018). *ADH1B*3* is mainly found among individuals of African ancestry (McCarthy et al., 2010). The *ADH1B*2* gene encodes the ADH1B2 enzyme, which has a 40-fold higher in vitro activity than the ADH1B1 enzyme encoded by *ADH1B*1* (Yin et al., 1984). Individuals with the *ADH1B*2* alleles are more likely to abstain from alcohol or to consume less alcohol and have a reduced risk of developing AUD, although the exact mechanism of action is still unknown. Studies among individuals without AUD have failed to demonstrate any effects of the *ADH1B* genotype on the rate of ethanol elimination, blood acetaldehyde

concentrations, or psychological responses to ethanol (Mizoi et al., 1994; Peng and Yin, 2009; Chen et al., 2021); however, among individuals with *ADH1B*2* who develop AUD, the rate of ethanol elimination is greater than that among individuals with *ADH1B*1* who develop AUD (Yokoyama et al., 2016). Therefore, individuals with an *ADH1B*1* genotype have a comparatively higher risk of alcohol dependence and of alcohol-related upper aerodigestive tract cancer (Thomasson et al., 1991; Higuchi et al., 1996, 2004; Yang et al., 2010; Guo et al., 2012).

(ii) ADH1C

The *ADH1C*1* allele encodes a hepatic ADH enzyme that metabolizes ethanol 2.5 times as fast in vitro as the ADH enzyme encoded by the *ADH1C*2* allele (Bosron and Li, 1986). However, the rate of ethanol elimination is not correspondingly increased, because it presumably is limited in the liver by the reoxidation rate of NADH (Cederbaum, 2012).

(iii) ALDH2

A single point mutation in the *ALDH2*1* gene results in the replacement of glutamate at position 487 with lysine in the ALDH2 subunit protein, which is expressed predominantly in the liver (Yoshida et al., 1984). This *ALDH2*2* allele causes dominantly inherited ALDH2 enzyme deficiency, with zero in vitro activity among individuals who are homozygous for the allele and ~17% activity among individuals who are heterozygous for the allele (Lai et al., 2014). This allele is limited to individuals of East Asian ancestry.

Among individuals who are carriers of the *ALDH2*2* allele, consuming alcohol results in facial flushing, tachycardia, palpitation, and dose-dependent increases in blood acetaldehyde concentrations. These individuals are more likely to abstain from alcohol or to consume less alcohol and are less likely to develop AUD or alcohol-related health problems, especially if they are homozygous for this allele (Harada et al., 1983; Crabb et al., 1989; Higuchi et al., 1996; Peng et al., 1999; Koyanagi et al., 2020; Chen et al., 2021).

3.1.2 Local exposure of target organs to acetaldehyde

Exposure to high concentrations of acetaldehyde, a potent genotoxic metabolite of ethanol, is a major determinant of alcohol-related carcinogenesis, at least in the upper aerodigestive tract (Fig. 3.1; see Section 3.1.3). Exposure to acetaldehyde is markedly enhanced by genetic polymorphism of the genes that encode the ADH and ALDH2 enzymes; additional sources of exposure include acetaldehyde in tobacco smoke, ethanol or acetaldehyde present in fermented or cooked food, acetaldehyde present in alcoholic beverages, and changes in the oral microbiome induced by chronic smoking, chronic heavy alcohol consumption, or poor oral hygiene (Fig. 3.1; Salaspuro, 2017, 2020; Nieminen and Salaspuro, 2018). Sections (a)–(f) below review the available evidence on the role of local acetaldehyde in the development of cancer at those sites that have been identified as being linked to alcohol consumption, i.e. oral cavity, pharynx, larynx, oesophagus, colorectum, liver, and breast.

(a) Oral cavity and pharynx

The oral microbiome, present in the oral cavity and pharynx, contains many bacteria and yeasts that can effectively oxidize ethanol to acetaldehyde both in vitro and in vivo (Homann et al., 1997; Tillonen et al., 1999a; Muto et al., 2000; Kurkivuori et al., 2007; Uittamo et al., 2009; Nieminen et al., 2009; Moritani et al., 2015). This microbiome includes a variety of ADH enzymes with different activities and variations in their Michaelis constant (K_M) values; in vitro salivary formation of acetaldehyde has been shown to vary over a 30-fold range, depending on an individual's oral microbiome (Yokoyama et al., 2018). Acetaldehyde accumulates in the saliva because of the very low ALDH activity in both the oral

mucosa and the oral microbiome (Dong et al., 1996; Pavlova et al., 2013).

High salivary acetaldehyde concentrations produce dose-dependent acetaldehyde–DNA adducts in the oral mucosa of humans and rhesus monkeys (Balbo et al., 2012, 2016; Guidolin et al., 2021). [On the basis of the results from Homann et al. (1997), Väkeväinen et al. (2000), Salaspuro and Salaspuro (2004), and Balbo et al. (2012), the Working Group estimated that salivary acetaldehyde concentrations as low as 10 μM can lead to acetaldehyde–DNA adducts in the oral mucosa.] A positive linear correlation ($r = 0.86$) has been demonstrated between local exposure to acetaldehyde via the saliva and the risk of oropharyngeal cancer (Salaspuro and Lachenmeier, 2020).

Acetaldehyde production in the saliva after a sip of an alcoholic beverage can be described as an instant phase and a long-term phase, as shown in a schematic representation in Fig. 3.2.

(i) Instant phase of acetaldehyde formation in saliva

In the absence of alcohol consumption or exposure to tobacco smoke, endogenous salivary acetaldehyde concentrations are < 1 μM (Fig. 3.2). After each sip of 5 mL of 40% alcohol (v/v), ethanol remains in the saliva, gradually decreasing in concentration from ~800 mM at 30 seconds to 6 mM at 15 minutes (Helminen et al., 2013). The instant phase of microbial acetaldehyde formation starts immediately, and the concentration peaks at ~260 μM within 2 minutes. The instant phase (mean concentration, ~150 μM) lasts for ~10 minutes and represents ~70% of the total acetaldehyde exposure of the oropharynx. Acetaldehyde remains detectable in the saliva for up to 20 minutes after a single ethanol exposure (Nieminen and Salaspuro, 2018) (Fig. 3.2).

The strong positive correlation between ethanol and acetaldehyde concentrations in the saliva (Homann et al., 1997; Linderborg et al., 2011; Helminen et al., 2013; Tagaino et al., 2021) may explain the higher risk of head and neck cancer among individuals who consume liquor than among individuals who consume beer (Huang et al., 2017).

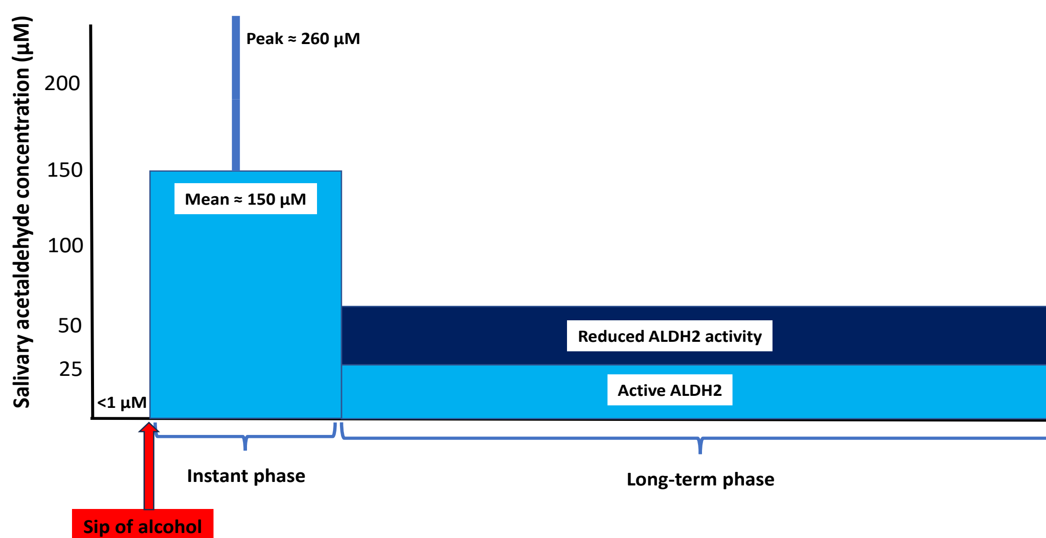
Alcoholic beverages may contain free acetaldehyde as a contaminant (see also Section 1.1.2). Ingestion of alcoholic beverages with high concentrations of free acetaldehyde (474–15 197 μM) has been found to result in a transitory peak in salivary acetaldehyde concentration up to > 1000 μM, which lasts for 1–2 minutes (Yokoyama et al., 2008; Lachenmeier and Monakhova, 2011; Linderborg et al., 2011).

(ii) Long-term phase of acetaldehyde formation in saliva

Long-term salivary acetaldehyde is derived from the ethanol that diffuses back to the saliva from the blood after systemic distribution. The long-term phase of acetaldehyde formation lasts for as long as ethanol stays in the human body and therefore depends on the total dose of alcohol consumed. During this phase, the mean salivary acetaldehyde concentration among individuals with the active ALDH2 enzyme variant is ~25 μM (Fig. 3.2; Lachenmeier and Salaspuro, 2017).

Daily exposure of the mucosa to acetaldehyde among individuals with moderate alcohol consumption (defined as 3 doses of alcohol per day) is proportionately less than exposure among individuals with heavy alcohol consumption (defined as 7 doses of alcohol per day), because individuals with moderate alcohol consumption take fewer sips of alcohol (hence, fewer instant phases of acetaldehyde formation) and ethanol is present in their bloodstream for a shorter period of time (hence, shorter long-term phases of acetaldehyde formation) (Nieminen and Salaspuro, 2018).

Fig. 3.2 Schematic representation of acetaldehyde concentrations in the saliva after a dose of alcohol



In the absence of alcohol intake or tobacco smoking, salivary acetaldehyde concentrations are < 1 µM.
In the instant phase, after a sip of 40% alcohol (5 mL kept in the mouth for 5 seconds), ethanol is distributes rapidly to the aqueous phase of the oral cavity and remains there at high concentrations for up to 20 minutes. Simultaneously, microbial production of acetaldehyde from ethanol occurs, reaching high concentrations (with a peak at ~260 µM) and lasting for 15–20 minutes. The *ALDH2* genotype has no effect on this phase.
In the long-term phase, alcohol is distributed evenly to the water phase of the body, including saliva, within 30 minutes after its ingestion. Among individuals with the active ALDH2 enzyme variant, this results in average acetaldehyde concentrations of ~25 µM, whereas among individuals with the ALDH2 variant with reduced activity, Acetaldehyde concentrations are twice as high (mean, ~53 µM). The long-term phase lasts as long as ethanol is present in the body and depends on the total amount of alcohol ingested.
The light blue represents the acetaldehyde produced by the microbial oxidation of ethanol; the dark blue represents excess acetaldehyde derived from salivary glands.
ALDH, aldehyde dehydrogenase.
Reproduced from Salaspuro (2020). Copyright © 2020 Karger Publishers, Basel, Switzerland.

(iii) Effects of ADH *and* ALDH2 *gene polymorphisms*

Ethanol elimination is faster among individuals with the high-activity *ADH1B*2* allele than among individuals with the low-activity *ADH1B*1* genotype. As a result, individuals with the low-activity *ADH1B*1* genotype are exposed to higher salivary acetaldehyde concentrations for longer periods of time (Yokoyama et al., 2016), and these individuals have a higher risk of squamous cell carcinomas of the upper aerodigestive tract cancer compared with individuals with the high-activity ADH1B enzyme (Higuchi et al., 2004; Yang et al., 2010; Ji et al., 2011; Chang et al., 2012; Guo et al., 2012).

Although the *ADH1C*1* allele is not associated with faster alcohol elimination (see Section 3.1.1(a)(ii)), individuals who are homozygous for the *ADH1C*1* allele have significantly higher concentrations of acetaldehyde in their saliva in the presence of ethanol compared with individuals who are heterozygous or homozygous for the *ADH1C*2* allele (Visapää et al., 2004). As a result, individuals who are homozygous for *ADH1C*1* and have heavy alcohol consumption have a significantly higher risk of head and neck cancer compared with individuals with other

genotypes (Visapää et al., 2004; Homann et al., 2006).

Among individuals with reduced ALDH2 activity (individuals who are heterozygous for *ALDH2*2*), the mean salivary acetaldehyde concentration during the long-term phase of ethanol-derived acetaldehyde formation is 2.1 times that among individuals with active ALDH2 (Väkeväinen et al., 2000; Yokoyama et al., 2008). These individuals are unable to efficiently eliminate the excess acetaldehyde formed in their salivary glands (Väkeväinen et al., 2001). Among individuals with heavy alcohol consumption, the excess acetaldehyde exposure associated with the reduced ALDH2 activity has been associated with a 7-fold higher risk of head and neck cancer (Lachenmeier and Salaspuro, 2017).

Individuals who are heterozygous for *ALDH2*2* provide a good human cancer model for local acetaldehyde exposure, underscoring the positive correlation between the risk of alcohol-related upper aerodigestive tract cancer and the elevated acetaldehyde exposure via saliva during the long-term phase of acetaldehyde formation from systemic distribution of ethanol. It should be noted that the *ALDH2* genotype has no effect on salivary acetaldehyde concentrations if ethanol is not present in the systemic circulation (Helminen et al., 2013). Consequently, the low concentrations of alcohol that are present in many "non-alcoholic" beverages and foods do not result in greater local acetaldehyde exposure in the upper aerodigestive tracts of individuals who are deficient in ALDH2 than in those of individuals with active ALDH2. This provides a logical explanation for the absence of associations between ALDH2 genotype and cancer among individuals who do not consume alcohol (Wu et al., 2014; Im et al., 2022).

(iv) Tobacco and poor oral hygiene

Alcohol consumption, tobacco use, and poor oral hygiene are synergistic risk factors for head and neck cancer (Hashibe et al., 2009; IARC, 2012; Hsiao et al., 2018). Chronic smoking, heavy alcohol consumption, and poor oral hygiene modify the oral microbiome, which results in enhanced local acetaldehyde exposure from ethanol (Fig. 3.1). How quickly the upper aerodigestive tract microbiome may return to normal after cessation of heavy alcohol consumption and/or smoking is currently unknown. For more details about the mechanistic interactions between tobacco smoking and alcohol consumption, see Section 3.1.4.

(b) Larynx

The risk of alcohol-related laryngeal cancer has been shown to be highest among individuals with the low-activity *ADH1B*1* genotype and slow or non-functional *ALDH2* genotypes, which leads to exposure of the upper aerodigestive tract mucosa to elevated local acetaldehyde concentrations for extended periods of time (Huang et al., 2017). However, no data exist about local acetaldehyde concentrations in the larynx after alcohol consumption.

(c) Oesophagus

Consumption of alcoholic beverages is causally related to squamous cell carcinoma of the oesophagus; there is no or little association with adenocarcinoma of the oesophagus (IARC, 2010). The ADH activity of the oesophageal mucosa is 7–12 times that of the oropharyngeal mucosa (Yin et al., 1993; Dong et al., 1996). Individuals who are homozygous for the highly active *ADH1C*1* allele and have heavy alcohol consumption have a significantly higher risk of oesophageal squamous cell carcinoma compared with individuals with other *ADH1C* genotypes (Visapää et al., 2004; Homann et al., 2006). In addition, ALDH activity in the oesophageal mucosa is 1/35th of that in the liver (Yin et al., 1993; Yao et al., 1997). ALDH2 deficiency markedly increases the risk of oesophageal squamous cell carcinoma in a dose-dependent manner among individuals with heavy alcohol consumption (Yang et al., 2010).

Furthermore, CYP2E1 is induced in the oesophageal mucosa by alcohol consumption (Millonig et al., 2011). These data are consistent with a role for increased local exposure to acetaldehyde in the genesis of oesophageal cancer; however, the concentrations of ethanol and acetaldehyde in the oesophagus after alcohol consumption are unknown.

(d) Colorectum

Both the mucosal and microbial oxidation of ethanol to acetaldehyde provide potential mechanisms for ethanol-related colorectal carcinogenesis.

(i) Bacteriocolonic oxidation of ethanol

The human colon can be inhabited by > 400 species of bacteria and ~10^{14} individual bacteria (Luckey, 1977; Maier et al., 2014; Sender et al., 2016). The characteristics of these bacteria and their living environment determine their functions in ethanol and acetaldehyde metabolism (Fig. 3.3; Salaspuro, 2003). The ADH activity of colonic bacteria varies greatly, as do their K_M values, which range from 0.06 mM to 29.9 mM (Jokelainen et al., 1996a; Nosova et al., 1997). In anaerobic conditions, anaerobic and facultative anaerobic bacteria that have the ADH enzyme produce endogenous ethanol from glucose. In the aerobic or microaerobic conditions that prevail close to mucosal surfaces, the bacteria produce acetaldehyde from endogenous or exogenous ethanol (Salaspuro et al., 1999).

The human colonic microbiome also has catalase activity, which probably is of bacterial origin (anaerobic and facultative anaerobic bacteria) and suggests that acetaldehyde also can be produced by catalase from intracolonic ethanol (Tillonen et al., 1998).

The colonic mucosal and bacterial ALDH enzymes have a limited capacity to eliminate acetaldehyde. As a result, acetaldehyde accumulates in the colon at ethanol concentrations known to be present in the large intestine after normal alcohol consumption (Yin et al., 1994; Koivisto and Salaspuro, 1996; Nosova et al., 1996, 1998).

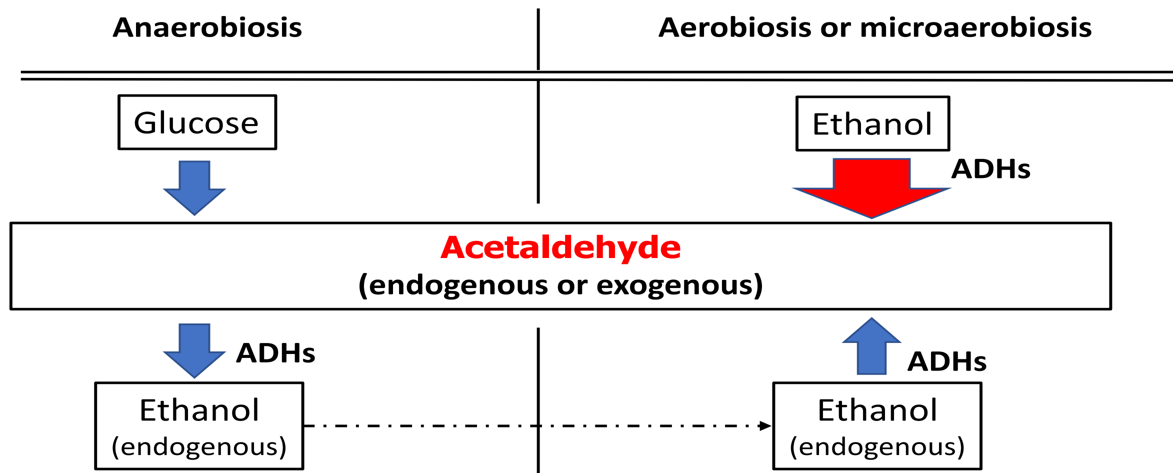
Alcohol administration results in significantly elevated acetaldehyde concentrations in the colonic mucosa of naive rats compared with germ-free animals (Seitz et al., 1990). In piglets, intracolonic acetaldehyde concentrations increased linearly (peak, 271 μM; $r = 0.85$) with increasing intracolonic ethanol levels (Jokelainen et al., 1996b). In rats, mean intracolonic acetaldehyde concentrations were 387 ± 185 μM after alcohol administration (intracolonic ethanol concentration, 28 ± 5 mM) (Homann et al., 2000b). Inhibition of ALDH2 in rats provokes a marked increase in intracolonic acetaldehyde concentration (8-fold increase vs blood concentrations) after an alcohol challenge (Visapää et al., 2002). [This supports the role of colonic mucosal ALDH2 in the regulation of intracolonic acetaldehyde levels.]

Reducing the colonic aerobic bacteria lowers the rate of ethanol elimination by ~9% in both rats and humans (Jokelainen et al., 1997; Nosova et al., 1999; Tillonen et al., 1999b). In rats, this results in almost total inhibition of the ethanol-induced increase in intracolonic acetaldehyde levels (Visapää et al., 1998). In contrast, reducing the colonic anaerobic bacteria induced a 5-fold increase in intracolonic acetaldehyde levels (Tillonen et al., 2000).

(ii) Genetic polymorphism

Human colonic mucosa expresses the ADH and ALDH enzymes (Yin et al., 1994; Seitz et al., 1996), and polymorphisms in these genes affect ethanol oxidation and elimination. ADH enzyme activity in rectal mucosa is 87% higher among individuals who are homozygous for *ADH1C*1* compared with individuals who are heterozygous (*ADH1C*1/*2* genotype); also, the activity of low-K_M enzymes (largely ALDH2) is 33% higher among individuals with the active *ALDH2* phenotype than among individuals

Fig. 3.3 Schematic representation of microbial production of acetaldehyde in the intestine



The characteristics of the microbiome and its living environment determine its functions regarding ethanol and acetaldehyde metabolism. Many bacteria and yeasts present in the normal intestinal microbiome contain alcohol dehydrogenase (ADH) enzymes with a variety of different values of the maximum velocity (V_{max}) and the Michaelis constant (K_M). Under anaerobic conditions, anaerobic and facultative anaerobic bacteria ferment glucose via pyruvate and acetaldehyde to ethanol. The second part of the reaction is catalysed by reversible ADH enzyme. Under the aerobic and microaerobic conditions that prevail in the mucosal surfaces, ethanol (endogenous or exogenous) is oxidized to acetaldehyde. The capacity of the microbiome and the mucosa to eliminate acetaldehyde is limited, which may lead to accumulation of acetaldehyde in the gastrointestinal tract.
Courtesy of Ville Salaspuro.

with the low-activity *ALDH2* phenotype (Chiang et al., 2012). Individuals with heavy alcohol consumption who are deficient in ALDH2 have a risk of colorectal cancer that is 3.4 times that among individuals with the active ALDH2 enzyme (Yokoyama et al., 1998; Murata et al., 1999; Matsuo et al., 2002). Also, the highly active *ADH1C*1/*1* genotype is more common (odds ratio, 1.67) in patients with colorectal neoplasia who have heavy alcohol consumption than in cancer-free controls (Homann et al., 2009). These observations support a causal role for acetaldehyde in alcohol-related colorectal carcinogenesis.

(e) Liver

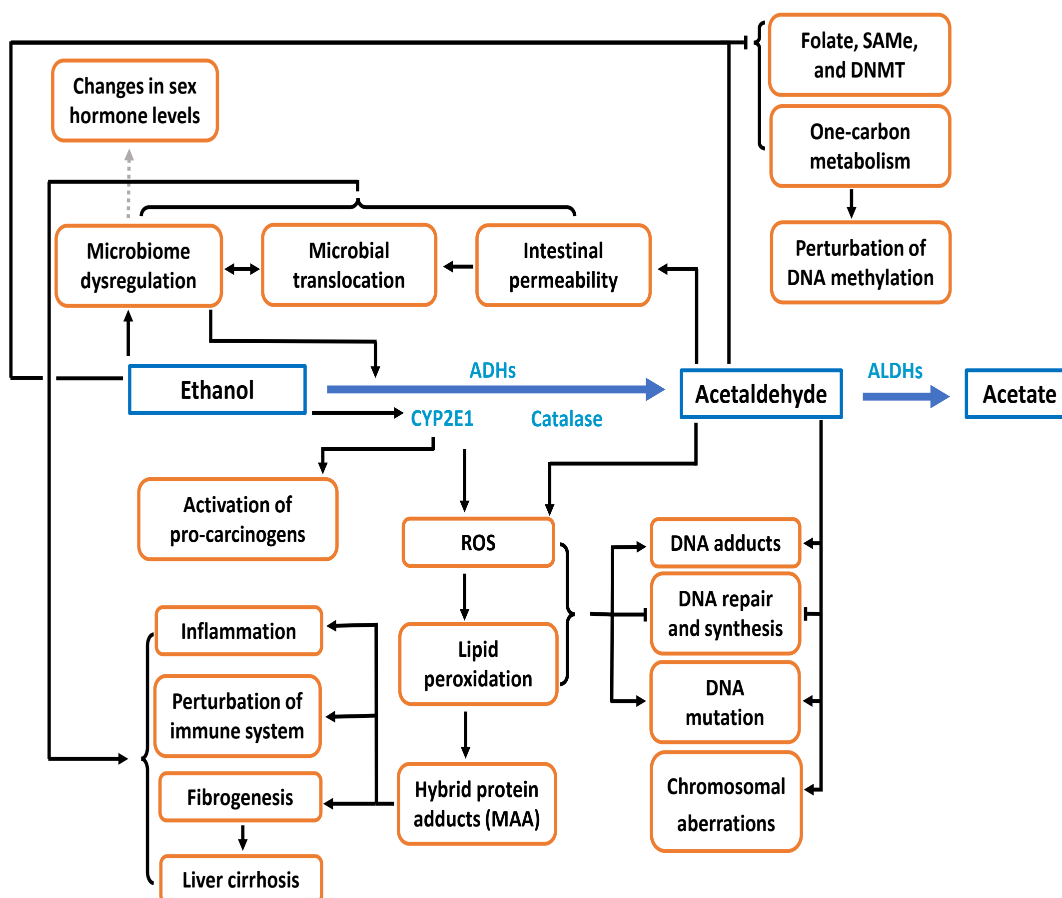
Chronic alcohol consumption is a risk factor for hepatocellular carcinoma (HCC), which is associated mainly with cirrhosis of the liver (IARC, 2012). Several studies have reported higher *ALDH2*1* allele frequency among individuals of Asian ancestry who have alcohol-related cirrhosis compared with healthy controls, suggesting that the inactive *ALDH2*2* allele does not predispose individuals with heavy alcohol consumption to HCC (Wang et al., 2020). Studies of the polymorphisms of *ALDH2* and *CYP2E1* indicate that acetaldehyde plays an insignificant role in hepatocellular carcinogenesis (Zhou et al., 2012; Chen et al., 2020). However, among individuals with hepatitis B virus-related cirrhosis and heavy alcohol consumption, those with the *ALDH2*2* allele have a significantly higher risk of HCC compared with individuals with the fully active ALDH2*1 phenotype (Tsai et al., 2022).

In addition to promoting cirrhosis, alcohol probably increases the risk of HCC by mechanisms that are not mediated by local levels of acetaldehyde (Fig. 3.4; Section 3.1.3).

(f) Breast

Although breast cancer is one of the most prevalent alcohol-related cancers, mechanisms of ethanol-induced breast cancer are hypothetical and largely unclear (Seitz et al., 2012; Castro and Castro, 2014; Ugai et al., 2019; Park et al., 2020; Mori et al., 2023). Human mammary tissue contains a class of ADH that has a limited potential to transform ethanol to acetaldehyde (Triano et al., 2003). There is no evidence that *ALDH2* is active in human breast tissue. Breast milk from women who are lactating does not contain measurable levels of acetaldehyde after they consume alcohol (Kesäniemi, 1974). Genetic polymorphism of ethanol- or acetaldehyde-metabolizing enzymes has not been shown to modify alcohol-related breast cancer risk (Freudenheim, 2020). An increased risk of breast cancer has been demonstrated among individuals who are homozygous for the *ALDH2*2* allele (Ugai et al., 2019); however, no evidence has been observed of

Fig. 3.4 Mechanisms for alcohol-induced carcinogenesis among humans



The grey dashed line indicates a hypothetical mechanism. For more details, see Section 3.1.3.
ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP2E1, cytochrome P450 2E1; DNMT, DNA methyltransferase; MAA, malondialdehyde–acetaldehyde–albumin adducts; ROS, reactive oxygen species; SAMe, *S*-adenosyl-L-methionine.
Prepared by the Working Group.

an interaction between the *ALDH2*2* genotype and alcohol consumption.

The CYP2E1 protein is expressed in both normal human breast and breast tumour tissues, and levels are higher in breast tumours (Kapucuoglu et al., 2003). However, no significant relationship has been found between the *CYP2E1* polymorphism and risk of breast cancer (Lu et al., 2017). Thus, the higher risk of breast cancer among women who consume alcohol does not appear to be mediated by local exposure to acetaldehyde.

Potential mechanisms of alcohol-related breast carcinogenesis possibly mediated by ethanol or acetaldehyde metabolism include oxidative stress, increased cell proliferation, effects on the intestinal microbiome, effects on sex and steroid hormones, and effects on one-carbon metabolism (see Section 3.1.3).

3.1.3 Alcohol-related mechanisms of carcinogenesis

Alcohol consumption leads to many disruptive changes in the human body, and several mechanisms have been described that could potentially be involved in alcohol-related carcinogenesis (Fig. 3.4). These have been discussed in many reviews (e.g. Rodriguez and Coveñas, 2021; Rumgay et al., 2021). A brief overview is presented here.

The genotoxic effects of alcohol have been comprehensively reviewed in several *IARC Monographs* volumes (IARC, 1988, 2010, 2012). The genotoxicity of ethanol is mediated mainly by its metabolism to acetaldehyde (discussed in Section 3.1.1). Acetaldehyde reacts with DNA, resulting in DNA damage that includes DNA adducts, chromosomal aberrations, and mutations (Guidolin et al., 2021; Hoes et al., 2021). The ethanol-inducible CYP2E1 enzyme (see Section 3.1.1) produces various reactive oxygen species, which lead to the formation of lipid peroxidation products such as malondialdehyde, and to oxidative stress, which can also lead to DNA damage and perturbation of DNA repair (Linhart et al., 2014). Moreover, acetaldehyde and malondialdehyde can react synergistically with proteins to form hybrid protein adducts, designated as malondialdehyde–acetaldehyde–albumin adducts, which are very immunogenic and have pro-inflammatory and fibrogenic properties. These adducts have been detected in patients with liver cirrhosis and hepatitis and may contribute to the development of alcohol-related liver damage (Rolla et al., 2000; Tuma, 2002). By inducing CYP2E1, alcohol also stimulates the metabolism of pro-carcinogens into carcinogens (Gao et al., 2018; Song et al., 2019).

Chronic alcohol consumption has a strong impact on both the oral microbiome and the intestinal microbiome. Alcohol consumption alters the composition of the intestinal microbiome, enhancing local levels of acetaldehyde production (discussed in Section 3.1.2(d)). High concentrations of acetaldehyde have a direct inhibitory effect on proteins involved in the formation of adherens junctions and tight junctions, which leads to epithelial barrier dysfunction and intestinal permeability. This results in increased translocation of microbiota and endotoxins (microbial products and lipopolysaccharide [LPS]) across the mucosa (Rao, 2009). The intestines and the liver are directly connected via the portal vein; microbial translocation from the intestines to the liver elicits chronic hepatic inflammation, severe hepatic injury such as cirrhosis, and eventually HCC (Giraud and Saleh, 2021; Ohtani and Hara, 2021; Petagine et al., 2021). Microbial translocation and endotoxaemia also trigger systemic inflammation, with increased risk of cancer through the effects of oxidative stress, changes in cytokine levels, and impaired anti-tumour immune systems (Greten and Grivennikov, 2019). In the oesophagus, chronic alcohol consumption could cause an inflammatory process known as pyroptosis, which may contribute to the development of

oesophageal cancer (Wang et al., 2018). Alcohol consumption also increases the permeability of the oral mucosa (Howie et al., 2001), possibly rendering the mouth more sensitive to the effects of other carcinogens, such as those found in tobacco smoke (Feller et al., 2013).

Additional mechanisms of alcohol-related carcinogenesis include reduction of folate concentrations in the colonic mucosa by local acetaldehyde generation. Heavy alcohol consumption reduces adsorption of folate, enhances urinary excretion of folate, and inhibits enzymes that are pivotal for one-carbon metabolism. Aberrant DNA methylation due to a deficiency in methyl donors is a common effect of alcohol-related folate deficiency (Sharma and Krupenko, 2020). Among women, alcohol consumption also increases the concentrations of estradiol, testosterone, and several other sex hormones in the circulation and decreases the concentration of sex hormone-binding globulin (SHBG), and these changes are hypothesized to be related to risk of breast cancer (Key et al., 2011; Freudenheim, 2020). Recently, an association between alterations in the intestinal microbiome and breast cancer has been reported, suggesting that the microbiome may play a role in regulating estrogen levels (Kwa et al., 2016; Parida and Sharma, 2019). In addition, consumption of alcoholic beverages leads to concentrations of estradiol that are 3-fold higher among women who are taking oral estrogen and progestin as postmenopausal hormone therapy (Ginsburg et al., 1996). Furthermore, in the Women's Alcohol Study, a controlled feeding trial conducted among healthy non-smoking postmenopausal women in the USA, direct assessments were performed of the impact of 1 or 2 drinks per day versus no drinks per day, and the participants served as their own controls in this feeding study. Changes in several end-points, including biomarkers of estrogen metabolism, oxidative stress, and inflammation, were measured, providing valuable insights into the effects of ethanol on mechanistic pathways relevant to cancer (Dorgan et al., 2001; Laufer et al., 2004; Mahabir et al., 2004, 2017; Hartman et al., 2005; Stote et al., 2016).

3.1.4 Mechanistic interactions between alcohol consumption and tobacco smoking

Epidemiological studies have provided consistent evidence for a synergistic interaction between alcohol consumption, tobacco smoking, and risk of cancers at several sites, including squamous cancers of the head and neck and the oesophagus (Hashibe et al., 2009; Anantharaman et al., 2011; Radoï et al., 2013). Data suggest several possible mechanisms associated with more risk than the effects of the two carcinogenic exposures combined:

(i) Alcohol may have a local permeabilizing effect on penetration of the oral mucosa by tobacco carcinogens (Du et al., 2000).

(ii) Induction of CYP2E1 by ethanol increases metabolic activation of tobacco carcinogens, leading to enhanced formation of reactive chemical species at target sites (IARC, 2012).

(iii) Ethanol also acts as a competitive inhibitor of CYP enzymes (e.g. CYP2E1, CYP1A1, 2B6, and 2C19). Direct inhibition of CYPs by ethanol in target tissues may increase exposure to genotoxic tobacco carcinogens that are substrates for these CYP enzymes (IARC, 2012).

(iv) Chronic smoking combined with chronic heavy alcohol consumption induces changes in the oral microbiome, especially in microbial strains that have high acetaldehyde formation activity (Homann et al., 2000a). Salaspuro and Salaspuro (2004) demonstrated that tobacco use modifies the efficiency of conversion of ethanol to acetaldehyde in the oral cavity, by measuring salivary acetaldehyde concentrations among individuals during controlled

exposures to ethanol and cigarette smoke (Fig. 3.5). Compared with individuals who do not smoke, individuals who smoke had an approximately 2-fold higher level of acetaldehyde in their saliva (~25 µM vs ~50 µM), even when they were not currently smoking, and this difference persisted for hours (Fig. 3.5A). After an ethanol challenge, salivary acetaldehyde concentrations during concomitant smoking among individuals who smoke were 7-fold higher than those among individuals who did not smoke, reaching 350–400 µM (Fig. 3.5B). Acetaldehyde is also a component of tobacco smoke, and smoking a single cigarette – without concomitant alcohol consumption – results in a rapid increase in salivary acetaldehyde concentrations (up to 250 µM), followed by a rapid decrease within 5–10 minutes (Salaspuro and Salaspuro, 2004). These data imply that in organs that have direct contact with saliva, exposure to tobacco and alcohol together results in more local acetaldehyde than the sum of the two exposures alone.

Fig. 3.5 Synergistic effect of alcohol consumption and tobacco smoking on salivary acetaldehyde concentration

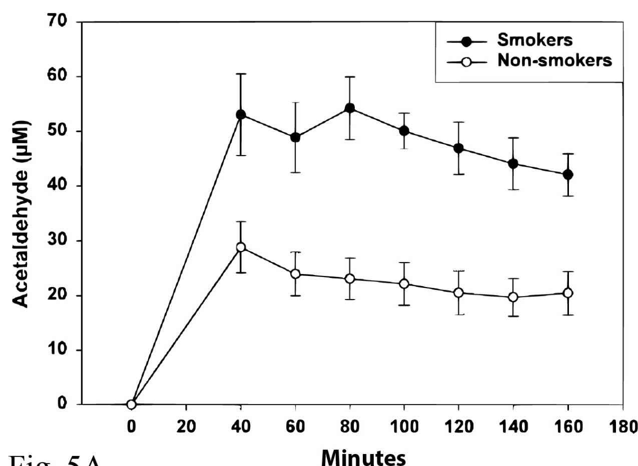


Fig. 5A

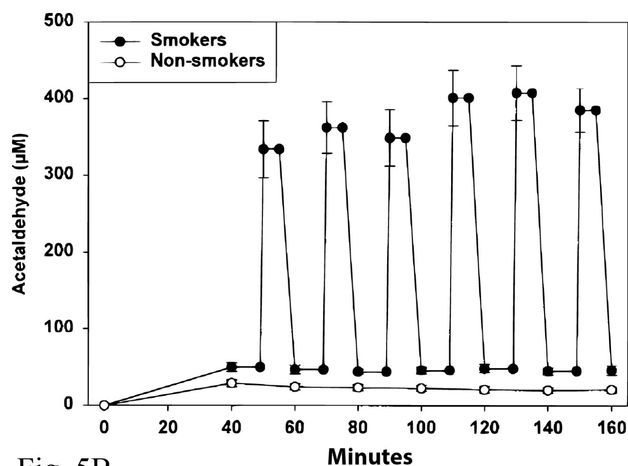


Fig. 5B

Acetaldehyde is present in tobacco smoke; without concomitant ethanol intake, salivary acetaldehyde concentration immediately increases on tobacco smoking to ~260 µM, and decreases within 10 minutes.
(A) After ethanol ingestion but without concomitant smoking, salivary acetaldehyde concentrations among individuals who smoke (smokers) are 2 times those among individuals who do not smoke (non-smokers). Differences between acetaldehyde concentrations were significant at all time points ($P < 0.05$).
(B) After an ethanol challenge (0.8 g of ethanol per kg of body weight), salivary acetaldehyde levels (area under the curve) among participants who were actively smoking (smokers) and who concomitantly smoked (i.e. 1 cigarette every 20 minutes) were 7 times those among individuals who did not smoke (non-smokers). Each peak corresponds to one cigarette smoked.
In both (A) and (B), the peak that would correspond to the instant phase of alcohol consumption alone (as shown in Fig. 3.2) does not appear, because in these experiments acetaldehyde was first measured 40 minutes after ethanol intake.
Adapted from Salaspuro and Salaspuro (2004). Copyright © 2004, John Wiley and Sons.

3.2 Cancer-related mechanistic changes after cessation of alcohol consumption

3.2.1 Study designs and limitations of the available studies

Section 3.2 reviews and assesses mechanistic data related to the effect of alcohol cessation on risk of cancer. No mechanistic studies of reduction in alcohol consumption (rather than cessation) were available to the Working Group. Several limitations of the available studies pertain to the different sections and are summarized here. First, several studies evaluated a relatively small number of individuals. A common research design was to examine changes in biomarkers among individuals at entry into a treatment programme for AUD and at intervals after cessation of alcohol consumption, and a comparison may have been made with healthy individuals in a control group or with clinically normal ranges for values, if available. In other studies, the comparison was between individuals with AUD who had become abstinent years before and individuals in a control group, meaning that the comparisons were between different groups of individuals. A small number of studies tested the effect of short-term alcohol exposure in a controlled setting.

In many studies, reporting of duration and intensity of previous alcohol consumption was lacking and participants were categorized as entering rehabilitation treatment or having AUD. It is worth noting that alcohol dependence and AUD were distinctly used in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association, 1994), whereas the 5th edition (DSM-5; American Psychiatric Association, 2013) conserved only the AUD terminology, which encompasses both alcohol dependence and AUD of DSM-IV (NIAAA, 2021). When information on previous alcohol consumption was provided, classification of levels of alcohol consumption varied (e.g. excessive vs non-excessive; mild, moderate, or heavy based on units of alcohol consumed per day); proof of abstinence in long-term studies was not always provided, and often the level of alcohol consumption among participants in the control group was not stated (e.g. not consuming alcohol vs consuming alcohol at a low level).

The demographic makeup of the studies was in many cases predominantly men and often only people of European ancestry. Sometimes, potential confounders (other medical illnesses, especially the presence of subclinical liver disease, smoking, nutritional status, and obesity) were not controlled for. It was difficult to appreciate the effect of the stress of alcohol withdrawal itself on the outcome measures, and the potential effects of pharmacological treatments used during rehabilitation or of compensatory behaviours (e.g. increase in cigarette smoking). Given the critical role of the alcohol–tobacco interaction in cancer etiology, lack of control for tobacco use and changes in use over the time course of these studies is a major limitation. Studies of inpatients in rehabilitation treatment centres did not take into account the change, and often improvement, in their dietary intake while they were hospitalized.

There were few studies on the target tissues of alcohol-related carcinogenesis, and surrogates such as circulating white blood cells may not reflect changes in the target organ. Given the known long period of persisting increased risk of cancer after cessation of alcohol consumption, few studies were of sufficient duration to evaluate for full resolution of the effects under consideration.

3.2.2 Genotoxicity

Studies investigating the genotoxic effects of alcohol consumption have focused mainly on measuring and quantifying chromosomal

aberrations and micronuclei. Several studies have focused more specifically on measuring covalent modification of DNA (DNA adducts). A few studies have investigated mitochondrial DNA deletions. Most of the studies measured DNA damage in peripheral blood mononuclear cells [a surrogate sample with cells characterized by type of exposure and turnover quite different from those characterizing the target tissues].

The body of literature that addressed the reversibility of ethanol-related DNA-damaging effects is summarized below. Detailed information about each study is given in Table 3.1. When assessing long periods of abstinence, most of the studies included groups of individuals with AUD, individuals who ceased consuming alcohol, and controls. Studies assessing the change in DNA damage among individuals with AUD who cease consuming alcohol are limited to observations during a period of at most 1 year. Some studies investigated the effects of alcohol ingestion by comparing the DNA damage before and after consumption of a specific dose of alcohol.

A first set of studies compared DNA damage among individuals who currently consume alcohol and among individuals who formerly consumed alcohol and had abstained for a certain period of time.

Castelli et al. (1999) compared the frequency of peripheral blood cells with chromosomal aberrations (percentage of aberrant cells) and of micronuclei (number of micronuclei per 1000 binucleated cells) among 3 groups composed of 11 participants with AUD, 9 participants with AUD who abstained from alcohol consumption for ≥ 1 year, and 10 healthy controls. All study participants, except for 3 individuals among the group with AUD and 4 individuals among the group that abstained, smoked heavily. The group with AUD had a significantly higher frequency of chromosomal aberrations (mean ± standard deviation [SD]), 4.00% ± 2.27%) than the group that abstained (no frequency provided) and the healthy controls (0.90% ± 0.74%) ($P < 0.01$). Similarly, the group with AUD had a higher frequency of micronuclei (11.00% ± 4.11%) than the group that abstained (no frequency provided) and the healthy controls (5.11% ± 2.60%) ($P < 0.05$). [The frequencies for the group that abstained were not reported; there was a lower percentage of individuals who smoked heavily in this group (5 of 9 individuals who abstained vs 8 of 11 individuals with AUD).]

Maffei et al. (2002) analysed the same markers in peripheral blood lymphocytes from 20 people with AUD, 20 people with AUD who abstained (for ≥ 1 year), and 20 controls who did not consume alcohol, with comparable composition for sex, age, and smoking status. The group with AUD had a significantly higher frequency of structural chromosomal aberrations (chromatid breaks and exchanges and chromosome breaks and exchanges) (mean ± SD, 4.35% ± 2.06%) than the group that abstained (2.00% ± 1.21%; $P = 0.001$) and the controls (1.45% ± 0.83%; $P = 0.001$). The group with AUD had a significantly higher frequency of binucleated cells with micronuclei (mean ± SD, 12.05% ± 5.43%) than the group that abstained (7.15% ± 2.64%; $P = 0.001$) and the controls (7.60% ± 1.57%; $P = 0.001$). The frequencies for the group that abstained were similar to those for the controls. A multiple regression analysis was performed to investigate whether the duration of AUD or of abstinence was correlated with either the frequency of chromosomal aberrations or the frequency of micronuclei, but none of these analyses resulted in significant findings.

Another set of studies monitored changes in DNA damage among individuals with AUD who abstained from consuming alcohol for various durations of time.

In a study in Japan, Matsushima (1987) compared the frequencies of chromosomal aberrations in lymphocytes from 25 participants who formerly consumed alcohol and reported varying periods of abstinence (< 5 years, 5–10 years, > 10 years) with those among 17 participants

Table 3.1 Effects of cessation of alcohol consumption on genotoxicity

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
Matsushima (1987) Japan	17 individuals with chronic AUD (ages, 22–74 years) 25 individuals with AUD who abstained (ages, 39–69 years), divided into 3 groups according to duration of abstinence: < 5 years, 5–10 years, and > 10 years Controls: 10 healthy volunteers, all women (ages, 19–21 years)	Controls were not matched All women, younger, non-drinkers, and non-smokers	All individuals with chronic AUD except 1 had been drinking heavily for > 10 years Individuals with AUD who abstained had been drinking heavily for > 20 years	Peripheral lymphocytes Chromosomal aberrations	Values are mean ± SD **Chromosome profiles (%)** ***Abnormal metaphases*** Individuals with chronic AUD: 20.6 ± 6.5 Individuals with AUD who abstained: 11.1±3.9*** Controls: 10.2 ± 3.1*** ***Gaps*** Individuals with chronic AUD: 14.4 ± 6.0 Individuals with AUD who abstained: 8.0 ± 3.4*** Controls: 6.9 ± 2.7*** ***Breaks*** Individuals with chronic AUD: 6.1 ± 3.2 Individuals with AUD who abstained: 2.7 ± 2.4*** Controls: 3.8 ± 2.2 ***Dicentric chromosomes*** Individuals with chronic AUD: 1.2 ± 1.0 Individuals with AUD who abstained: 0.4 ± 0.5*** Controls: 0.2 ± 0.6** ***Rings*** Individuals with chronic AUD: 1.1 ± 1.2 Individuals with AUD who abstained: 0.2 ± 0.5*** Controls: 0.2 ± 0.6* ***Interchanges*** Individuals with chronic AUD: 0.2 ± 0.5 Individuals with AUD who abstained: 0.0 Controls: 0.0 *P < 0.05, **P < 0.01, ***P < 0.001 vs individuals with chronic AUD

Table 3.1 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
Gattás and Saldanha (1997) Brazil	55 individuals with AUD who abstained (45 men; ages, 24–70 years; 10 women; ages, 29–63 years); mostly heavy smokers Controls: 55 healthy volunteers (31 men; ages, 23–56 years; 24 women; ages, 19–47 years)	Sex and age Controls were not screened for alcohol consumption or smoking Smoking, drug use, and sex were considered in the statistical analysis	Individuals with AUD had been drinking heavily for > 10 years before abstinence Duration of abstinence: range, 1 month to 32 years (average, 46 months)	Peripheral lymphocytes Chromosomal aberrations	**Cells with structural aberrations (%)** Individuals with AUD who abstained: 7.1 Controls: 2.4 $P < 0.0001$
Castelli et al. (1999) Italy	11 individuals with chronic AUD (4 women, 7 men; ages 29–63 years) 9 individuals with AUD who abstained (2 women, 7 men; ages 31–69 years) Controls: 10 healthy individuals (4 women, 6 men; ages 30–60 years) All individuals were in a fair state of general nutrition	All individuals with AUD except 3 and all individuals with AUD who abstained except 4 were heavy smokers (> 20 cigarettes per day); all controls were heavy smokers Sex and age	Alcohol consumption: > 120 g per day Duration of alcohol consumption: average, 19 years (range, 3–30 years) Duration of abstinence: ≥ 1 year	Peripheral lymphocytes Chromosomal aberrations and micronuclei score	Values are mean ± SD **Aberrant cells (%)** Individuals with chronic AUD: 4.00 ± 2.27 Controls: 0.90 ± 0.74 Individuals with AUD who abstained: similar to controls $P_{\text{AUD vs controls}} < 0.01$ **Micronuclei/1000 binucleated cells** Individuals with chronic AUD: 11.00 ± 4.11 Controls: 5.11 ± 2.60 Individuals with AUD who abstained: similar to controls $P_{\text{AUD vs controls}} < 0.05$
Hüttner et al. (1999) Germany	31 individuals with chronic AUD (26 men; ages, 23–59 years; 5 women; ages, 36–48 years) Controls: 31 healthy non-drinking volunteers (26 men, 5 women; ages, 24–60 years)	Drinking status, smoking status, sex, and age	Alcohol consumption: 120–400 g per day Duration of AUD: 5–37 years	Peripheral lymphocytes Samples collected after abstinence for 1 week (31 participants), 3 months (8 participants), and 1 year (14 participants) Chromosomal aberrations	Values are mean ± SD (range) **Aberrant cells (%)** Controls: 1.28 Individuals with chronic AUD First week of abstinence: 3.01 ± 1.17 (0.50–5.50) $P_{\text{first week vs controls}} \leq 0.001$ After 3 months of abstinence: 3.81 ± 1.16 (2.50–6.00) After 1 year of abstinence: 4.61 ± 2.14 (1.50–9.00) $P_{\text{first week vs 1 year of abstinence}} < 0.001$

Table 3.1 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
Tsuchishima et al. (2000) Japan	4 healthy volunteers 56 individuals with ALD who abstained (mean age ± SD, 57 ± 11 years) Controls: 106 healthy individuals without chronic AUD (mean age ± SD, 54 ± 18 years)	Age	Healthy volunteers abstained from alcohol for ≥ 1 month and were then administered 23 g of ethanol every night until white blood cell mitochondrial DNA heteroplasmy was detected Individuals with ALD had consumed > 80 g of ethanol per day for > 5 years	White blood cells For individuals with ALD who abstained, samples collected after abstinence for 3 days (56 individuals) and 4 weeks (18 individuals) Mitochondrial DNA heteroplasmy within the ATPase region (PCR and fluorography)	**Number of individuals with heteroplasmy/total number of individuals (%)** Controls: 0/106 (0%) Healthy volunteers 4 days after start of alcohol intake: 4/4 (100%) 7 days after alcohol cessation: 0/4 (0%) Individuals with ALD who abstained After 3 days of abstinence: 38/56 (68%) After 4 weeks of abstinence: 8/18 (44%)
Maffei et al. (2002) Italy	20 individuals with chronic AUD (mean age ± SD, 49.9 ± 9.9 years) 20 individuals with AUD who abstained (mean age ± SD, 52.2 ± 10.6 years) Controls: 20 (mean age ± SD, 47.5 ± 10.2 years) 13 men and 7 women in each group	Sex, age, and smoking status	Alcohol consumption for 4–40 years, > 120 g per day. Abstainers had the same consumption for ≥ 5 years (range, 12–60 years), were abstinent for ≥ 1 year (range, 12–60 years)	Peripheral lymphocytes Chromosomal aberrations and micronuclei	Values are mean ± SD **Aberrant cells (%)** Individuals with chronic AUD: 4.10 ± 1.94 Individuals with AUD who abstained: 1.95 ± 1.10 Controls: 1.45 ± 0.83 $P_{\text{AUD vs abstaining AUD and controls}} = 0.001$ **Structural chromosomal aberrations (%)** Individuals with chronic AUD: 4.35 ± 2.06 Individuals with AUD who abstained: 2.00 ± 1.21 Controls: 1.45 ± 0.83 PAUD vs abstaining AUD and controls = 0.001 **Binucleated cells with micronuclei (%)** Individuals with chronic AUD: 12.05 ± 5.43 Individuals with AUD who abstained: 7.15 ± 2.64 Controls: 7.60 ± 1.57 $P_{\text{AUD vs abstaining AUD and controls}} = 0.001$

Table 3.1 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
Maffei et al. (2002) (cont.)					**NDI** Individuals with chronic AUD: 1.38 ± 0.16 Individuals with AUD who abstained: 1.44 ± 0.13 Controls: 1.37 ± 0.05 Mean NDI values were similar in the 3 groups
Burim et al. (2004) Brazil	29 individuals with chronic AUD (23 men, 6 women; 20 smokers, 9 non-smokers) 11 individuals with AUD who abstained (9 men, 2 women; 4 smokers, 7 non-smokers) Controls: 10 healthy volunteers (9 men, 1 woman; 5 smokers, 5 non-smokers)	Not reported	Individuals with chronic AUD: > 60 g of alcohol consumption per day for ≥ 3 years Individuals with AUD who abstained: 3 months to 4 years of abstinence	Peripheral lymphocytes Chromosomal aberrations (mitotic indexes, proliferation indexes); genomic translocation (FISH)	**Chromosomal aberrations (per 100 cells), mean ± SEM** Individuals with chronic AUD: 5.15 ± 0.37* Individuals with AUD who abstained: 3.87 ± 0.34* Controls: 1.72 ± 0.52 *Significantly different from controls, $P < 0.001$ **Genomic frequency of translocations (F_G/100)** Individuals with chronic AUD: 0.790 Individuals with AUD who abstained: 0.577 Controls: 0.198 $P_{\text{AUD vs controls}} < 0.05$ Chromosomal aberration frequency and duration of abstinence: direct association Chromosomal aberration frequency and increased periods of dependence: no association
Balbo et al. (2012) USA	10 healthy volunteers with moderate alcohol consumption (5 men, 5 women; ages 21–31 years) with no history of AUD Controls: baseline samples from the same participants serve as their own controls	Sex and age; all non-smokers	Increasing doses of alcohol to target blood alcohol levels of 0.03% (~1 drink) (week 1), 0.05% (~2 drinks) (week 2), and 0.07% (~3 drinks) (week 3), based on body weight and sex	Oral cell DNA Samples collected 1 week before consumption of the first dose, and also before and 2, 4, 6, 24, 48, and 120 hours after each dose of alcohol Acetaldehyde-derived DNA adduct N^2-ethylidene-dGuo (LC/MS)	**N^2-ethylidene-dGuo** Increased up to 100-fold above baseline within 4 hours after each dose in a dose-dependent manner Returned to baseline concentrations within 24 hours after alcohol intake $P = 0.001$

ALD, alcohol-related liver disease; ATPase, adenosine triphosphatase; AUD, alcohol use disorder; F_G, genomic frequency of translocations; FISH, fluorescence in situ hybridization; LC, liquid chromatography; MS, mass spectrometry; N^2-ethylidene-dGuo, N^2-ethylidenedeoxyguanosine; NDI, nuclear division index; PCR, polymerase chain reaction; SD, standard deviation; SEM, standard error of the mean.

with AUD and 10 healthy controls. The individuals with AUD had a significantly higher frequency of abnormal metaphases (mean ± SD, 20.6% ± 6.5%) than the individuals who formerly consumed alcohol (11.1% ± 3.9%; $P < 0.001$) and the controls (10.2% ± 3.1%; $P < 0.001$). No significant correlation was found between the number of years of abstinence and the frequency of chromosomal aberrations. The frequency of chromosomal aberrations in the three groups with varying durations of abstinence was comparable to that observed among the controls. [The control group included only women, of much younger age and non-smoking, whereas among the groups of individuals who currently or formerly consumed alcohol, all participants except for one were men and all smoked.]

Gattás and Saldanha (1997) compared the frequencies of structural or numerical chromosomal aberrations in lymphocytes from 55 participants with AUD who had been abstinent for from 1 month to 32 years with those among 55 healthy controls. The participants with AUD who abstained had an almost 3-fold higher frequency of structural chromosomal aberrations in peripheral blood lymphocytes compared with the controls ($P < 0.0001$), and aberrations such as breaks, gaps, and rearrangements were more prevalent among the participants with AUD. The frequency of structural chromosomal aberrations did not change with increased duration of abstinence; the frequency (mean ± SD) was 10.23% ± 1.5% for the individuals with AUD who had abstained for > 5 years and 9.17% ± 1.7% for those who had abstained for < 5 years ($P = 0.7$). [Controls were not screened for alcohol consumption, and comparisons were not made with a group of participants who currently consume alcohol, resulting in some limitations in this study. As the period of abstinence gets longer, other factors and exposures could contribute to these aberrations. Specifically, they could be affected by smoking (in particular, when smoking intensity increases to make up for the abstinence from alcohol consumption) and ageing.]

Hüttner et al. (1999) investigated the frequency of structural chromosomal aberrations in peripheral blood lymphocytes from 31 individuals with chronic AUD at the beginning of a treatment programme and then repeated the analysis on a subset of participants at 3 months and 12 months after the start of the sobriety programme. Most individuals recruited into the study smoked. The mean frequency of chromosomal aberrations among the individuals with AUD during the first week of abstinence (3.01%) was significantly higher than that among the 31 controls who did not consume alcohol (1.28%; $P \leq 0.001$). The mean frequency of chromosomal aberrations was 3.81% among the group of 8 individuals with AUD who were re-analysed after 3 months of abstinence, and it increased to 4.61% after 12 months of abstinence. This increase from the first sample to the third was significant ($P < 0.001$). [The increase over time was attributed to an increase in smoking (documented by measurement of carboxyhaemoglobin) in compensation for alcohol abstinence.]

Burim et al. (2004) compared the frequency of chromosomal aberrations in lymphocytes from 29 individuals with chronic AUD, 11 individuals with AUD who abstained (over a duration of 3 months to 4 years), and 10 controls. The frequencies of chromosomal aberrations among the individuals with chronic AUD (5.15%) and among the individuals who abstained (3.87%) were higher than those among the controls (1.72%). Chromosomal translocations for chromosomes 1, 3, and 6 were analysed in a subset of samples from 6 individuals with AUD, 6 individuals with AUD who abstained, and 6 controls, using a fluorescence in situ hybridization method. The calculated genomic translocation frequencies were not significantly different between individuals with AUD and individuals with AUD who abstained, suggesting that DNA damage may persist for a long time. [The

measurement of translocation frequency was performed on samples from 6 individuals per group only. The group with AUD who abstained was older, on average, than the group with AUD who did not abstain.]

Another set of studies focused on quantifying acetaldehyde-derived DNA adducts in genomic DNA isolated from samples collected from individuals with AUD and compared with controls (Fang and Vaca, 1995; Matsuda et al., 2006).

A specific investigation of the effects of alcohol abstinence on the levels of these adducts is currently missing from the literature. However, Balbo et al. (2012) measured the levels of the major acetaldehyde-derived DNA adduct, N^2-ethylidenedeoxyguanosine (N^2-ethylidene-dGuo), in oral cell DNA isolated from healthy participants who were exposed to three increasing doses of alcohol administered once a week for 3 weeks in a controlled clinical setting and resulting in a blood alcohol level of 0.03% ± 0.01% for week 1, 0.05% ± 0.01% for week 2, and 0.07% ± 0.01% for week 3. Oral cell samples were collected 1 week before ingestion of the first dose and 2, 4, 6, 24, 48, and 120 hours after each dose. A significant increase in the levels of N^2-ethylidene-dGuo was detected after ingestion of the lowest dose (comparable to ~1 standard alcoholic drink). The adduct levels increased significantly, as much as 100-fold from baseline, within 4 hours after each dose among all the participants and in a dose-dependent manner. The adduct levels returned to baseline within 24 hours after each dose was administered.

Tsuchishima et al. (2000) investigated the DNA-damaging effects of alcohol consumption on mitochondrial DNA. Heteroplasmy (the presence of ≥ 2 mitochondrial DNA variants within the same cell, usually due to de novo mutations in the germline or somatic tissues) in peripheral blood mitochondrial DNA was assessed by using polymerase chain reaction (PCR) to amplify the adenosine triphosphatase region with a 491-base pair deletion. Healthy volunteers (n = 4) were exposed to alcohol for several days until heteroplasmy was detected (shortly before the beginning of day 4); then participants abstained from alcohol and were followed up for several days by collecting daily samples from them. Mitochondrial DNA heteroplasmy was no longer detected in any of the participants 7 days after they became abstinent. [Only 4 volunteers were included in the alcohol dosing part of the study.] The same assessment was performed on blood collected from patients with alcohol-related liver disease (ALD) who had abstained for 4 weeks. Among 10 of the 18 patients tested, the mitochondrial DNA heteroplasmy disappeared within 4 weeks of abstinence.

3.2.3 Epigenetics

Alcohol-induced epigenetic modifications have been implicated in variations in ethanol consumption (Wolstenholme et al., 2011), addiction (Berkel and Pandey, 2017), and mediation of physiological responses to alcohol exposure, and they may serve as biomarkers of exposure (Liu et al., 2018). Mechanistic studies of alcohol withdrawal have reported a range of effects of epigenetic modifications, with most studies examining methylation, including global DNA hypomethylation and hypermethylation of individual gene promoters. Chronic alcohol exposure can reduce folate availability, which deprives enzymes of the methyl groups that process methylation changes to DNA. Ethanol and acetaldehyde alter the activity of methionine synthase, methionine adenosyltransferase, and DNA methyltransferase (Varela-Rey et al., 2013). Detailed studies have catalogued the epigenetic modifications associated with alcohol exposure in cancers of the upper aerodigestive tract, liver, colorectum, and breast (Varela-Rey et al., 2013). A few studies have examined how a reduction in alcohol exposure modulates these mechanisms with or without abstinence (Table 3.2).

Table 3.2 Effects of cessation of alcohol consumption on epigenetic modifications

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point (test used)	Results[a]
Heberlein et al. (2015) Germany	99 men with AD (mean age ± SD, 42.90 ± 9.01 years) admitted for detoxification treatment Controls: 33 healthy men (mean age ± SD, 42.2 ± 10.32 years) All individuals who participated in this study were active smokers Exclusion criteria: psychiatric illness, substance abuse other than alcohol or nicotine, severe somatic illnesses, known autoimmune diseases, known HPA axis deregulations, and history of cerebral damage	Age Adjusted for carbamazepine and clomethiazole dose and for thrombocyte count for *BDNF*	Consumption (mean ± SD) of 195.43 ± 81.61 g of alcohol per day for a duration (mean ± SD) of 9.79 ± 7.67 years	Blood DNA and serum Samples collected at abstinence and on days 1, 7, and 14 CpG methylation within the promoter regions of *BDNF* exon IV (bisulfite sequencing); serum BDNF concentration (ELISA)	Significant change in mean overall and *BDNF* promoter methylation during alcohol withdrawal ($P < 0.001$) Significant association between *BDNF* promoter methylation and duration of abstinence on day 14 ($P < 0.001$) *BDNF* serum concentrations were not correlated with mean methylation ($P = 0.170$) or methylation of individual CpG dinucleotides ($P = 0.322$)
Witt et al. (2020) Germany	99 men with AUD (mean age ± SD, 47.6 ± 9.1 years), of which 80% were smokers, with severe withdrawal symptoms upon abstinence Controls: 95 healthy men (mean age ± SD, 47.4 ± 8.9 years), of which 19% were smokers Exclusion criteria: mental illness, severe physical illness, other dependence syndromes according to DSM-IV	Age Comparison adjusted for technical quality and batch effects, cell type distribution, and smoking	NR	Blood DNA For individuals with AUD, samples collected 1–3 days after admission (time point 1) and after 2 weeks (time point 2). For controls, samples collected within first week Epigenome-wide methylation analysis at 710 944 CpG sites; single-site analysis as well as an analysis of differentially methylated regions and gene ontology analysis	**Number of differentially methylated CpG sites:** 2876 in participants with AUD at time point 1 vs after 2 weeks, FDR < 0.05 9845 in participants with AUD at time point 1 vs controls, FDR < 0.05 6094 at time point 2 vs controls, FDR < 0.05 Most significant single-site difference at *SCAP* Top differentially methylated region at *TRIM39*

Table 3.2 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point (test used)	Results[a]
Dugué et al. (2021) Australia	5606 people (68% men; median age, 61 years; IQR, 54–65 years) selected for inclusion in 1 of 7 previously conducted nested case–control studies of DNA methylation At follow-up, participants who reported weekly or current consumption > 200 g per day	Age, sex, smoking status, BMI, country of birth, sample type and white blood cell composition, and batch effects	Alcohol use questionnaire at baseline in 5606 participants, and 11 years later in 1088 participants	DNA from blood spots stored on Guthrie cards or from frozen buffy coats Epigenome-wide methylation analysis to detect the methylation status of 485 577 CpGs; single-site analysis as well as an analysis of differentially methylated regions	**Number of differentially methylated CpG sites:** 1414 CpGs associated with alcohol consumption at $P < 10^{-7}$, with 1078 replicated in 2 independent data sets 530 of the 1414 CpGs were differentially methylated for former vs current drinking using nominal *P* values ($P < 0.05$) 513 of the 1414 CpGs were differentially methylated with a change in alcohol consumption, some of which were replicated in 1 independent data set
Proskynitopoulos et al. (2021) Germany	34 men with AUD (mean age ± SD, 53 ± 8.8 years) Controls: 43 healthy men (mean age ± SD, 36 ± 17.0 years) Exclusion criteria: psychiatric illness, substance abuse other than alcohol or nicotine, cerebral ischaemia, cerebral haemorrhage, epilepsy, cardiovascular disease, and renal disease	None Measurements adjusted for multiple comparisons	Alcohol use severity (assessed by questionnaire): mean ± SD: 2.3 ± 1.3	Blood DNA For individuals with AUD, samples collected 1, 2, 3, 4, and 7–10 days after alcohol withdrawal. For controls, samples collected at baseline *ANP* and *VP* promoter region methylation (bisulfite DNA sequencing)	No significant difference in mean methylation for *VP* or *ANP* across time points for AUD Methylation of *ANP* at CpG 114 site: lower in AUD at baseline vs controls ($P = 0.000$) Methylation of *VP* at 5 CpG sites (CpG 033, CpG 064, CpG 103, CpG 118, and CpG 194): higher in AUD at baseline vs controls ($P < 0.05$) Methylation of *VP* at 3 CpG sites (CpG 053, CpG 060, and CpG 214): lower in AUD at baseline vs controls ($P < 0.05$)

Table 3.2 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point (test used)	Results[a]
Soundara-rajan et al. (2021) India	52 men with AUD (mean age ± SD, 33.98 ± 4.3 years) Controls: 52 healthy men (mean age ± SD, 32.17 ± 4.9 years) Exclusion criteria: use of any substance other than nicotine or any major psychiatric and medical disorders, based on clinical history and diagnosis	Age Ruled out the need to adjust for white blood cell count, age, BMI, FTND, medication, and dose of medication used during treatment	Duration of AUD (mean ± SD): 8.27 ± 5.4 years Alcohol consumption (mean ± SD): 12.87 ± 6.2 units per day 43 individuals were smokers Abstinence was defined as alcohol-free during ≥ 80% of the follow-up period	Blood (leukocyte) DNA and RNA Samples collected at baseline (T1), after detoxification (T2; mean ± SD of 7.81 ± 2.0 days), and after 3 months (T3) CpG-site DNA methylation in the 5′ regions of the *ALDH2* and *MTHFR* genes, and global *LINE-1* methylation	Participants with AUD vs controls: At baseline (T1): Significantly higher in *ALDH2* ($P < 0.001$) Significantly higher in *MTHFR* ($P = 0.001$) Significantly lower in *LINE-1* ($P = 0.004$) The significant differences persisted at T2 and T3 for *ALDH2*, *MTHFR*, and *LINE-1*

AD, alcohol dependence; *ALDH2*, aldehyde dehydrogenase gene; *ANP*, atrial natriuretic peptide gene; AUD, alcohol use disorder; *BDNF*, brain-derived neurotrophic factor gene; BMI, body mass index; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ELISA, enzyme-linked immunosorbent assay; FDR, false discovery rate; FTND, Fagerström Test for Nicotine Dependence; HPA, hypothalamic–pituitary–adrenal; IQR, interquartile range; *LINE-1*, long interspersed element 1 gene; *MTHFR*, methylenetetrahydrofolate reductase gene; NR, not reported; SCAP, sterol regulatory element-binding protein cleavage-activating protein gene; SD, standard deviation; *TRIM39*, tripartite motif-containing 39 gene; *VP*, vasopressin gene.

[a] https://www.genecards.org/

Heberlein et al. (2015) performed hypothesis-driven analyses of targeted epigenomic modifications that may affect continuing ethanol consumption, among 99 men with alcohol dependence and 33 age-matched healthy men as controls, and measured promoter methylation in the brain-derived neurotrophic factor (*BDNF*) gene using DNA extracted from whole blood. *BDNF*, a gene that encodes a neurotrophic growth factor that has previously been linked to addictive behaviour, has significantly higher methylation in its promoter region among individuals with alcohol dependence than among controls. The level of methylation decreased significantly ($P < 0.001$) from day 1 to day 7 after the individuals with alcohol dependence underwent withdrawal treatment, and was similar to that among controls on day 14. Compared with controls, the difference in the means was 0.063 on day 1, 0.033 on day 7, and 0.005 on day 14. The return of methylation state to control levels after the 14-day abstinence was not reflected in the serum concentration of the BDNF protein.

Witt et al. (2020) conducted an epigenome-wide analysis of blood DNA methylation among 99 men with alcohol dependence, when they were admitted for treatment and 2 weeks after they stopped consuming alcohol, with additional comparisons with 95 age-matched healthy men as controls. Abstinence resulted in widespread changes in patterns of methylation at individual CpG dinucleotides and in differentially methylated regions. Increases and decreases in methylation were observed at many individual sites and differentially methylated regions across many chromosomes. These included changes in promoters of withdrawal-associated genes (e.g. *SLC29A1*, *FYN*). The most significant single-site difference (false discovery rate [FDR], $P = 2.0 \times 10^{-19}$) in the longitudinal comparison was in sterol regulatory element-binding protein chaperone (SCAP), an escort protein required for cholesterol synthesis and lipid homeostasis. Analysis of differentially methylated regions showed the largest effect at tripartite motif containing 39 (*TRIM39*), an E3 ubiquitin ligase gene in the major histocompatibility complex (MHC) class I region, which is involved in inflammatory processes. [The study was undersized for a full genomic analysis, but many findings remained significant using FDR *P* values.]

Dugué et al. (2021) conducted an epigenome-wide analysis of the effect of alcohol exposure on blood DNA methylation among 5606 participants in the Melbourne Collaborative Cohort Study (MCCS) overall, which included 1088 participants who had alcohol consumption recorded at baseline and 11 years later. The longitudinal analysis focused on the subset of CpG sites ($n = 1414$) that were significantly associated ($P < 10^{-7}$) with alcohol consumption at baseline, and the authors extracted similar results from an available data set from the Cooperative Health Research in the Augsburg Region (KORA) study, in which alcohol consumption was measured 7 years apart (Wilson et al., 2017). A change in alcohol consumption was associated with changes in methylation at 267 CpGs in the MCCS study cohort and at 331 CpGs in the KORA study cohort, and 92 CpGs were different in both study cohorts. [Only 88 individuals in the MCCS became abstinent during the 11-year interval between measurements, limiting the strength of the results when accounting for multiple comparisons. Also, residual confounding by other key personal exposures, such as tobacco smoking and body mass index, could not be ruled out.]

Proskynitopoulos et al. (2021) studied 34 men with AUD and 43 healthy men as controls. They studied promoter methylation changes in atrial natriuretic peptide (*ANP*) and vasopressin (*VP*), two genes associated with alcohol cravings and withdrawal symptoms. Although there were significant differences in methylation patterns at baseline, there were no changes over the first 7–10 days after treatment started.

Soundararajan et al. (2021) studied promoter methylation in *ALDH2* and methylenetetrahydrofolate reductase (*MTHFR*), two genes relevant to alcohol-induced carcinogenesis, as well as long interspersed element 1 (*LINE-1*) repetitive element methylation, a proxy for global DNA methylation. They recruited 52 men with AUD and 52 age-matched healthy men as controls and measured blood DNA methylation at baseline and after the men with AUD had stopped consuming alcohol for 3 months. There were significant differences at baseline between men with AUD and controls, and none of the measures changed after 3 months of abstinence.

Several groups have investigated the effect of alcohol withdrawal on epigenetic changes in genes associated with alcohol cravings. [Although these hypotheses have not been directly linked to mechanisms associated with cancer in alcohol target organs, this work is included to show the breadth of studies investigating the impact of alcohol cessation on epigenetic modifications.]

3.2.4 Endocrine system

Mechanistic studies of the physiological impact of alcohol withdrawal on the endocrine system are confined to the effects of ethanol exposure or to the effects of withdrawal among individuals with alcohol dependence. The clearest link that has been described between alcohol modulation of the endocrine system and cancer is for breast cancer.

(a) Sex hormones

(i) Among humans

Endocrine mechanisms linking alcohol to breast cancer include induction of higher serum estrogen and dehydroepiandrosterone sulfate concentrations (Liu et al., 2015) and enhanced estrogen receptor activity (Dumitrescu and Shields, 2005); modulation of SHBG also may be involved (Assi et al., 2020). Among women, alcohol consumption increases the concentrations of estradiol, testosterone, and several other sex hormones in the circulation and decreases the concentration of SHBG, and these changes are hypothesized to be related to risk of breast cancer (Key et al., 2011). Alcohol consumption increases the risk of both premenopausal and postmenopausal breast cancer, and the risk is higher for estrogen receptor-positive tumours than for estrogen receptor-negative tumours (Sun et al., 2020). Studies on reduction or cessation of alcohol consumption are presented below, and detailed data among humans are given in Table 3.3.

Välimäki et al. (1982) studied 29 men with chronic AUD, including 13 with cirrhosis and 16 without cirrhosis. Blood samples were collected after 1–2 weeks of abstinence. Compared with the participants without cirrhosis, those with cirrhosis had significantly lower levels of serum testosterone and significantly higher levels of luteinizing hormone, prolactin, and estrone, but there were no differences in levels of estradiol or SHBG. [The effects of alcohol withdrawal were not ascertained, because the measurements were at the end of the observation period. However, these findings suggest that liver damage modulates the effects of alcohol withdrawal on circulating levels of sex hormones.]

Välimäki et al. (1984) studied 32 men with AUD and without cirrhosis at admission and after 1–2 weeks of alcohol withdrawal. The mean serum testosterone concentration increased by 19%, and among 4 men who had low testosterone concentrations at admission, the values returned to the normal range.

Iturriaga et al. (1995) studied 30 men with AUD at admission and at discharge after an average of 11 days in the treatment unit. They also recruited 15 healthy volunteers as controls. They measured levels of testosterone, estradiol, follicle-stimulating hormone, luteinizing hormone, and SHBG at both time points among the participants being treated and once among the controls. At discharge among the treatment group, levels of testosterone, estradiol, and

Table 3.3 Effects of cessation of alcohol consumption on the endocrine system

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
Välimäki et al. (1982) Finland	29 men with chronic AUD (ages, 28–58 years), 13 with cirrhosis and 16 without cirrhosis 15 healthy controls (ages, 25–53 years) after ≥ 1 week of abstinence Exclusion criteria: use of certain pharmaceuticals	Drinking history	NR	Blood Samples collected after abstinence for 7–14 days Hormonal status Reference values correspond to the normal range of concentrations in men aged 20–60 years	Values are mean ± SEM **Testosterone (nmol/L)** Reference values: 14–38 With cirrhosis: 11.7 ± 2.2*** Without cirrhosis: 25.2 ± 1.5 **LH (IU/L)** Reference values: 10–20 With cirrhosis: 31.2 ± 6.0* Without cirrhosis: 17.0 ± 2.7 **Prolactin (mU/L)** Reference values: 120–220 With cirrhosis: 478 ± 72** Without cirrhosis: 251 ± 31 **Estrone (pmol/L)** Reference values 110–210 With cirrhosis: 464 ± 59*** Without cirrhosis: 229 ± 25 *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$
Loosen et al. (1983) USA	29 participants with chronic AUD (men aged 30–66 years) who had abstained for ≥ 2 years 17 healthy controls (men aged 37–55 years) None of the participants were taking medication	Age	Duration of abstinence: range, 2–29 years before baseline	Blood Samples collected at baseline and after injection of 0.5 mg of TRH TSH, T3, T4, prolactin, cortisol, testosterone, thyroid-binding globulin The differences (Δ) in T3, T4, TSH, and prolactin levels were calculated between value after injection and baseline value	Values are mean ± SE **ΔTSH (μU/mL)** Chronic AUD during abstinence: 8.3 ± 0.9 Controls: 12.3 ± 1.5 $P < 0.02$ **ΔT3 (ng/dL)** AUD during abstinence: 51 ± 6 Controls: 36 ± 9 *P*: NS **ΔTotal T4 (μg/dL)** AUD during abstinence: 1.2 ± 0.2 Controls: 1.0 ± 0.2 *P*: NS **ΔProlactin (ng/mL)** AUD during abstinence: 24.9 ± 3.6 Controls: 25.8 ± 2.6 *P*: NS

Table 3.3 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
Loosen et al. (1983) (cont.)					**Cortisol (μg/dL)** AUD during abstinence: 10.6 ± 0.7 Controls: 10.7 ± 1.2 *P*: NS **Testosterone (ng/mL)** AUD during abstinence: 5.2 ± 0.4 Controls: 5.1 ± 0.4 *P*: NS **Thyroid-binding globulin (μg/mL)** AUD during abstinence: 17.7 ± 0.6 Controls: 15.7 ± 0.5 $P < 0.01$
Välimäki et al. (1984) Finland	32 men (ages, 28–51 years) with AUD and without cirrhosis who volunteered for withdrawal therapy Exclusion criteria: use of certain pharmaceuticals	Drinking history	7–30 years of drinking history before admission	Blood Samples collected at admission and after 1 week and 2 weeks of abstinence Plasma testosterone and serum cortisol and ACTH	Values are mean ± SEM **Testosterone (nmol/L)** Reference range: 14–38 1 day of abstinence: 21.6 ± 1.3 8 days of abstinence: 25.8 ± 1.6** 15 days of abstinence: 24.0 ± 1.8 **Serum cortisol (nmol/L) (morning)** Reference range: 200–800 1 day of abstinence: 590 ± 27 8 days of abstinence: 481 ± 25** 15 days of abstinence: 479 ± 34** **Serum cortisol (nmol/L) (evening)** Reference range: 100–400 1 day of abstinence: 224 ± 18 8 days of abstinence: 185 ± 16 15 days of abstinence: 152 ± 21*** **ACTH (ng/L)** Reference range: 10–80 1 day of abstinence: 148 ± 32 8 days of abstinence: 86 ± 24** 15 days of abstinence: 82 ± 27* *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs day 1

Table 3.3 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
Marchesi et al. (1992) Italy	11 individuals with AUD (ages, 29–51 years) who had been abstinent for 4 weeks 9 men (ages, 31–66 years) with AUD who had been abstinent for ≥ 1 year 9 healthy controls (ages, 28–58 years)	Age	Among the participants with AUD: Duration of AUD (mean ± SD): 22.7 ± 10.3 years Duration of abstinence (mean ± SD): 3.7 ± 0.8 years before baseline	Blood Samples collected just before (time 0) and 10, 20, 30, 45, and 60 minutes after injection of TRH TSH and prolactin levels after TRH stimulation were evaluated with a specific double-antibody radioimmunoassay The differences (Δ) in TSH and prolactin levels were calculated between value after injection and baseline value	Values are mean ± SD **ΔTSH (mU/L)** Abstinence (4 weeks): 10.4 ± 17.31 Abstinence (≥ 1 year): 8.05 ± 5.14 Controls: 7.83 ± 3.58 $P_{ANOVA} = 0.54$ **ΔProlactin (ng/mL)** Abstinence (4 weeks): 50.60 ± 26.78 Abstinence (≥ 1 year): 33.75 ± 19.55 Controls: 27.46 ± 7.4 $P_{ANOVA} = 0.043$ AUD with 4-week abstinence had significantly higher prolactin response to TRH vs other 2 groups (at time 10 minutes, $P_{ANOVA} < 0.01$)
Iturriaga et al. (1995) Chile	30 men with chronic AUD (ages, 24–51 years) and without liver failure and without severe systemic illness Controls: 15 healthy volunteers	NR	Alcohol consumption > 150 g per day for 2–33 years Duration of abstinence (mean ± SD): 1.9 ± 1.7 days	Blood For participants with AUD, samples collected at admission and at discharge (mean ± SD, 11.1 ± 4.7 days after admission). For controls, samples collected at baseline Hormonal status	Values are mean ± SD **Testosterone (ng/mL)** Controls: 8.2 ± 1.4 AUD at admission: 6.9 ± 2.5 AUD at discharge: 6.2 ± 2.6† **Estradiol (pg/mL)** Controls: [ND] AUD at admission: 10.5 ± 6.8 AUD at discharge: 10.1 ± 5.6 **FSH (mIU/mL)** Controls: 10.8 ± 2.7 AUD at admission: 7.7 ± 4.0† AUD at discharge: 8.0 ± 4.3 **LH (mIU/mL)** Controls: 13.5 ± 4.1 AUD at admission: 12.9 ± 4.1 AUD at discharge: 8.2 ± 5.3††*

Table 3.3 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
Iturriaga et al. (1995) (cont.)					**SHBG (mmol/L)** Controls: 32.5 ± 39.0 AUD at admission: 117.2 ± 33.3††† AUD at discharge: 65.4 ± 21.6†††** **P* < 0.001, ***P* < 0.0001 for discharge vs admission †*P* < 0.01, ††*P* < 0.02, †††*P* < 0.0001 vs controls
Rajzer et al. (1997) Poland	50 men (ages, 25–45 years) who met the DSM-III-R criteria for alcohol abuse and volunteered to stop drinking and undergo detoxification	NR	Alcohol consumption: 500–1500 mL (mean, 860 mL) of 40% ethanol per day for a duration (mean ± SD) of 12.4 ± 3.3 years	Blood samples collected 2–7 days and 4 weeks after abstinence Serum glucose and insulin measurement after an overnight fast and during a standard oral glucose tolerance test	Values are mean ± SD **Natural log of sum of secreted insulin (mU/L per minute)** After 2–7 days: 8.957 ± 0.474 After 4 weeks: 8.558 ± 0.651 *P* < 0.0001 Serum glucose levels not significantly different between 4 weeks and 2–7 days
Ozsoy et al. (2006) Türkiye	39 men (ages, 20–55 years) treated as inpatients for AD and alcohol withdrawal, divided into subgroups by aggression level, age at onset of AUD, and family history Controls: 28 healthy men (ages, 20–55 years) Exclusion criteria: any psychiatric disease, substance abuse other than alcohol or cigarette, any significant medical and endocrine disorder, and liver disease	Age and smoking status	Duration of alcohol consumption: 9–35 years Amount of alcohol consumed: 150–630 g per day	Blood Samples collected for early withdrawal (1 day after cessation) and late withdrawal (day 28 of cessation). For controls, samples collected at baseline Levels of fT4, fT3, and TSH	Values are mean ± SD **fT3 and fT4 (pg/mL)** $fT3_{controls}$: 3.32 ± 0.41 $fT4_{controls}$: 11.95 ± 1.49 $fT3_{1\text{-day cessation}}$: 3.18 ± 0.72 $fT4_{1\text{-day cessation}}$: 12.68 ± 2.50 $fT3_{28\text{-day cessation}}$: 2.71 ± 0.56* $fT4_{28\text{-day cessation}}$: 10.80 ± 1.86* **TSH (uIU/mL)** $TSH_{controls}$: 1.48 ± 0.71 $TSH_{1\text{-day cessation}}$: 1.93 ± 1.83 $TSH_{28\text{-day cessation}}$: 1.61 ± 0.86 **P* < 0.05 vs controls and early withdrawal (1-day cessation)

Table 3.3 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
Ozsoy et al. (2007) Türkiye	22 men (ages, 25–55 years) treated as inpatients for AD, divided into subgroups based on their withdrawal symptom severity scores on day 21 of alcohol cessation: continuing withdrawal symptoms (*n* = 8) and no withdrawal symptoms (recovered withdrawal group; *n* = 14) Exclusion criteria: some medical and endocrinological disorders Controls: 23 healthy men (ages, 25–55 years)	Age, BMI, and smoking status Individuals received diazepam and multivitamins for up to 3 weeks	NR	Blood Samples collected on day 21 of abstinence from individuals with AD and from controls GH level (baclofen challenge test); 20 mg of baclofen was given orally to the participants, and blood samples were collected every 30 minutes for the next 150 minutes	Values are mean ± SD **Basal GH (mIU/mL)** Controls: 0.06 ± 0.03 Participants who abstained: 0.18 ± 0.15* **ΔGH (μIU/mL)** Controls: 0.53 ± 0.84 Recovered withdrawal group: 0.80 ± 1.78 Continuing withdrawal group: 0.11 ± 0.27* **P* < 0.05 vs controls
Alvisa-Negrín et al. (2009) Spain	48 participants with AUD (3 women), 28 who abstained and 20 who did not abstain 28 healthy controls (3 women) who did not consume alcohol heavily	Age and BMI	Alcohol consumption: mean ± SD, 204 ± 82 g per day Duration of consumption: mean ± SD, 28.4 ± 11.4 years Controls were people who consumed < 10 g of ethanol per day, as assessed at baseline	Bone and blood Bone mineral content, bone mineral density (dual-energy X-ray absorptiometry of lumbar spine and hip, and whole body) Serum osteocalcin (immunometric chemiluminescence assay) Serum telopeptide (1-step ELISA)	AUD with continuing alcohol consumption after 6 months: Loss of bone mass Decrease in osteocalcin Increase in telopeptide AUD after 6 months of abstinence: No change or increase in bone mass Increase in osteocalcin Increase in telopeptide

Table 3.3 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
Mehta et al. (2018) United Kingdom	94 participants who abstained (43 men, 51 women; mean age ± SD, 45.5 ± 1.2 years) who completed 1 month with no alcohol consumption Controls: 47 participants (22 men, 25 women; mean age ± SD, 48.7 ± 1.8) who continued their usual alcohol consumption Individuals were not randomized to these groups Exclusion criteria: > 3 days of abstinence from alcohol before study start, presence of known liver disease, AD, and diabetes requiring treatment	Abstinence outcome models were controlled for diet and exercise	Previous alcohol consumption was > 64 g per week (men) or > 48 g per week (women)	Blood Samples collected at baseline and after 1 month from abstinence group and from controls Insulin resistance as HOMA score	**HOMA score, median (IQR)** Baseline: 1.4 (1.0–2.1) 1-month abstinence: 1.0 (0.7–1.4); mean decrease of 25% $P < 0.001$ No significant change in controls A multivariate model including changes in diet and exercise over the month showed that abstinence was associated with a significant improvement in HOMA score ($P = 0.002$) but changes in lifestyle were not
Uribe et al. (2018) USA	25 Latino adults (60% men; ages, 25–65 years), 17 without and 8 with hepatitis C virus infection Exclusion criteria: previous diagnosis of diabetes or use of antidiabetic agents, presence of cirrhosis, HIV, or chronic hepatitis B virus	Drinking history	NR	Blood Samples collected at baseline and 6 weeks after alcohol discontinuation Peripheral insulin resistance (steady-state plasma glucose); hepatic insulin resistance (2-step, 240-minute insulin suppression test); insulin secretion rate (graded glucose infusion test)	**Hepatic insulin resistance, mean ± SD** Baseline: 13.9 ± 5.7 Follow-up: 16.5 ± 5.8 $P = 0.014$ Peripheral insulin resistance and insulin secretion rates remained unchanged

Table 3.3 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
Price and Nixon (2021) USA	12 men (mean age ± SD, 43.42 ± 10.54 years) and 7 women (mean age ± SD, 39.57 ± 15.12 years) with moderate to severe AUD who sought treatment Exclusion criteria: use of steroidal inhalers or injections	Age, education level, monthly alcohol consumption, < 6 weeks of abstinence, and smoking habits	NR	Hair Samples collected at ~6 weeks after start of treatment (alcohol abstinence) Segment (proximal, mid-segment, and distal) hair cortisol concentrations (testing of neuroendocrine hormones) Proximal: representing sustained alcohol abstinence Mid-segment: representing the previous month, in which abstinence was attained Distal: representing the previous 2 months of active drinking	**Mean difference in cortisol (pg/mg)** Distal vs mid-segment: Not provided $P = 0.51$ Proximal vs distal: 0.200 (95% CI, 0.076–0.325) $P = 0.004$ Proximal vs mid-segment: 0.175 (95% CI, 0.100–0.249) $P < 0.001$

ACTH, adrenocorticotropic hormone; AD, alcohol dependence; ANOVA, analysis of variance; AUD, alcohol use disorder; BMI, body mass index; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd revised edition; ELISA, enzyme-linked immunosorbent assay; FSH, follicle-stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; GH, growth hormone; HOMA, homeostatic model assessment; IQR, interquartile range; LH, luteinizing hormone; ND, not detected; NR, not reported; NS, not significant; SD, standard deviation; SEM, standard error of the mean; SHBG, sex hormone-binding globulin; T3, triiodothyronine; T4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

follicle-stimulating hormone were unchanged, but levels of luteinizing hormone and SHBG were significantly lower. The SHBG levels remained elevated, twice as high as among the controls.

(ii) Among experimental animals

Forquer et al. (2011) studied changes in concentrations of testosterone and 17β-estradiol during ethanol intoxication and ethanol withdrawal among male and female WSR and WSP mice. Among the WSP strain, compared with controls, ethanol intoxication led to significantly higher testosterone concentrations among females and significantly lower testosterone concentrations among males. Compared with controls, neither male nor female WSR mice had a significant change in total testosterone concentrations after chronic intoxication. Changes after ethanol withdrawal were strain-specific among both male and female mice. Among male WSP mice, testosterone concentrations began to normalize 24 hours after withdrawal and had returned to normal after 21 days; among male WSR mice, there was a similar but amplified pattern, with higher testosterone levels after 21 days compared with controls. In both strains, among female mice there was a reduction in testosterone concentrations during the first 24 hours after ethanol withdrawal. After 21 days, among female WSP mice testosterone concentrations had returned to normal levels, whereas in female WSR mice testosterone concentrations were significantly increased compared with controls. [The strain-specific effects make direct extrapolation to humans difficult, but the findings among female mice showed that altered testosterone concentrations persist for ≥ 3 weeks after alcohol exposure ends.] Concentrations of 17β-estradiol were only modestly changed by ethanol withdrawal among both strains and sexes of mice.

(b) Insulin

Insulin, insulin resistance, and diabetes have been widely studied for their relevance to cancer in many organs (Pearson-Stuttard et al., 2021). Peripheral insulin concentrations may be elevated during chronic heavy alcohol consumption (Piccardo et al., 1994). In contrast, moderate alcohol consumption has been linked to reduced fasting insulin concentrations and insulin resistance among postmenopausal women (Davies et al., 2002). Only one study examined the effects of abstinence on these end-points.

Rajzer et al. (1997) recruited 50 men who met the Diagnostic and Statistical Manual of Mental Disorders, third revised edition (DSM-III-R) criteria for alcohol abuse (American Psychiatric Association, 1987) and who volunteered to stop consuming alcohol. Blood was collected 2–7 days and again 4 weeks after the men became abstinent, which was verified by blood analysis and self-reporting. The authors measured serum glucose and insulin after fasting and during standard oral glucose tolerance tests and calculated a variety of insulin-resistance indices based on these measures. They reported a significant reduction in the sum of the insulin secreted during the test, 8.558 ± 0.651 mU/L per minute versus 8.957 ± 0.47 mU/L per minute ($P < 0.0001$), which is an improvement in insulin resistance but not a normalization. They reported no differences in the other markers and indices, including serum insulin, glucose, the sum of glucose measured during the test, and the ratio of glucose to insulin.

Uribe et al. (2018) studied 25 Latino adults (10 women and 15 men) without diabetes or cirrhosis and with a history of moderate alcohol consumption, which was defined among the women as no more than 3 drinks in any day or 7 drinks in a week and among the men as no more than 4 drinks in a day or 14 drinks in a week. In addition to assessing body size, the authors performed a variety of standard serum measurements (e.g.

alanine transaminase, aspartate aminotransferase) and assessed the insulin secretion rate and peripheral and hepatic insulin resistance at baseline and after a median of 7 weeks of abstinence. Body mass index, alanine transaminase, aspartate aminotransferase, fasting glucose, and fasting insulin levels and peripheral insulin resistance and insulin secretion rates remained unchanged. In contrast, hepatic insulin resistance was significantly higher among the individuals after they abstained from alcohol.

Mehta et al. (2018) recruited healthy individuals with regular alcohol consumption of > 64 g per week for men or > 48 g per week for women and asked them to indicate whether they would abstain from alcohol for 1 month or continue their usual consumption. A total of 77 participants completed the abstinence protocol and returned for the second visit, and 40 continued their usual consumption and returned for the second visit. The primary aim was to measure insulin resistance using homeostatic model assessment (HOMA). After 1 month, the HOMA score was reduced by a mean of 25% in the group that abstained from alcohol ($P < 0.001$), whereas there was no significant change ($P = 0.42$) in the group that continued their usual consumption. To account for other changes in lifestyle that the participants may have undertaken, the authors measured changes in diet and exercise using a questionnaire. In a multivariate model, only abstinence was associated with improvement in the HOMA score. [Participants who abstained from alcohol also showed improvement in blood pressure, weight, cholesterol, alanine transaminase and aspartate aminotransferase levels, and other markers, whereas among the controls, the only significant difference was higher aspartate aminotransferase levels.]

(c) Other hormones

The human hormonal system includes a wide array of messengers and targets and may contribute to many health outcomes associated with alcohol exposure, but much of the current body of research has been directed towards understanding human craving, addiction, and withdrawal symptoms, with little information directly relevant to cancer target organs. Alcohol consumption has been shown to affect the activity of the hypothalamic–pituitary–adrenal axis, including levels of adrenocorticotropic hormone (ACTH) and cortisol and other related hormones (Gianoulakis et al., 2003). Thyroid hormones also have been investigated alone or in combination with ACTH. Many of the hormonal responses that have been studied were in pathways that may not yet be tied directly to cancer in a specific organ. In many instances, the studies have focused on how the hormonal responses are associated with alcohol cravings and other aspects of addiction. Hormone studies also have included vitamin D, a fat-soluble secosteroid hormone that has been studied extensively with regard to risk of breast cancer (Visvanathan et al., 2023), colorectal cancer (McCullough et al., 2019), and other cancer types.

(i) Among humans

Thyroid hormones are reactive to illness and have been studied in the earliest days (Melander et al., 1982) and weeks (Välimäki et al., 1984) after individuals become abstinent, but these short-term changes probably do not reflect their hormonal status after the initial treatment period.

Loosen et al. (1983) studied 29 men who had been abstinent for ≥ 2 years and 17 healthy men as controls. They compared levels of triiodothyronine (T3), thyroxine (T4), thyrotropin (or thyroid-stimulating hormone [TSH]), and several other related hormones and calculated indices at study baseline and after injection with thyrotropin-releasing hormone (TRH). Several parameters, such as T3, T3:T4 ratio, TSH at baseline, and TSH and T4 after administration of TRH, were significantly different. Basal cortisol, basal testosterone, and prolactin levels at baseline and after TRH treatment did not differ. There was

also a significant increase in thyroid-binding globulin among participants who were abstinent.

Marchesi et al. (1992) studied 11 individuals with AUD who had abstained for 4 weeks, 9 men with AUD who had abstained for ≥ 1 year, and 9 age-matched healthy controls. There was no difference in the TSH levels among the groups after administration of TRH, but there was a marginally significant increase in prolactin response in the group that had abstained for 4 weeks.

Ozsoy et al. (2006) studied 39 men who were being treated for AUD and 28 healthy men as controls. Concentrations of free thyroxine, free triiodothyronine, and TSH were measured once among the controls and on day 2 and day 28 of withdrawal among the individuals with AUD. On day 2, the concentrations of the three thyroid hormones did not differ from those among the controls. On day 28, the levels of both free thyroxine and free triiodothyronine were significantly lower among the individuals being treated for AUD than among the controls (measured at the first time point). Subanalyses by age at onset of AUD, family history, and aggressiveness showed that all factors modified these changes.

Ozsoy et al. (2007) assessed gamma-aminobutyric acid (GABA) dysfunction by measuring growth hormone responses to oral baclofen treatment among 22 men with alcohol dependence after they had abstained for 21 days compared with 23 healthy men as controls. The participants with AUD were divided into two groups on the basis of their withdrawal symptom severity scores on day 21 of alcohol cessation: those with continuing withdrawal symptoms, and those with no withdrawal symptoms (recovered withdrawal group). As expected, baclofen treatment significantly increased growth hormone responsiveness among the participants in the control group, but not among the men with AUD who had abstained. This impairment was evident only among the men with continuing withdrawal symptoms, whereas responsiveness had been restored among those in the recovered withdrawal group.

Alvisa-Negrín et al. (2009) studied levels of osteocalcin, vitamin D, and other bone health markers among individuals with AUD before and after alcohol withdrawal. They enrolled 77 participants with AUD (68 men and 9 women) at baseline; 48 (including 3 women) were evaluated 6 months later, when 28 were abstinent and 20 were not abstinent. After 6 months, the individuals who continued to consume alcohol had lost bone mass, whereas those who abstained had either no change or an increase in bone mass. The participants who abstained had a significant increase in osteocalcin, whereas there was a decrease among those who continued to consume alcohol. Changes in serum telopeptide levels were similar among the two groups. In a subset of participants, serum levels of insulin-like growth factor 1 (IGF-1), vitamin D, and parathyroid hormone were measured at entry and after 6 months. IGF-1 concentrations were unchanged, vitamin D levels increased, and parathyroid hormone levels increased non-significantly [quantitative data for these changes were not reported].

Price and Nixon (2021) used segmental hair analysis among individuals (12 men and 7 women) with AUD ~6 weeks after alcohol withdrawal to study changes in cortisol concentrations over time. Cortisol accumulated in hair during alcohol consumption, and abstinence led to significantly lower cortisol concentrations; there were no differences between men and women.

(ii) Among experimental animals

Although their relevance to humans and to carcinogenesis is currently unknown, the few available studies in experimental animals about the effects of alcohol withdrawal on other hormones are summarized below.

Rasmussen et al. (2000) examined the effects of ethanol withdrawal on the hypothalamic–

pituitary–adrenal axis in male Sprague-Dawley rats and pair-fed and ad libitum-fed controls. The animals were administered ethanol over a 3-week gradual introduction to a 5% weight by volume diet, then 4 weeks of continuing administration, and then ethanol withdrawal over a 3-week period. After the 3-week withdrawal period, anterior pituitary pro-opiomelanocortin (POMC) messenger RNA (mRNA) concentrations were significantly suppressed among the exposed group compared with the pair-fed and ad libitum-fed control groups; thymus and spleen weights were also higher among the exposed rats.

Li et al. (2010) examined whether alcohol withdrawal could reverse alcohol-induced exocrine pancreatic insufficiency, which is more common among individuals with alcohol dependence. They used male Wistar rats, among which ethanol alone cannot induce chronic pancreatitis but is known to alter markers of sufficiency. A total of 48 rats were divided evenly into 4 groups: a group exposed at final exposure (incremental exposure over 4 weeks) to 25% ethanol (v/v) for 6 months; a group exposed to 25% ethanol for 6 months, followed by 3 months of enforced abstinence; a 6-month distilled water control group; and a 9-month distilled water control group. Ethanol exposure for 6 months led to significantly reduced levels of amylase and lipase, and the levels in the group with ethanol exposure followed by enforced abstinence were not restored to those among the paired control group. A similar irreversible effect was noted for cholecystokinin, measured by radioimmunoassay in pancreatic acinar cells and small intestinal cells. Ethanol administration had no effect on cholecystokinin A receptors.

Allen et al. (2018) assessed ACTH and cortisol levels in a study in which adult male experimentally naive rhesus macaques were exposed to ethanol for 14 months, followed by periods of enforced abstinence that lasted ~3 months. Exposed animals (n = 8) had ethanol and water available from two different bottles, and they developed a wide array of patterns of voluntary ingestion. Yoked-control animals (n = 4) had water available from both bottles. Serum cortisol and ACTH concentrations were measured during the three periods of enforced abstinence. During the first period of abstinence, a sharp increase and subsequent decrease in cortisol concentrations were seen in all groups. During the second period, cortisol concentrations remained higher among the animals with heavy ethanol consumption. During the third period, cortisol concentrations increased, and they remained elevated among all three groups. ACTH concentrations were more variable than those of cortisol and were not correlated to the alternating phases of exposure and enforced abstinence.

3.2.5 Microbiome

The human microbiome may play roles in alcohol-induced cancer. The oral microbiome plays an important role in the metabolism of alcohol in the mouth, and alcohol consumption can induce changes in the composition and abundance of the oral microbiome (see Section 3.1). Chronic alcohol consumption also has an impact on the intestinal microbiome; this may act through metabolism, inflammation, and intestinal permeability, including translocation of microbes (see Section 3.2.6). Studies assessing the effects of alcohol cessation on the oral and intestinal microbiomes are described in Table 3.4.

(a) Oral microbiome

Heavy alcohol consumption has been shown to decrease secretion of saliva, change the electrolyte concentration in saliva, and decrease protein synthesis in the salivary glands; this suggests an impact on the oral microbiome (Inenaga et al., 2017). Furthermore, it has been suggested that alcohol influences the inflammatory effect of the oral microbiota or facilitates enhanced pathogenicity of commensal

Table 3.4 Effects of cessation of alcohol consumption on the oral and intestinal microbiome

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point (test used)[a]	Results
Oral microbiome					
Yokoyama et al. (2007) Japan	80 men with AUD who were admitted to a 3-week treatment programme for alcoholism. Among the 34 individuals tested after 3 weeks, 12 were heterozygous for *ALDH2*	67 smokers and 13 non-smokers All participants continued drinking until the day before admission to the hospital, had never used alcohol-aversive drugs, and had no signs or symptoms of liver cirrhosis	NR	Saliva Acetaldehyde production capacity measured at admission and after 3 weeks (n = 34); bacteria and yeast counts	Values are median (Q1, Q3) **Acetaldehyde production (μM)** AUD at baseline: 270 (179, 397) AUD after abstinence (3 weeks): 132 (82, 195) $P_{\text{abstinence vs baseline}} < 0.0001$ **Salivary bacteria and yeast counts ($\log_{10}$ CFU/mL)** Total salivary bacteria and yeast counts AUD at baseline: 7.45 (7.32, 7.78) AUD after abstinence (3 weeks): 7.04 (6.81, 7.30) $P_{\text{abstinence vs baseline}} = 0.0002$ Correlated decreases in total salivary bacteria and yeast counts and acetaldehyde production (r = 0.35; P = 0.042) *Stomatococcus* species AUD at baseline: 5.60 (< DL, 6.26) AUD after abstinence (3 weeks): 5.30 (< DL, 6.15) $P_{\text{abstinence vs baseline}} = 0.96$ *Corynebacterium* spp. AUD at baseline: 6.00 (< DL, 6.53) AUD after abstinence (3 weeks): 5.26 (< DL, 6.26) $P_{\text{abstinence vs baseline}} = 0.58$ α-Haemolytic *Streptococci* AUD at baseline: 7.20 (6.96, 7.62) AUD after abstinence (3 weeks): 6.70 (6.38, 7.04) $P_{\text{abstinence vs baseline}} < 0.0001$

Table 3.4 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point (test used)[a]	Results
van Zyl and Joubert (2015) South Africa	30 men with AUD (median age, 42 years; IQR, 29–48 years) who were admitted to a 21-day inpatient rehabilitation programme followed by 9 weeks of observation (total of 12 weeks of observation) Racial distribution: 15 Black, 11 White, and 4 mixed race A smaller pilot study was conducted among 7 men from the treatment centre who were compared with 7 men from the general population Exclusion criteria: antibiotic use during the previous month and dependence on drugs other than alcohol, nicotine, or marijuana	Sex	The 30 study participants included 10 who consumed > 60 units per week, 4 who consumed 40–59 units per week, 13 who consumed 15–39 units per week, and 3 who consumed < 15 units per week During the 12 weeks, 16 participants remained abstinent and 13 participants resumed drinking	Saliva Acetaldehyde production capacity measured 2, 4, 11, and 18 days after admission to the programme	Values are median (Q1, Q3) **Salivary acetaldehyde production capacity (µmol/L)** AUD after abstinence (18 days): 178 (172, 188) AUD resumed drinking (18 days): 168 (161, 180) $P_{\text{abstinence vs drinking}} = 0.02$ The difference between the 2 groups was not statistically significant on days 2, 4, and 11
Intestinal microbiome					
Leclercq et al. (2014) Belgium	60 participants with AUD (47 men, 13 women) entering an inpatient rehabilitation programme for 19 days. Participants were tested on the day after admission and divided into 2 groups: with high IP and with low IP. Among the 44 individuals who remained abstinent during the 19 days, 13 (8 men, 5 women) were tested for intestinal microbiota composition and functionality before and after abstinence 15 healthy controls who consumed < 20 g of alcohol per day	Age, sex, and BMI	AUD was diagnosed according to DSM-IV	Faecal samples Intestinal microbiota analysis (pyrosequencing and qPCR of 16S rDNA in faecal samples) Intestinal permeability (^{51}Cr-EDTA)	**Microbial composition** ***$AUD_{high\text{-}IP}$ at baseline*** Family level Decreased *Ruminococcaceae* and *Incertae Sedis XIII* vs $AUD_{low\text{-}IP}$ and controls $P < 0.05$ Increased *Lachnospiraceae* and *Incertae Sedis XIV* vs $AUD_{low\text{-}IP}$ and controls $P < 0.05$ Genus level Decreased *Ruminococcus*, *Faecalibacterium*, *Subdoligranulum*, *Clostridia*, and *Oscillibacter* vs $AUD_{low\text{-}IP}$ and controls $P < 0.05$ Decreased *Anaerofilum* vs $AUD_{low\text{-}IP}$ and controls *P*: NR

Table 3.4 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point (test used)[a]	Results
Leclercq et al. (2014) (cont.)	Exclusion criteria: BMI > 30 kg/m^{2}, diabetes, inflammatory bowel disease, other chronic inflammatory diseases such as rheumatoid arthritis, cancer, or use of antibiotics, probiotics, glucocorticoids, or non-steroidal anti-inflammatory drugs in the 2 months before admission				Increased *Dorea*, *Blautia*, and *Megasphaera* vs $AUD_{low\text{-}IP}$ and controls $P < 0.05$ ***$AUD_{high\text{-}IP}$ after abstinence (19 days)*** Increased *Ruminococcaceae* $P_{19\text{-}day\ abstinence\ vs\ baseline} < 0.05$ Decreased family *Erysipelotrichaceae* and genus *Holdemania* $P_{19\text{-}day\ abstinence\ vs\ baseline} < 0.05$ Increased genera *Ruminococcus* and *Subdoligranulum* $P_{19\text{-}day\ abstinence\ vs\ baseline} = 0.11$ (NS) ***$AUD_{low\text{-}IP}$ after abstinence (19 days)*** Decreased family *Erysipelotrichaceae* and genus *Holdemania* $P_{19\text{-}day\ abstinence\ vs\ baseline} < 0.05$ **Microbial abundance, $\log_{10}$ (bacterial cells/g faeces)** ***$AUD_{high\text{-}IP}$ at baseline*** Decreased total amount of bacteria vs $AUD_{low\text{-}IP}$ and controls $P < 0.01$ Decreased *Faecalibacterium prausnitzii* and *Bifidobacterium* spp. vs $AUD_{low\text{-}IP}$ and controls $P < 0.05$ Decreased *Lactobacillus* spp. vs $AUD_{low\text{-}IP}$ and controls $P > 0.05$, NS ***$AUD_{high\text{-}IP}$ after abstinence (19 days)*** Increased total amount of bacteria, *Bifidobacterium* spp., and *Lactobacillus* spp. $P_{19\text{-}day\ abstinence\ vs\ baseline} < 0.05$ *Faecalibacterium prausnitzii:* no change

Table 3.4 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point (test used)[a]	Results
Ames et al. (2020) USA	22 participants with AUD entering a 4-week inpatient detoxification programme (14 men, 8 women; average age ± SD, 45.82 ± 13.0 years) Racial distribution: 13 White, 6 Black, 2 mixed race, 1 of unknown race	16/22 participants smoked, 8/22 used illicit substances, and 10/22 tested positive for cannabinoids in urine. None of the participants had cirrhosis or liver failure. 86% of the participants were diagnosed with periodontal disease. 3 participants were taking antibiotics	Participants were divided into 2 groups: VHD (≥ 10 drinks per day) and LHD (< 10 drinks per day) They were followed up during 3 weeks of abstinence	Stool homogenization and oral tongue brushings analysed with a microbiome sequencing kit to examine 6 of the 9 hypervariable regions of the *16S* gene	**Microbial composition, average relative abundance (%)** *Erysipelotrichaceae* LHD at baseline: 13 VHD at baseline: 0.01–0.05 *P*: NR *Lachnospiraceae* LHD at baseline: 13 VHD at baseline: 0.01–0.05 *P*: NR After abstinence (3 weeks), greater changes in VHD group than in LHD group **Shannon diversity index** No significant difference between LHD and VHD groups at baseline or after abstinence (3 weeks) 1/8 LHD and 4/14 VHD participants: significant linear diversity changes from baseline to after abstinence (3 weeks) *P*: NR **BSDD** Average BSDD values across the 2 groups were analysed using pairwise comparisons between day 1 and day 5 ($P = 0.03$) and day 1 and week 3 ($P = 0.02$) Between-group differences were significant: values 0.10 higher in VHD group than in LHD group Average BSDD range after abstinence (3 weeks) LHD: 0.1–0.2 VHD: 0.13–0.43 $P_{\text{VHD vs LHD}} = 0.02$

Table 3.4 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point (test used)[a]	Results
Gao et al. (2020) Belgium	30 participants with AUD (23 men, 7 women; median age, 42 years; range, 27–59 years) entering a 3-week detoxification programme Participants were divided into 2 groups: with high CAP (> 300 dB/m) and with low CAP (< 300 dB/m) Controls: 8 healthy volunteers (6 men, 2 women; median age, 52 years; range, 37–71 years) who consumed < 20 g of alcohol per day, defined as social drinking	Age, sex, and BMI	Participants with AUD had consumed 60 g of alcohol per day for ≥ 1 year Detoxification programme for participants with AUD: 1 week of inpatient detoxification, followed by 1 week of outpatient care and 1 week of inpatient treatment	Stool samples (collected from first bowel movement after each hospitalization) Microbial composition and microbial pathways (shotgun metagenomic sequencing) Liver steatosis (transient elastography combined with CAP measurements) LDA effect size used to identify the features most likely to account for between-group differences	**LDA score ($\log_{10}$)** (LDA threshold: > 2.0) ***All participants with AUD after abstinence (2 weeks)*** Isoprene biosynthesis I $P_{\text{abstinence vs baseline}} < 0.05$ $P_{\text{abstinence vs controls}} < 0.01$ Phytol degradation $P_{\text{abstinence vs baseline}} < 0.05$ $P_{\text{abstinence vs controls}} < 0.05$ L-isoleucine biosynthesis II $P_{\text{abstinence vs baseline}} < 0.05$ $P_{\text{abstinence vs controls}}$: NS Superpathway of geranylgeranyl diphosphate biosynthesis II $P_{\text{abstinence vs baseline}} < 0.01$ $P_{\text{abstinence vs controls}}$: NS NAD salvage pathway II $P_{\text{abstinence vs baseline}} < 0.01$ $P_{\text{abstinence vs controls}}$: NS Glutaryl-coenzyme A degradation $P_{\text{abstinence vs baseline}} < 0.05$ $P_{\text{baseline vs controls}} < 0.05$ $P_{\text{abstinence vs controls}} < 0.05$ Superpathway of geranylgeranyl diphosphate biosynthesis I $P_{\text{abstinence vs baseline}} < 0.05$ $P_{\text{abstinence vs controls}} < 0.05$ ***$AUD_{high\text{-}CAP}$ after abstinence (2 weeks)*** L-isoleucine biosynthesis II, superpathway of β-D-glucuronosides degradation, superpathway of hexuronide and hexuronate degradation, superpathway of geranylgeranyl diphosphate biosynthesis II (via MEP), and glutaryl-coenzyme A degradation: LDA > 2.0 Heterolactic fermentation: LDA < –2.0

Table 3.4 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point (test used)[a]	Results
Gao et al. (2020) (cont.)					***AUD$_{low\text{-}CAP}$ after abstinence (2 weeks)*** Adenosine nucleotides degradation II, guanosine nucleotides degradation III, superpathway of pyrimidine ribonucleosides degradation, purine nucleotides degradation II (aerobic), and ppGpp biosynthesis: LDA > 2.0
Maccioni et al. (2020) Belgium	106 individuals with AUD (78 men; mean age ± SEM, 46 ± 9.2 years) entering a 3-week detoxification programme Participants were divided into 2 groups, with high IP and with low IP Controls: 24 healthy volunteers (14 men, 10 women; mean age ± SEM, 42 ± 11 years) who consumed < 20 g of alcohol per day, defined as social drinking	Age, sex, and BMI (1 to 4 ratio)	Participants with AUD who had consumed > 60 g of alcohol per day for ≥ 1 year Participants with AUD admitted to a detoxification programme consisting of 1 week of inpatient detoxification followed by 1 week of outpatient care and 1 week of inpatient treatment	Blood, urine, and faecal samples collected at the beginning of the programme and after 2 weeks of abstinence Microbial translocation (measuring Gram-negative and Gram-positive serum markers by ELISA); microbiota (16S rRNA sequencing) IP (urinary excretion of ^{51}Cr-EDTA), faecal albumin content, and immunohistochemistry in distal duodenal biopsies	**sCD14** AUD after abstinence (2 weeks): decrease $P_{abstinence\ vs\ baseline} = 0.0001$ **Lipopolysaccharide binding protein** AUD after abstinence (2 weeks): no change **Peptidoglycan recognition proteins** AUD after abstinence (2 weeks): no change **α-diversity (Shannon diversity index)** AUD$_{high\text{-}IP}$ after abstinence (2 weeks): increase $P_{abstinence\ vs\ baseline} = 0.076$ AUD$_{low\text{-}IP}$ after abstinence (2 weeks): no change $P_{abstinence\ vs\ baseline} = 0.6$ AUD$_{progressive\ ALD}$ after abstinence (2 weeks): no change $P_{abstinence\ vs\ baseline} = 0.8$ AUD$_{non\text{-}progressive\ ALD}$ after abstinence (2 weeks): increase $P_{abstinence\ vs\ baseline} = 0.15$ **α-diversity (Simpson diversity index)** AUD$_{high\text{-}IP}$ after abstinence (2 weeks): increase $P_{abstinence\ vs\ baseline} = 0.065$ AUD$_{low\text{-}IP}$ after abstinence (2 weeks): no change $P_{abstinence\ vs\ baseline} = 0.8$ AUD$_{progressive\ ALD}$ after abstinence (2 weeks): no change $P_{abstinence\ vs\ baseline} = 0.8$ AUD$_{non\text{-}progressive\ ALD}$ after abstinence (2 weeks): increase $P_{abstinence\ vs\ baseline} = 0.15$ **β-diversity** AUD after abstinence (2 weeks): no change

Table 3.4 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point (test used)[a]	Results
Hartmann et al. (2021) Belgium	66 participants with AUD (47 men; average age ± SD, 45 ± 12 years) entering a 3-week detoxification programme Controls: 18 healthy volunteers (14 men, 4 women; average age ± SD, 41 ± 12 years) who consumed < 20 g of alcohol per day, defined as social drinking	Age, sex, and BMI 80% of participants with AUD and 20% of controls were smokers	Participants with AUD had consumed > 60 g of alcohol per day for ≥ 1 year Participants with AUD admitted to a detoxification programme consisting of 1 week of inpatient detoxification, followed by 1 week of outpatient care and 1 week of inpatient treatment	Blood and stool samples (collected from first bowel movement after each hospitalization) DNA from faecal samples characterized using fungal metagenomic sequencing and internal transcribed spacer 2 amplicon Principal coordinate analyses performed to summarize outcomes of the relative abundance of all fungal genera between the different groups LDA effect size used to identify the features most likely to account for between-group differences	**Principal coordinate analyses** $P_{\text{baseline vs controls}} = 0.001$ $P_{\text{abstinence vs baseline}} = 0.001$ **LDA score ($\log_{10}$)** Participants with AUD after abstinence (2 weeks) vs participants with AUD at baseline Genus level *Candida*, *Malassezia*, *Pichia*, *Kluyveromyces*, *Issatchenkia*, *Claviceps*, *Cyberlindnera*, and *Hanseniaspora*: LDA < –2 *Trichosporon*: LDA > 2 Species level *C. albicans*, *C. zeylanoides*, *I. orientalis*, and *Cyberlindnera jadinii*: LDA < –2 Family level *Saccaromycodaceae*, *Malasseziaceae*, *Cystostereaceae*, *Didymellaceae*, and *Clavicipitiaceae*: LDA < –2 *Metschnikowiaceae* and *Trichosporonaceae*: LDA > 2

Table 3.4 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point (test used)[a]	Results
Hsu et al. (2022) Belgium	62 participants with AUD (44 men; average age ± SD, 44.4 ± 11.9 years) entering a 3-week detoxification programme Controls: 16 healthy volunteers (13 men, 3 women; average age ± SD, 40.8 ± 12.3 years) who consumed < 20 g of alcohol per day, defined as social drinking	Age, sex, and BMI	Participants with AUD who had consumed > 60 g of alcohol per day for ≥ 1 year Detoxification programme consisting of 1 week of inpatient detoxification, followed by 1 week of outpatient care and 1 week of inpatient treatment	Blood and stool samples (collected from first bowel movement after each hospitalization) Viral nucleic acid analysis (metagenomic sequencing) Principal coordinate analyses performed to identify differences in the relative abundance of all phages grouped according to their hosts LDA effect size used to identify the features most likely to account for between-group differences	**Principal coordinate analyses** Participants with AUD after abstinence (2 weeks) vs controls and participants with AUD at baseline: $P = 0.027$ **LDA effect size** Participants with AUD at baseline Decreased % of individuals with bacteriophages targeting *Propionibacterium* vs controls: $P_{\text{baseline vs controls}} < 0.001$ Participants with AUD after abstinence (2 weeks): $P_{\text{abstinence vs baseline}}$ Increased phages targeting *Lactococcus*: $P = 0.020$ Increased phages targeting *Leuconostoc*: $P = 0.016$ Increased phages targeting *Streptococcus*: $P = 0.077$ Increased phages targeting *Propionibacterium*: $P = 0.030$ Increased phages targeting *Lactobacillus*: $P = 0.007$ Increased % of individuals with bacteriophages targeting *Lactobacillus*: $P < 0.001$ Increased % of individuals with bacteriophages targeting *Propionibacterium*: $P = 0.005$ Relative abundance of *Propionibacterium* phages in participants with AUD at baseline and after abstinence vs controls: $P_{\text{Kruskal–Wallis}} = 0.002$

[a] % ^{51}Cr-EDTA is the percentage of the ingested dose of ^{51}Cr-EDTA found in urine, normalized for creatinine.
16S rDNA, 16S ribosomal DNA subunit; ALD, alcohol-related liver disease; *ALDH2*, aldehyde dehydrogenase gene; AUD, alcohol use disorder; BMI, body mass index; BSDD, binary Sørensen–Dice dissimilarity coefficient; CAP, controlled attenuation parameter; CFU, colony-forming unit; DL, detection level (1.30 $\log_{10}$ CFU/mL for bacteria); DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EDTA, ethylenediaminetetraacetic acid; ELISA, enzyme-linked immunosorbent assay; IP, intestinal permeability; IQR, interquartile range; LDA, linear discriminant analysis; LHD, less heavy drinking; MEP, methyl-D-erythritol 4-phosphate; NAD, nicotinamide adenine dinucleotide; NR, not reported; NS, not significant; ppGpp, guanosine 3′,5′-bis(diphosphate); Q1, first quartile; Q3, third quartile; qPCR, quantitative polymerase chain reaction; sCD14, soluble CD14; SD, standard deviation; SEM, standard error of the mean; VHD, very heavy drinking.

microorganisms. A potential interaction between alcohol and the oral microbiome, leading to a malignant transformative event, also has been suggested, which supports the hypothesis that the microbiome could influence the level of acetaldehyde, mediating its genotoxic effects. The interaction between the oral microbiome and ethanol metabolism is a complex and widely unexplored process, with numerous possible genus- or species-related outcomes. One of the main links between alcohol consumption and the oral microbiome is the enzyme ADH. It is found in several species of commensal bacteria (e.g. *Neisseria mucosa* and *Streptococcus* species) and the fungus *Candida albicans*, which have the potential to produce genotoxic levels of acetaldehyde (Nieminen and Salaspuro, 2018; Yokoyama et al., 2018; O'Grady et al., 2020). In addition, alcohol consumption (along with other exogenous factors, e.g. tobacco smoking) can alter the composition of the oral microbiome and change its metabolic contributions (Hsiao et al., 2018). Details about the role of the microbiome in ethanol metabolism are provided in Section 3.1. Host genetics also was found to have an impact on the microbiome in a comparison of data from the Human Microbiome Project in hosts for which a genome-wide association study (GWAS) analysis was performed (Blekhman et al., 2015). This could imply that different genetic backgrounds may lead to variations in the oral microbiome that could ultimately affect its influence on acetaldehyde production and metabolism (see Section 3.1).

To characterize changes in the oral microbiome associated with abstinence, studies have measured the impact of abstinence on the capacity of salivary microbes to metabolize ethanol to acetaldehyde, by collecting saliva samples and exposing them ex vivo to ethanol (Homann et al., 2001). These studies are described below and in Table 3.4.

In a study in Japan, Yokoyama et al. (2007) measured the salivary microbiome as bacteria and yeast counts in saliva samples collected from 80 men with AUD who entered a rehabilitation treatment programme. Saliva specimens were collected immediately after admission and 3 weeks later from 34 participants. Acetaldehyde production capacity was significantly correlated with the number of microorganisms measured in the saliva. The number of salivary bacteria and yeasts decreased after 3 weeks of abstinence and correlated with a decrease in acetaldehyde production in saliva ($r = 0.35$; $P = 0.042$). Specifically, the prevalence and number of α-haemolytic *Streptococci*, *Stomatococcus* sp., and *Corynebacterium* sp. were very high at admission, and the number of α-haemolytic *Streptococci*, which are known to be associated with increased salivary acetaldehyde production, was significantly reduced after 3 weeks of abstinence ($P < 0.001$).

van Zyl and Joubert (2015) investigated acetaldehyde production capacity in saliva samples collected from 30 individuals 2, 4, 11, and 18 days after they were admitted to a rehabilitation programme. Among the selected participants, 16 remained abstinent during the 12 weeks of observation, and 13 resumed alcohol consumption. No differences in the levels of acetaldehyde production were detected between the samples collected at baseline and those collected at the later time points. Statistically significant differences were found in the acetaldehyde production after 12 weeks between the group that remained abstinent and the group that resumed alcohol consumption. [These results are of limited significance because acetaldehyde production capacity is an indirect measurement of bacterial function, which is potentially influenced by an individual's endogenous acetaldehyde production and is also likely to be affected by other major sources of acetaldehyde exposure, such as tobacco smoking.]

[These studies underscore the complexity of the influence of alcohol on the oral microbiome. Consumption of alcohol influences the composition and abundance of the oral microbiome,

which in turn may affect local metabolism of ethanol and, consequently, the effects of alcohol mediated by acetaldehyde. These particular interactions in the oral cavity support the need to consider the oral microbiome separately from the intestinal microbiome.]

(b) Intestinal microbiome

Chronic alcohol consumption changes the composition and abundance of the intestinal microbiome, which results in an insult to the intestinal mucosal barrier, compromising intestinal homeostasis and leading to an imbalance in the microbiota with loss of beneficial microbes and expansion of pathogenic ones, also known as intestinal dysbiosis. AUD further increases intestinal mucosal damage and intestinal permeability, causing an increase in the translocation of microbial products into peripheral circulation (Donnadieu-Rigole et al., 2018; see Section 3.2.6). Recently, an association between alterations in the intestinal microbiome and breast cancer has been reported, suggesting that the microbiome may play a role in regulating estrogen levels (Parida and Sharma, 2019). However, this area of research is only in its infancy. Changes in the intestinal microbiome are considered a risk factor for the progression of ALD, which ultimately may develop into HCC (Hsu et al., 2022).

Bajaj et al. (2014) compared stool samples from individuals with alcohol-related cirrhosis with those from individuals with cirrhosis with etiologies other than solely alcohol. Among the individuals with alcohol-related cirrhosis, the beneficial taxa of the phyla *Firmicutes*, such as *Lachnospiraceae* and *Ruminococcaceae*, were less abundant, whereas organisms in the phyla *Proteobacteria,* including *Enterobacteriaceae*, were drastically increased in abundance (all variations were significant at $P < 0.05$). In another study, an even greater significance ($P < 0.0001$) for differences in abundance was reported when comparing individuals with cirrhosis with healthy controls (Qin et al., 2014). These studies are described below and in Table 3.4.

Leclercq et al. (2014) assessed the effects of AUD on intestinal permeability and microbiome composition among individuals entering a detoxification programme at baseline and 19 days after abstinence, and among individuals in a control group. (Results for intestinal permeability are presented in Section 3.2.6 and Table 3.4.) Among a subset of 13 participants, intestinal microbiome composition and functionality were assessed. Non-metric multidimensional scaling revealed that the bacterial profiles of the participants with AUD who had high intestinal permeability differed from those of the participants with low intestinal permeability and the controls. Specifically, at the family level, bacteria from *Ruminococcaceae* and *Incertae Sedis XIII* were less abundant ($P < 0.05$), whereas bacteria from *Lachnospiraceae* and *Incertae Sedis XIV* were more abundant ($P < 0.05$) among individuals with high intestinal permeability than among those with low intestinal permeability and the controls. When the effects of abstinence were considered, a significant increase in *Ruminococcaceae* was observed among participants with high intestinal permeability ($P < 0.05$). In addition, bacteria from the family *Erysipelotrichaceae* and the genus *Holdemania* decreased significantly among all participants with AUD ($P < 0.05$) after they abstained. Alcohol withdrawal had no impact on the abundance of the other families or genera that were found to be modified among the participants with high intestinal permeability at entry into the programme. However, quantitative PCR analysis revealed that the total amount of bacteria, as well as the levels of *Bifidobacterium* spp. and *Lactobacillus* spp., increased significantly during alcohol withdrawal among individuals with high intestinal permeability and returned to the levels of controls ($P < 0.05$). [The number of participants with AUD was very small, with < 7 per

group when investigating the effects of alcohol withdrawal on the microbiome.]

Ames et al. (2020) collected samples from 22 individuals with AUD who were classified as having "less heavy drinking" (LHD) (< 10 drinks per day, $n = 8$) or "very heavy drinking" (VHD) (≥ 10 drinks per day, $n = 14$) and entered an inpatient treatment programme for 28 days. Homogenized whole stool was analysed using a microbiome sequencing kit to examine 6 of the 9 hypervariable regions of the *16S* gene. The average relative microbial abundance for each time point showed some genera specificity for each group (LHD vs VHD). *Erysipelotrichaceae* and *Lachnospiraceae* were significantly more abundant at the first time point in the LHD group than in the VHD group. Changes in the intestinal microbiota among the LHD and VHD groups differed significantly from day 1 to day 5 ($P = 0.03$) and from day 1 to week 3 ($P = 0.02$). The VHD group had a greater change from baseline than the LHD group. The Shannon diversity index of the intestinal microbiome changed significantly during abstinence among 5 participants, and among 4 individuals there was a significant increase in diversity over time. [The analyses over time of abstinence were performed on an extremely small number of samples, in some cases only 2 or 3 samples.]

A series of studies performed with participants from a cohort in Belgium reported on changes in the intestinal microbiome after abstinence (Gao et al., 2020; Maccioni et al., 2020; Hartmann et al., 2021; Hsu et al., 2022). In these studies, participants with AUD entered a 3-week detoxification and rehabilitation programme in which 2 weeks of inpatient treatment (week 1 and week 3) were separated by 1 week of outpatient care. Stool samples were collected from each participant's first bowel movement after hospital admission, i.e. at the beginning of week 1 and week 3 (reflecting 2 weeks of abstinence). [Abstinence during the week of outpatient treatment (week 2) was not confirmed with any specific testing.]

In the first study (Gao et al., 2020), shotgun metagenomic sequencing was used to assess the reversibility of functional alterations in the intestinal microbiota among individuals with AUD when they were abstinent for 2 weeks. Samples from 30 participants with AUD and 8 controls without AUD were compared. Seven microbial pathways were found to be sensitive to abstinence, with a linear discriminant analysis score > 2.0; all of them were enriched in the sample at week 3 [after 2 weeks of abstinence]. These pathways were isoprene biosynthesis I, phytol degradation, L-isoleucine biosynthesis II, superpathway of geranylgeranyl diphosphate biosynthesis II (via methyl-D-erythritol 4-phosphate), NAD salvage pathway II, glutaryl-coenzyme A degradation, and superpathway of geranylgeranyl diphosphate biosynthesis I (via mevalonate). Among these, four pathways were different when comparing the participants with AUD with the controls at week 1 or week 3. In particular, the relative abundance of the glutaryl-coenzyme A degradation gene was lower among the participants with AUD at week 1 compared with the controls, and it was higher at week 3 than at week 1 but remained lower at week 3 compared with the controls. Furthermore, the link between functional alterations in the intestinal microbiota and alcohol-associated steatosis was investigated. The microbial functional responses were assessed by characterizing microbial composition and controlled attenuation parameter (CAP). Participants with AUD were divided into two groups: high CAP (> 300 dB/m) and low CAP (< 300 dB/m). Functional microbial responses to abstinence were found to vary among individuals with AUD depending on the degree of hepatic steatosis. Among the high-CAP group, five microbial pathways were enriched at week 3: L-isoleucine biosynthesis II, the superpathway of β-D-glucuronosides degradation, the superpathway of hexuronide and hexuronate degradation, the

superpathway of geranylgeranyl diphosphate biosynthesis II (via methyl-D-erythritol 4-phosphate), and glutaryl-coenzyme A degradation. One microbial pathway was enriched at week 1: heterolactic fermentation. Among the low-CAP group, five microbial pathways were enriched at week 1: adenosine nucleotides degradation II, guanosine nucleotides degradation III, the superpathway of pyrimidine ribonucleosides degradation, purine nucleotides degradation II (aerobic), and guanosine 3′,5′-bis(diphosphate) (ppGpp) biosynthesis.

In the second study (Maccioni et al., 2020), samples were collected from 106 individuals with AUD and 24 healthy controls. Intestinal permeability was measured among 86 individuals. Among the participants who had both high urinary excretion of ^{51}Cr-labelled ethylenediaminetetraacetic acid (^{51}Cr-EDTA) and high faecal albumin content, values at week 3 had returned to those observed among the controls, whereas levels of intestinal permeability remained low among the participants with AUD who had normal levels at admission (see Section 3.2.6). Microbial translocation was assessed with serum levels of three markers: the Gram-negative markers soluble CD14 (sCD14) and LPS binding protein (LBP) and the Gram-positive marker peptidoglycan recognition proteins (PGRPs). Serum sCD14 levels decreased significantly upon abstinence ($P = 0.0001$). In contrast, neither LBP nor PGRP levels were modified by alcohol cessation, supporting the observations that increased intestinal permeability is not an absolute requirement for microbial translocation. The microbial composition in the stool was also assessed at the end of the 2-week detoxification programme among participants with AUD, who were subdivided according to both intestinal permeability and stage of ALD. The authors found an increased evenness among species, as expressed by the Shannon and Simpson diversity indexes, only among the participants with AUD who had high intestinal permeability; the number of observed species remained the same. In contrast, α-diversity indexes (richness and evenness) did not change among participants with AUD who had normal intestinal permeability. In addition, a minor change in α-diversity indexes was observed among participants with AUD who had non-progressive ALD but not among those who had progressive ALD. [However, these results were not significant.] Overall, microbial profile (β-diversity) did not change with abstinence. [These results support the concept of a possible link between faecal microbiota dysbiosis and leaky intestines but not with ALD progression among humans.]

The third study (Hartmann et al., 2021) focused on investigating changes in the fungal microbiome in faecal samples from 66 participants with AUD and 18 healthy controls. Principal coordinate analysis of the mycobiome among participants with AUD who were consuming alcohol ($n = 63$) and paired samples from individuals after 2 weeks of abstinence showed a significant difference between the two groups ($P = 0.001$). Specifically, at the genus level, the relative abundance of *Candida*, *Malassezia*, *Pichia*, *Kluyveromyces*, *Issatchenkia*, *Claviceps*, *Cyberlindnera*, and *Hanseniaspora* was significantly reduced after abstinence, whereas *Trichosporon* was significantly enriched after abstinence compared with during alcohol consumption. Abstinence among participants with AUD was associated with significantly lower proportions of the species *C. albicans, C. zeylanoides, I. orientalis,* and *Cyberlindnera jadinii* than before abstinence. In addition, the relative abundance of the families *Saccaromycodaceae*, *Malasseziaceae*, *Cystostereaceae*, *Didymellaceae*, and *Clavicipitiaceae* was significantly more depressed among participants with AUD after abstinence compared with during alcohol consumption; participants with AUD who abstained had significantly higher levels of the families *Metschnikowiaceae* and *Trichosporonaceae*. The specific anti-*C. albicans* immunoglobulin G

(IgG) and IgM serum levels were significantly higher among participants with AUD compared with controls, whereas anti-*C. albicans* IgA levels were similar between the groups. Abstinence resulted in a significant decrease in anti-*C. albicans* IgG levels, whereas the anti-*C. albicans* IgM and IgA levels were not significantly different. [Significance was defined as $P < 0.05$.]

Finally, the effects of abstinence on the intestinal virome were investigated (Hsu et al., 2022). Stool samples from 62 participants with AUD and 16 healthy controls were analysed. Significant differences in the faecal virome, specifically in the composition of bacteriophage species, were observed when comparing the controls with the participants with AUD, regardless of alcohol consumption status. The faecal virome was significantly different among participants with AUD after 2 weeks of abstinence. Phages targeting specific *Lactococcus*, *Leuconostoc*, and *Streptococcus* species and those targeting *Propionibacterium* and *Lactobacillus* species as a whole were more abundant. Significantly fewer individuals who were actively consuming alcohol than who were abstinent had bacteriophages targeting *Lactobacillus* bacteria. Furthermore, in a set of samples collected from participants with AUD entering the programme at week 1, the proportion of samples with *Propionibacterium* phages was significantly smaller than among the samples collected from the controls and from participants after 2 weeks of abstinence. The relative abundance of *Propionibacterium* phages also differed significantly across these three groups ($P = 0.002$, Kruskal–Wallis test), with significantly lower abundance among individuals with AUD who were actively consuming alcohol compared with the controls ($P < 0.001$) and participants with AUD who abstained ($P = 0.005$).

[All these studies are characterized by small sample sizes and unclear descriptions of whether the results obtained are from sample sets from the same participants with AUD and controls, because they all originate from the same cohort. Also, the Working Group noted that the relatively short duration of the abstinence period and the parallel drastic change in dietary and lifestyle habits due to the inpatient nature of the rehabilitation programme limit the strength of the findings about the beneficial effects of abstinence.]

3.2.6 Inflammatory and immune responses

The tumour microenvironment comprises stromal cells (e.g. fibroblasts and endothelial cells) and immune cells (e.g. resident macrophages and lymphocytes), blood vessels, and the extracellular matrix (Anderson and Simon, 2020). Inflammation in the microenvironment contributes to oncogenesis through the production of reactive chemical species, which in turn contribute to DNA mutations (see Sections 3.1.3 and 3.2.1). Stromal cells may also provide survival signals that promote tumour cell growth in primary or metastatic cancer sites (Inamura et al., 2022).

Alcohol consumption can alter the microenvironment of the gastrointestinal tract by increasing microbial translocation. This can result from generation of acetaldehyde (which affects paracellular permeability), direct epithelial damage by high concentrations of alcohol (as encountered in oropharyngeal and oesophageal mucosa, causing increased transcellular permeability), and other mechanisms that are less well characterized (Maccioni et al., 2020). Alcohol consumption alters the intestinal microbiome (see Section 3.2.5) and the mucosal immune system, inducing a local inflammatory state and altering the mucosal-associated invariant T (MAIT) cells (Li et al., 2019). Microbial translocation to the portal vein activates hepatic inflammation, a critical step in the development of alcohol-related hepatitis (ARH) and cirrhosis, which is a well-known precursor of HCC development. Levels of other microbial products, such as LPS, also are increased in peripheral blood (Liangpunsakul et al., 2017), and inflammatory

changes have been found in the adipose tissue of people with liver disease who have heavy alcohol consumption (Voican et al., 2015). As a result, the blood levels of numerous cytokines and circulating immune cells are altered among individuals with heavy alcohol consumption, contributing to a chronic inflammatory state and potentially impairing tumour immune surveillance (Greten and Grivennikov, 2019). The time course of reversal of alcohol-initiated activation of the innate immune system varies, and it may be prolonged among individuals with ARH.

The available studies assessing the effects of alcohol cessation on intestinal permeability and levels of translocation markers and on changes in cytokines are described below, and details are given in Table 3.5.

(a) Intestinal permeability and microbial translocation in the gastrointestinal microenvironment

The upper gastrointestinal tract is exposed to very high molar concentrations of alcohol, which may have effects not seen in tissues exposed to systemic alcohol concentrations; these tissues are also exposed to high concentrations of locally generated acetaldehyde or acetaldehyde present in beverages or tobacco smoke (see Section 3.1).

A study among 40 individuals with alcohol dependence (Leclercq et al., 2012) found increases in intestinal permeability (measured by absorption of ^{51}Cr-EDTA from the intestines) and associated increases in plasma LPS levels, which resolved by 19 days of abstinence (consisting of hospitalization for 1 week, outpatient treatment for 1 week, and inpatient care for 1 week). Direct assessment of intestinal permeability among 60 individuals with alcohol dependence showed that 26 (43%) of them exhibited increased intestinal permeability (Leclercq et al., 2014). The change in intestinal permeability was more marked in the small intestine than in the colon and was trending towards normal by 19 days of abstinence, although it did not normalize in all participants.

In a group of individuals entering alcohol treatment (Maccioni et al., 2020), intestinal permeability was measured among 86 individuals using urinary excretion of ^{51}Cr-EDTA, and among 78 individuals using faecal albumin content (a measure of capillary leakiness). At admission, two thirds of the participants with AUD had intestinal permeability measurements close to those of the controls, whereas 36–40% had high intestinal permeability. This led to a separation of participants into two categories: high and low intestinal permeability. Among individuals with both high urinary excretion of ^{51}Cr-EDTA ($P = 0.0036$ vs controls) and high faecal albumin content ($P = 0.0025$ vs controls), the intestinal permeability returned to values observed among the controls over the 3-week period of abstinence. However, the two measures of intestinal barrier function were not correlated with each other. Intestinal injury, assessed by measuring serum levels of intestinal fatty acid binding protein (I-FABP), a marker of enterocyte death, was not seen (Leclercq et al., 2014; Maccioni et al., 2020).

In a study in Brazil, Varella Morandi Junqueira-Franco et al. (2006) reported improvement in intestinal permeability measured using urinary excretion of ^{51}Cr-EDTA [and oxidative stress (see Section 3.2.7)] among 10 individuals with alcohol-related pellagra who had heavy alcohol consumption (> 90 g per day) after hospitalization for 27 days for abstinence and treatment with the antioxidant niacin (100 mg per day). The percentage of urinary excretion of ^{51}Cr-EDTA (mean ± SD) was 4.29% ± 1.92% before abstinence and 1.90% ± 1.19% after abstinence ($P < 0.05$). [This study did not have any comparison with control samples, and any positive effects resulting from abstinence remain unclear because participants had daily administration of niacin. The participants probably also benefited from an improved diet. Because alcohol is

Table 3.5 Effects of cessation of alcohol consumption on the immune system

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Maier et al. (1999) Germany	21 participants with AUD who were abstinent for < 5 days (group A1); 6 participants with AUD who were abstinent for 5–10 days (group A2) 25 healthy controls	Unknown	Participants who consumed ≥ 80 g of alcohol per day for > 2 years	Endoscopic biopsy of the duodenum Quantitative immunohistochemistry	Group A1 vs controls: 37% increase in B lymphocytes $P < 0.005$ 50% decrease in CLA-positive interepithelial leukocytes $P < 0.05$ 54% decrease in macrophages $P < 0.025$ These differences were not seen in group A2
González-Quintela et al. (2000) Spain	29 participants (6 women, 23 men; median age, 47 years) who were admitted for AWS after abstaining from drinking for 24–48 hours. Many participants had liver disease Controls: 5 healthy men	None	Average alcohol consumption in participants: > 120 g per day for ≥ 5 years	Serum samples collected at admission and after a median of 6 days (range, 2–15 days) of hospital stay and subsequent alcohol abstinence Enzyme immunoassay	At baseline: participants with AWS vs controls IL-6 and IL-10 increased $P \leq 0.0007$ IL-8 and IL-12 increased $P = 0.1$, NS After a median of 6 days of abstinence IL-6 and IL-10 decreased $P_{\text{abstinence vs baseline}} \leq 0.004$ IL-8 and IL-12 did not change significantly
Varella Morandi Junqueira-Franco et al. (2006) Brazil	10 men (average age, 35 years) with alcohol-related pellagra who had heavy alcohol consumption and were entering a 27-day inpatient detoxification programme Exclusion criteria: previously treated with vitamins	No information reported about age, BMI, or smoking status	Alcohol consumption: > 90 g of ethanol per day Participants were given 100 mg of niacin per day	Urine IP (^{51}Cr-EDTA)	**IP (% ^{51}Cr-EDTA)**, mean ± SD Baseline: 4.29 ± 1.92 After 27-day abstinence: 1.90 ± 1.19 $P_{\text{abstinence vs baseline}} < 0.05$

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Leclercq et al. (2012) Belgium	52 individuals with AD admitted for alcohol detoxification (40 at 18–19 days of abstinence) (81% men; average age ± SD, 47 ± 11 years) 16 controls	Age and BMI Screened for liver disease; none had advanced fibrosis	Abstinence for 18–19 days	Plasma and urine IP (^{51}Cr-EDTA); CRP (multiplex immunoassay)	**IP (% ^{51}Cr-EDTA)** ***Small intestine*** Increased in AD vs controls at baseline $P_{\text{AD vs controls}} < 0.05$ Decreased in AD after abstinence vs baseline $P_{\text{abstinence vs baseline}} < 0.001$ Same levels in AD and controls after abstinence $P_{\text{AD vs controls}} = 0.32$ ***Colon*** Increased in AD vs controls at baseline $P_{\text{AD vs controls}}$: NS Decreased in AD after abstinence vs baseline $P_{\text{abstinence vs baseline}} < 0.05$ Same levels in AD and controls after abstinence $P_{\text{AD vs controls}}$: NR ***Total IP*** Increased in AD vs controls at baseline $P_{\text{AD vs controls}}$: NS Decreased in AD after abstinence vs baseline $P_{\text{abstinence vs baseline}} < 0.01$ Same levels in AD and controls after abstinence: $P_{\text{AD vs controls}}$: NR **LPS (EU/mL)** Increased in AD vs controls at baseline $P_{\text{AD vs controls}} < 0.05$ Decreased in AD after abstinence vs baseline $P_{\text{abstinence vs baseline}} < 0.05$ Same levels in AD and controls after abstinence $P_{\text{AD vs controls}}$: NS **TNF-α (pg/mL)** Increased in AD vs controls at baseline $P_{\text{AD vs controls}} < 0.001$ Decreased in AD after abstinence vs baseline $P_{\text{abstinence vs baseline}}$: NS Increased in AD vs controls after abstinence $P_{\text{AD vs controls}} < 0.01$

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Leclercq et al. (2012) (cont.)					**IL-6 (pg/mL)** Increased in AD vs controls at baseline $P_{\text{AD vs controls}} < 0.05$ Decreased in AD after abstinence vs baseline $P_{\text{abstinence vs baseline}}$: NS Increased in AD after abstinence vs controls $P_{\text{AD vs controls}} < 0.05$ **hsCRP (mg/dL)** Increased in AD vs controls at baseline $P_{\text{AD vs controls}} < 0.05$ Decreased in AD after abstinence vs baseline $P_{\text{abstinence vs baseline}}$: NS But still increased in AD vs controls after abstinence $P_{\text{AD vs controls}} < 0.01$ **IL-10 (pg/mL)** Increased in AD vs controls at baseline $P_{\text{AD vs controls}}$: NR Decreased in AD after abstinence vs baseline $P_{\text{abstinence vs baseline}} < 0.001$ Same levels in AD and controls after abstinence $P_{\text{AD vs controls}}$: NR
Leclercq et al. (2014) Belgium	60 participants with AD entering a detoxification programme (47 men, 13 women) and 15 HC Exclusion criteria: obesity, diabetes, chronic inflammatory conditions, liver fibrosis or cirrhosis, and resumption of drinking during follow-up Participants with AD were divided into high-IP and low-IP groups	Age, sex, and BMI	Abstinence for 19 days	Plasma and urine IP (^{51}Cr-EDTA)	**IP (% ^{51}Cr-EDTA)**, mean ± SD ***Small intestine: 0–4 hours*** Controls: 2.36 ± 0.87 At baseline: $AD_{\text{high-IP}}$: 7.81 ± 5.46 $AD_{\text{low-IP}}$: 2.58 ± 0.79 $P_{\text{AD high-IP vs low-IP}} < 0.001$ $P_{\text{AD high-IP vs controls}} < 0.001$ Abstinence for 19 days: $AD_{\text{high-IP}}$: 3.26 ± 2.54 $AD_{\text{low-IP}}$: 1.93 ± 1.11 $P_{\text{AD high-IP vs low-IP}} < 0.05$

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Leclercq et al. (2014) (cont.)					***Colon: 4–24 hours*** Controls: 1.08 ± 0.37 At baseline: $AD_{\text{high-IP}}$: 2.79 ± 1.73 $AD_{\text{low-IP}}$: 0.90 ± 0.26 $P_{\text{AD high-IP vs low-IP}}$ < 0.001 $P_{\text{AD high-IP vs controls}}$ < 0.001 Abstinence for 19 days: $AD_{\text{high-IP}}$: 1.46 ± 1.01 $AD_{\text{low-IP}}$: 1.00 ± 0.63 ***Total: 0–24 hours*** Controls: 1.34 ± 0.43 At baseline: $AD_{\text{high-IP}}$: 3.71 ± 2.15 $AD_{\text{low-IP}}$: 1.22 ± 0.28 $PAD_{\text{high-IP vs low-IP}}$ < 0.001 $PAD_{\text{high-IP vs controls}}$ < 0.001 Abstinence for 19 days: $AD_{\text{high-IP}}$: 1.86 ± 1.34 $AD_{\text{low-IP}}$: 1.23 ± 0.75 **TNF-α (pg/mL)** At baseline: Increased in $AD_{\text{high-IP}}$ vs controls *P* < 0.01 Increased in $AD_{\text{low-IP}}$ vs controls *P* < 0.05 Abstinence for 19 days: Increased in $AD_{\text{high-IP}}$ vs controls *P* < 0.01 Increased in $AD_{\text{low-IP}}$ vs controls *P* < 0.05 **IL-6 (pg/mL)** At baseline: Increased in $AD_{\text{high-IP}}$ vs controls *P* < 0.10 $AD_{\text{low-IP}}$ vs controls: no significant change

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Leclercq et al. (2014) (cont.)					Abstinence for 19 days: Increased in $AD_{high\text{-}IP}$ vs controls $P < 0.05$ Increased in $AD_{low\text{-}IP}$ vs controls $P < 0.05$ **IL-10 (pg/mL)** At baseline: Increased in $AD_{high\text{-}IP}$ vs controls $P < 0.001$ Increased in $AD_{low\text{-}IP}$ vs controls $P < 0.001$ Abstinence for 19 days: Increased in $AD_{high\text{-}IP}$ vs controls $P < 0.01$ Increased in $AD_{low\text{-}IP}$ vs controls $P < 0.001$ **IL-8 (pg/mL)** At baseline: Increased in $AD_{high\text{-}IP}$ vs controls $P < 0.001$ Increased in $AD_{low\text{-}IP}$ vs controls $P < 0.05$ Increased in $AD_{high\text{-}IP}$ vs $AD_{low\text{-}IP}$ $P < 0.05$ Abstinence for 19 days: Increased in $AD_{high\text{-}IP}$ vs controls $P < 0.001$ Increased in $AD_{low\text{-}IP}$ vs controls $P < 0.05$ **IL-1β (pg/mL)** At baseline: $AD_{high\text{-}IP}$ or $AD_{low\text{-}IP}$ vs controls: no significant change Abstinence for 19 days: $AD_{high\text{-}IP}$ or $AD_{low\text{-}IP}$ vs controls: no significant change

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Leclercq et al. (2014) (cont.)					**hsCRP (mg/mL)** At baseline: $AD_{high\text{-}IP}$ or $AD_{low\text{-}IP}$ vs controls: no significant change Abstinence for 19 days: Increased in $AD_{high\text{-}IP}$ vs controls $P < 0.05$ $AD_{low\text{-}IP}$ vs controls: no significant change
Voican et al. (2015) France	47 participants with ALD (38 men, 9 women) Participants divided into 2 groups: mild ALD (35 participants) and severe ALD (12 participants)	NR	Participants had drinking history of 50 g per day during the previous year and had not stopped drinking before admission Alcohol withdrawal was started at admission under strict medical surveillance	Blood and liver and subcutaneous adipose tissue Samples collected at 1 week of abstinence Cytokines and fibrosis markers (mRNAs); macrophage marker (real-time qPCR)	**Mild ALD (abstinence vs admission)** Decreased expression of macrophage markers in adipose tissue $P < 0.05$ Decreased mRNA expression of cytokines/chemokines (IL-18, CCL2, osteopontin, semaphorin 7A) and macrophage marker CD68 **Severe ALD (abstinence vs admission)** Increased expression of macrophage marker CCL18 $P < 0.01$
Donnadieu-Rigole et al. (2016) France	Longitudinal study of 40 participants with AUD who were admitted for detoxification and 20 matched HC (85% men)	Age and sex	Participants with AUD consumed mean ± SD of 202 ± 125 g of pure alcohol per day, and 87.5% were active tobacco smokers 2 weeks of abstinence	Blood (monocytes) Flow cytometry	Values are mean ± SD **$CD14^{+}CD16^{-}$ cells (%)** Controls: (median, 86.5) AUD at baseline: 75.3 ± 11.9 (median, 78.6) AUD after abstinence (2 weeks): 78.1 ± 13.4 $P_{baseline\ vs\ controls} < 0.0001$ $P_{abstinence\ vs\ baseline} = 0.09$ **$CD14^{dim}CD16^{+}$ cells (%)** Controls: (median, 2.5) AUD at baseline: 10.3 ± 7.7 (median, 8.6) AUD after abstinence (2 weeks): 6.7 ± 6.4 $P_{baseline\ vs\ controls} < 0.0001$ $P_{abstinence\ vs\ baseline} < 0.01$

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
García-Marchena et al. (2017) Spain	85 participants with AUD who were abstinent and 55 HC (65% men; mean age, 46.6 years) from an outpatient psychiatry clinic	BMI, sex, and age Participants with AUD included individuals with pancreatic disease	Average duration of alcohol consumption, 13 years Mean duration of abstinence, 9 months; minimum, 4 weeks	Plasma Cytokines/chemokines (multiplex immunoassay)	Values are mean (95% CI) **CXCL12 (pg/mL)** Controls: 349.95 (319.15–384.59) Abstinent with AUD: 285.76 (266.07–307.61) $P < 0.001$ **CX3CL1 (pg/mL)** Controls: 5.689 (4.966–6.516) Abstinent with AUD: 4.592 (4.140–5.105) $P < 0.05$ **IL-8, MCP1, and MIP1α**: no significant change [Levels of cytokines before abstinence not reported]
Li et al. (2017) USA	Longitudinal 12-month study 68 individuals with ARH (61% men; average age, 44 years) 65 HDC without liver disease (57% men; average age, 43 years) 20 HC (55% men; average age, 38 years)	Age, sex, and alcohol consumption for HDC Age and sex for HC	The HDC group had consumed significantly more drinks in the 30 days before enrolment than the ARH group	Plasma Multiplex immunoassay, ELISA	Values are median (IQR) **TNF-α (pg/mL)** HC: 6.5 (4.8–10) ARH at baseline: 17.9 (12.5–35.8) HDC at baseline: 10.2 (6.8–19.2) $P_{\text{ARH vs H}}C < 0.001$ $P_{\text{ARH vs HDC}} < 0.001$ ARH after abstinence (180 days): 27.7 (15.5–32.0) HDC after abstinence (180 days): 8.3 (5.6–13.4) $P_{\text{ARH vs HDC}} < 0.01$ ARH after abstinence (360 days): 27.3 (21.8–45.0) HDC after abstinence (360 days): 11.9 (5.1–17.9) $P_{\text{ARH vs HDC}} < 0.01$ **IL-6 (pg/mL)** HC: 1.4 (0.9–3.3) ARH at baseline: 13.5 (6.6–36.2) HDC at baseline: 2.6 (0.9–6) $P_{\text{ARH vs HC}} < 0.001$ $P_{\text{ARH vs HDC}} < 0.001$ ARH after abstinence (180 days): 7.3 (4.9–19.3) HDC after abstinence (180 days): 4.2 (0.9–7.8) $P_{\text{ARH vs HDC}} < 0.05$ ARH after abstinence (360 days): 6.2 (4.0–8.5) HDC after abstinence (360 days): 2.4 (1.4–5.7) $PA_{\text{RH vs HDC}}$: NS

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Li et al. (2017) (cont.)					**IL-8 (pg/mL)** HC: 6.9 (4.9–16.7) ARH at baseline: 314.2 (117.9–608.4) HDC at baseline: 8.0 (4.7–15.2) $P_{\text{ARH vs HC}} < 0.001$ $P_{\text{ARH vs HDC}} < 0.001$ ARH after abstinence (180 days): 40.4 (23.5–65.2) HDC after abstinence (180 days): 8.3 (5.8–47.6) $P_{\text{ARH vs HDC}} < 0.05$ ARH after abstinence (360 days): 44.2 (25.7–111.4) HDC after abstinence (360 days): 9.4 (5.4–22.8) $P_{\text{ARH vs HDC}} < 0.01$ **IP-10 (pg/mL)** HC: 507 (344–610) ARH at baseline: 1144 (767–1531) HDC at baseline: 629 (429–847) $P_{\text{ARH vs HC}} < 0.001$ $P_{\text{ARH vs HDC}} < 0.001$ ARH after abstinence (180 days): 1317 (882–1764) HDC after abstinence (180 days): 648 (324–1041) $P_{\text{ARH vs HDC}} < 0.01$ ARH after abstinence (360 days): 1169 (861–1274) HDC after abstinence (360 days): 689 (472–1214) $P_{\text{ARH vs HDC}}$: NS **IL-4 (pg/mL)** HC: 4.5 (4.5–14.7) ARH at baseline: 4.5 (4.5–17) HDC at baseline: 4.5 (4.5–7.1) $P_{\text{ARH vs HC}}$: NS $P_{\text{ARH vs HDC}} < 0.05$ ARH after abstinence (180 days): 8.5 (4.5–18.4) HDC after abstinence (180 days): 4.5 (4.5–8.1) $P_{\text{ARH vs HDC}}$: NS ARH after abstinence (360 days): 8.7 (4.5–31.7) HDC after abstinence (360 days): 4.5 (4.5–8.7) $P_{\text{ARH vs HDC}}$: NS

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Li et al. (2017) (cont.)					**IL-9 (pg/mL)** HC: 1.4 (1.2–5.7) ARH at baseline: 1.4 (1.2–5.8) HDC at baseline: 1.2 (0.6–3.6) $P_{\text{ARH vs HC}}$: NS $P_{\text{ARH vs HDC}} < 0.05$ ARH after abstinence (180 days): 2.8 (1.2–5.6) HDC after abstinence (180 days): 1.9 (1.2–4.0) $P_{\text{ARH vs HDC}}$: NS ARH after abstinence (360 days): 4.1 (1.2–15.3) HDC after abstinence (360 days): 1.2 (0.9–1.9) $P_{\text{ARH vs HDC}}$: NS **IL-10 (pg/mL)** HC: 2.7 (1.6–5.6) ARH at baseline: 14.3 (6.4–35.2) HDC at baseline: 5.6 (1.8–10.3) $P_{\text{ARH vs HC}}$: NS $P_{\text{ARH vs HDC}} < 0.001$ ARH after abstinence (180 days): 10.9 (2.8–27.4) HDC after abstinence (180 days): 8.3 (1.1–11.4) $P_{\text{ARH vs HDC}}$: NS ARH after abstinence (360 days): 17.5 (7.6–34.2) HDC after abstinence (360 days): 9.3 (7.6–11.7) $P_{\text{ARH vs HDC}}$: NS **FGF-2 (pg/mL)** HC: 81.6 (54.1–133.1) ARH at baseline: 66.3 (49.3–136.7) HDC at baseline: 56 (26.4–95.9) $P_{\text{ARH vs HC}}$: NS $P_{\text{ARH vs HDC}} < 0.05$ ARH after abstinence (180 days): 102.8 (66.3–122) HDC after abstinence (180 days): 91.9 (62.4–104.3) $P_{\text{ARH vs HDC}}$: NS ARH after abstinence (360 days): 109.1 (83.6–225.3) HDC after abstinence (360 days): 83.6 (58.2–91.9) $P_{\text{ARH vs HDC}} < 0.05$

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Li et al. (2017) (cont.)					**IL-7 (pg/mL)** HC: 1.4 (1.4–3.3) ARH at baseline: 8.1 (1.4–15.2) HDC at baseline: 2.1 (1.4–9.7) $P_{\text{ARH vs HC}} < 0.05$ $P_{\text{ARH vs HDC}} < 0.05$ ARH after abstinence (180 days): 7.2 (4.7–10.9) HDC after abstinence (180 days): 5.5 (1.4–10.1) $P_{\text{ARH vs HDC}}$: NS ARH after abstinence (360 days): 12 (8.4–18.9) HDC after abstinence (360 days): 7.4 (1.4–8.7) $P_{\text{ARH vs HDC}} < 0.05$ **IL-15 (pg/mL)** HC: 4.0 (2.1–8.1) ARH at baseline: 14.5 (8.5–23.7) HDC at baseline: 5.2 (2–9.3) $P_{\text{ARH vs HC}} < 0.001$ $P_{\text{ARH vs HDC}} < 0.001$ ARH after abstinence (180 days): 10.7 (5.3–23.1) HDC after abstinence (180 days): 6.4 (1.3–17.9) $P_{\text{ARH vs HDC}}$: NS ARH after abstinence (360 days): 6.5 (3.5–27.6) HDC after abstinence (360 days): 4.5 (2.4–13.3) $P_{\text{ARH vs HDC}}$: NS **TGF-α (pg/mL)** HC: 1.7 (1.2–4.6) ARH at baseline: 5.8 (2.9–12.4) HDC at baseline: 2.4 (1–5.1) $P_{\text{ARH vs HC}} < 0.05$ $P_{\text{ARH vs HDC}} < 0.01$ ARH after abstinence (180 days): 4.7 (2.7–13) HDC after abstinence (180 days): 2.5 (0.8–16.1) $P_{\text{ARH vs HDC}}$: NS ARH after abstinence (360 days): 4.0 (2–40.3) HDC after abstinence (360 days): 5.1 (2.2–13.6) $P_{\text{ARH vs HDC}}$: NS

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Yen et al. (2017) Taiwan (China)	Longitudinal study 78 men with AD (mean age, 40.3 years) admitted into a 4-week detoxification programme Controls: 86 healthy men (mean age, 38.8 years)	Liver disease, age, and BMI	4 weeks of abstinence Only 48 men with AD completed the 4-week abstinence	Plasma Samples collected at baseline and after abstinence Multiplex immunoassay	Values are mean ± SD **IL-2 (pg/mL)** Controls: 1.26 ± 0.89 AD at baseline: 4.56 ± 2.84 AD after abstinence (4 weeks): 1.83 ± 1.47 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs controls}} = 0.022$ $P_{\text{abstinence vs baseline}} < 0.001$ **IFN-γ (pg/mL)** Controls: 1.36 ± 1.10 AD at baseline: 4.73 ± 3.87 AD after abstinence (4 weeks): 2.66 ± 1.89 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs controls}} < 0.001$ $P_{\text{abstinence vs baseline}} < 0.001$ **TNF-α (pg/mL)** Controls: 2.12 ± 1.68 AD at baseline: 8.49 ± 5.41 AD after abstinence (4 weeks): 3.35 ± 2.19 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs controls}} < 0.001$ $P_{\text{abstinence vs baseline}} < 0.001$ **IL-4 (pg/mL)** Controls: 4.76 ± 4.07 AD at baseline: 23.86 ± 17.08 AD after abstinence (4 weeks): 6.09 ± 4.08 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs controls}} = 0.031$ $P_{\text{abstinence vs baseline}} < 0.001$ **IL-5 (pg/mL)** Controls: 1.06 ± 0.95 AD at baseline: 3.45 ± 2.16 AD after abstinence (4 weeks): 2.56 ± 1.59 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs controls}} < 0.001$ $P_{\text{abstinence vs baseline}} = 0.011$

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Yen et al. (2017) (cont.)					**IL-6 (pg/mL)** Controls: 0.99 ± 0.82 AD at baseline: 3.43 ± 2.76 AD after abstinence (4 weeks): 1.98 ± 1.74 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs controls}} < 0.001$ $P_{\text{abstinence vs baseline}} = 0.001$ **IL-10 (pg/mL)** Controls: 1.51 ± 1.22 AD at baseline: 4.42 ± 2.93 AD after abstinence (4 weeks): 2.78 ± 2.58 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs controls}} < 0.001$ $P_{\text{abstinence vs baseline}} < 0.001$ **IL-1β (pg/mL)** Controls: 0.19 ± 0.20 AD at baseline: 0.89 ± 0.98 AD after abstinence (4 weeks): 0.63 ± 0.62 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs controls}} < 0.001$ $P_{\text{abstinence vs baseline}} = 0.02$ **IL-8 (pg/mL)** Controls: 2.26 ± 2.17 AD at baseline: 12.28 ± 10.54 AD after abstinence (4 weeks): 5.04 ± 4.78 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs controls}} < 0.001$ $P_{\text{abstinence vs baseline}} < 0.001$ **GM-CSF (pg/mL)** Controls: 1.01 ± 0.71 AD at baseline: 3.82 ± 3.06 AD after abstinence (4 weeks): 0.97 ± 0.49 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs controls}} = 0.731$ $P_{\text{abstinence vs baseline}} < 0.001$

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Donnadieu-Rigole et al. (2018) France	41 participants with AUD (30 men, 11 women; average age, 48.2 years) entering a 6-week treatment programme Controls: 100 heathy volunteers from blood donation banks usually characterized by a population of 51% women and aged 44–55 years Exclusion criteria: history of chronic inflammation diseases, current infections, HIV, or undergoing immunomodulatory or immunosuppressive treatments	Controls not matched	NR	Blood IP assessed indirectly by measuring I-FABP or zonulin (ELISA) Microbial translocation monitored by measuring serum levels of LBP and sCD14 (ELISA) or plasma 16S or 23S rDNA (qPCR)	Values are mean ± SD **I-FABP (µg/mL)** Controls: 310.5 ± 196.7 AUD at baseline: 944.1 ± 442.5 AUD after abstinence (6 weeks): 1151.4 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs baseline}} = 0.21$ AUD with heavy alcohol consumption at baseline: higher I-FABP vs AUD with less alcohol consumption $P = 0.03$ AUD with heavy alcohol consumption after abstinence (6 weeks): smaller decrease in I-FABP vs AUD with less alcohol consumption $P = 0.02$ **Zonulin (µg/mL)** Controls: 36.0 ± 17.02 AUD at baseline: 46.47 ± 16.82 AUD after abstinence (6 weeks): 34.2 $P_{\text{baseline vs controls}}$: NS $P_{\text{abstinence vs baseline}} = 0.639$ AUD with high BMI at baseline: higher zonulin vs AUD with low BMI $P = 0.0001$ AUD with high BMI after abstinence (6 weeks): larger decrease in zonulin vs AUD with low BMI $P = 0.005$ **LBP (µg/mL)** Controls: 5.3 ± 6.2 AUD at baseline: 41 ± 13.3 AUD after abstinence (6 weeks): 39 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs baseline}} = 0.043$ Cannabis-smoking AUD after abstinence (6 weeks): smaller decrease in LBP vs non-cannabis-smoking AUD $P = 0.04$

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Donnadieu-Rigole et al. (2018) (cont.)					**16S rDNA (copies/µL)** Controls: 9.2 ± 1.9 AUD at baseline: 13.9 ± 4.6 AUD after abstinence (6 weeks): 13.9 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs baseline}}$: NS **sCD14 (µg/mL)** Controls: 5.2 ± 1.6 AUD at baseline: 5.9 ± 1.6 AUD after abstinence (6 weeks): 5.1 $P_{\text{baseline vs controls}} = 0.024$ $P_{\text{abstinence vs baseline}} = 0.001$ Cannabis-smoking AUD after abstinence (6 weeks): smaller decrease in sCD14 vs non-cannabis-smoking AUD $P = 0.008$
Girard et al. (2019) France	115 participants with AD admitted for detoxification (88 men; average age, 47 years) 27 individuals relapsed (no abstinence at all), 44 relapsed at least once during the first 6 months after withdrawal (14 abstinent again at 6 months), and 30 remained abstinent at all follow-up visits (abstainers)	No control group No comment on presence of liver disease Variable periods of abstinence during 6 months All of the participants were smokers	Follow-up during 6-month abstinence Average duration of AD, 9.7 years	Serum Samples collected at 48 hours and 1, 2, 4, and 6 months after admission Multiplex immunoassay	Values are mean ± SD **TNF-α (pg/mL)** AD at baseline: 1.35 ± 4.11 AD after abstinence (1 month): 0.63 ± 1.36 $P = 0.002$ **IL-6 (pg/mL)** AD at baseline: 2.76 ± 3.49 AD after abstinence (1 month): 2.16 ± 3.31 $P = 0.01$ **IL-8 (pg/mL)** AD at baseline: 21.47 ± 32.42 AD after abstinence (1 month): 11.98 ± 17.23 $P < 0.001$ **IL-10 (pg/mL)** AD at baseline: 0.58 ± 0.91 AD after abstinence (1 month): 0.58 ± 1.07 $P = 0.408$ **MCP1 (pg/mL)** AD at baseline: 433.29 ± 266.24 AD after abstinence (1 month): 382.47 ± 161.77 $P = 0.054$

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Girard et al. (2019) France (cont.)					**IL-1β (pg/mL)** AD at baseline: 0.45 ± 0.83 AD after abstinence (1 month): 0.28 ± 0.58 $P < 0.001$ **IFN-γ (pg/mL)** AD at baseline: 0.07 ± 0.22 AD after abstinence (1 month): 0.09 ± 0.24 $P = 0.489$ **IL-12 (pg/mL)** AD at baseline: 17.85 ± 70.78 AD after abstinence (1 month): 15.16 ± 62.23 $P_{\text{abstinence vs baseline}} = 0.035$
Li et al. (2019) USA	56 participants with ARH, 45 HDC without overt liver disease, and 59 HC	Age, sex, race, and alcohol consumption	NR	Blood Samples collected at baseline and 6-month and 12-month follow-up MAIT cells (flow cytometry)	Values are median (Q1, Q3) **MAIT cells (% of T cells)** HC: 1.25 (0.63, 2.32) ARH at baseline: 0.16 (0.09, 0.34) HDC at baseline: 0.56 (0.23, 1.41) $P_{\text{ARH vs HC}} < 0.001$ $P_{\text{ARH vs HDC}} < 0.001$ $P_{\text{HC vs HDC}} < 0.01$ ARH after abstinence (180 days): increase HDC after abstinence (180 days): increase $P_{\text{ARH abstinence vs ARH baseline}}$: NS $P_{\text{HDC abstinence vs HDC baseline}}$: NS ARH after abstinence (360 days): 0.31 (0.14, 0.61) HDC after abstinence (360 days): 0.63 (0.17, 1.26) $P_{\text{ARH abstinence vs ARH baseline}} < 0.01$ $P_{\text{HDC abstinence vs HDC baseline}}$: NS

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Chaturvedi et al. (2020) India	17 men with AUD admitted for 7-day inpatient detoxification programme (average age, 32 years;) Controls: 12 men (average age, 34 years) with normal liver function tests and no known psychiatric or physical illnesses	Age and sex	Average duration of AUD, 6 years 7-day inpatient abstinence; patients followed up for 1 month after treatment	Serum CD200, a suppressor of inflammation (ELISA)	Values are mean ± SD **CD200 (pg/mL)** Controls: 23.30 ± 6.41 AUD at baseline: 16.25 ± 5.03 AUD after abstinence (1 week): 17.02 ± 4.16 AUD after abstinence (1 month): 17.83 ± 5.36 $P_{\text{baseline vs controls}} = 0.003$ $P_{\text{1-month abstinence vs baseline}} = 0.677$ $P_{\text{all time points vs controls}} < 0.05$
García-Marchena et al. (2020) Spain	85 abstinent participants with AUD and 55 HC (65% men; mean age, 46.6 years) Participants with AUD included individuals with pancreatic disease	BMI, sex, and age	Average duration of AUD, 13 years Mean duration of abstinence, 9 months; minimum, 4 weeks	Plasma Multiplex immunoassay	Abstinent AUD vs HC Increased IL-1β and IL-6 $P < 0.001$ Increased TNF-α $P < 0.01$ Decreased IL-4 and IL-17A $P < 0.001$ Decreased IFN-γ $P < 0.05$
Maccioni et al. (2020) Belgium	106 individuals with AUD (78 men; mean age ± SEM, 46 ± 9.2 years) entering a 3-week detoxification programme Controls: 24 healthy volunteers (14 men, 10 women; mean age ± SEM, 42 ± 11 years) who consumed < 20 g of alcohol per day, defined as social drinking	Age, sex, and BMI (1 to 4 ratio) Stratified based on degree of liver injury and IP	Individuals with AUD had consumed > 60 g of alcohol per day for ≥ 1 year Detoxification programme consisted of 1 week of inpatient detoxification, followed by 1 week of outpatient care and 1 week of inpatient treatment	Urine and stool IP (^{51}Cr-EDTA); faecal albumin content (ELISA)	**IP (% ^{51}Cr-EDTA) after 3 weeks of abstinence** Decreased in $AUD_{\text{high-IP}}$ $P_{\text{abstinence vs baseline}} = 0.0036$ $AUD_{\text{low-IP}}$: no change **Faecal albumin content (3 weeks abstinence) (µg/g of stool)** Decreased in $AUD_{\text{high-IP}}$ $P_{\text{abstinence vs baseline}} = 0.0025$ $AUD_{\text{low-IP}}$: no change

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Jung et al. (2021) Austria and Germany	37 participants with AUD (26 men, 11 women; average age, 49 years) entering an inpatient alcohol rehabilitation programme 17 controls (10 men, 7 women; average age, 45.1 years) who consumed < 10 g per day of alcohol	Sex and age	Participants had ALD (24 low fibrosis, 12 advanced fibrosis based on transient elastography) 1-week inpatient abstinence	Serum I-FABP (western blot); LPS (limulus amoebocyte lysate assay); LBP and zonulin (ELISA); TLR2 and TLR4 ligands (reporter gene assays)	**LPS (EU/mL)** Controls: 1 AUD at baseline: 1.6 AUD after abstinence: 1.4 $P_{\text{AUD vs abstinent}} < 0.05$ $P_{\text{AUD vs controls}}$: NS **LBP (µg/mL)** Controls: 25 AUD at baseline: 40 AUD after abstinence: 45 $P_{\text{AUD baseline or AUD abstinent vs controls}} < 0.05$ $P_{\text{AUD vs abstinent}}$: NS **Zonulin (ng/mL)** Controls: 2.25 AUD at baseline: 1.8 AUD after abstinence: 2.0 $P_{\text{AUD vs abstinent}} < 0.05$ $P_{\text{AUD baseline or AUD abstinent vs controls}}$: NS **I-FABP (intensity units)** Controls: 2.3 M AUD at baseline: 1.7 M AUD after abstinence: 2 M $P_{\text{AUD vs abstinent}} < 0.05$ $P_{\text{AUD baseline or AUD abstinent vs controls}}$: NS **TLR4 ligands (fold over controls)** AUD at baseline: 2.5 AUD after abstinence: 2.0 All comparisons: $P < 0.05$ **TLR2 ligands (fold over controls)** AUD at baseline: 4.5 AUD after abstinence: 3.0 All comparisons: $P < 0.05$ [Levels before and after 1-week abstinence were estimated from figures]

Table 3.5 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)[a]	Results
Shiba et al. (2021) Japan	Inpatient alcohol rehabilitation treatment 72 men with AD (average age, 52 years) 13 men without AD as controls	Sex	Participants consumed > 60 g per day; 8 with cirrhosis (none with Child–Pugh score of C) 4-week inpatient treatment ensuring abstinence	Circulating blood mononuclear cells Cytokine release (flow cytometry) after *ADH1B* and *ALDH2* genotyping (PCR)	**CD14+CD16− cells (% of PBMC)** Controls: 19 AD at baseline: 11 AD after abstinence: 15 $P_{\text{AD baseline vs controls}} < 0.05$ $P_{\text{AD baseline vs AD abstinence}} < 0.05$ $P_{\text{AD baseline vs controls}}$: NS **$CD14^{int}CD16^{+}$ or $CD14^{-}CD16^{+}$ cells (% of PBMC)** No difference for either subset between controls, AD at baseline, or AD after abstinence **TNF-α after LPS stimulation of $CD14^{+}CD16^{-}$ cells (pg/nL)** Controls: 400 AD at baseline: 100 AD after abstinence: 200 All comparisons: *P* < 0.05 **IL-6 after LPS stimulation of CD14+CD16− cells (pg/nL)** Controls: 6000 AD at baseline: 1000 AD after abstinence: 2000 All comparisons: *P* < 0.05
Yang et al. (2021) USA	79 participants with ARH, 66 HDC without liver disease, and 46 HC	Sex and alcohol consumption for HDC; age and sex for HC	Follow-up of abstinence at 6 months and 12 months	Plasma REG3α and TFF3 (specific ELISA kits)	Baseline: increased TFF3 and REG3α in ARH vs HC and HDC *P* < 0.001 The elevated levels persisted at 6 months and 12 months after abstinence

[a] % ^{51}Cr-EDTA is the percentage of the ingested dose of ^{51}Cr-EDTA found in urine, normalized for creatinine.

16S rDNA, 16S ribosomal DNA subunit; AD, alcohol dependence; *ADH1B*, alcohol dehydrogenase 1B gene; ALD, alcohol-related liver disease; *ALDH2*, aldehyde dehydrogenase gene; ARH, alcohol-related hepatitis; AUD, alcohol use disorder; AWS, alcohol withdrawal syndrome; BMI, body mass index; CCL2, C–C motif chemokine ligand 2; CLA, common leukocyte antigen; CRP, C-reactive protein; CX3CL1, chemokine C–X3–C motif ligand 1; CXCL12, chemokine C–X–C motif ligand 12; EDTA, ethylenediaminetetraacetic acid; ELISA, enzyme-linked immunosorbent assay; EU, endotoxin unit; FGF-2, fibroblast growth factor 2; GM-CSF, granulocyte macrophage colony-stimulating factor; HC, healthy controls; HDC, heavy drinking controls; hsCRP, high-sensitivity C-reactive protein; I-FABP, intestinal fatty acid binding protein; IFN-γ, interferon γ; IL, interleukin; IP, intestinal permeability; IP-10, IFN-γ-induced protein 10; IQR, interquartile range; LBP, lipopolysaccharide binding protein; LPS, lipopolysaccharide; MAIT, mucosal-associated invariant T; MCP1, monocyte chemoattractant protein 1; MIP1α, macrophage inflammatory protein 1 alpha; mRNA, messenger RNA; NR, not reported; NS, not significant; PBMC, peripheral blood mononuclear cells; PCR, polymerase chain reaction; Q1, first quartile; Q3, third quartile; qPCR, quantitative polymerase chain reaction; rDNA, ribosomal DNA; REG3α, regenerating islet-derived protein 3α; sCD14, soluble CD14; SD, standard deviation; SEM, standard error of the mean; TFF3, trefoil factor 3; TGF-β, tumour growth factor β; TLR, toll-like receptor; TNF-α, tumour necrosis factor α.

known to cause oxidative stress, the correlation between improved oxidative stress measures (see Section 3.2.7) and improved intestinal permeability points towards a decrease in cancer risk upon cessation of alcohol consumption.]

In a study in France, Donnadieu-Rigole et al. (2018) assessed the beneficial effects of alcohol withdrawal on intestinal permeability and microbial translocation among 41 individuals (mostly men) with AUD. Intestinal permeability was assessed indirectly by measuring levels of I-FABP or zonulin, a modulator of intestinal tight junctions. In addition, plasma levels of three microbial translocation markers were measured: LBP, the LPS co-receptor sCD14, and the 16S or 23S ribosomal DNA subunits (16S or 23S rDNA). Levels of these markers were compared with those among controls (blood samples from 100 healthy women aged 40–55 years) and with samples collected again from the same individuals with AUD at 3 weeks and 6 weeks after alcohol withdrawal. At baseline, levels of the markers LBP, 16S rDNA, and sCD14 were significantly higher among the individuals with AUD than among the controls. The mean plasma levels of I-FABP were significantly higher among the individuals with AUD than among the controls; no significant difference was found in the zonulin levels. At 6 weeks after alcohol withdrawal, the plasma levels of sCD14 and LBP decreased significantly, but the mean levels of 16S rDNA remained unchanged. [Although these changes were statistically significant, they were numerically small and may not be clinically significant.] The levels of the intestinal permeability markers I-FABP and zonulin did not change significantly after 6 weeks of alcohol withdrawal. [These results could have been affected by cannabis use, high body mass index, and use of women as controls for men.]

Jung et al. (2021) examined the effect of 1 week of abstinence on markers of intestinal injury and microbial translocation. They compared 37 participants with heavy alcohol consumption and ALD (ranging from fatty liver without fibrosis to cirrhosis) with 17 age- and sex-matched individuals with very light alcohol consumption (< 10 g per day). Circulating levels of I-FABP and zonulin were not significantly lower among the participants with heavy alcohol consumption and increased after 1 week of abstinence. LPS levels among the participants with ALD were not significantly higher than those among the controls, because 24 of the 37 participants with ALD did not have elevated LPS levels at admission. LBP levels were higher at admission and remained higher after 1 week of abstinence. A novel method was used to assess bacterial translocation: cell lines expressing reporter genes responding to ligands of toll-like receptor 2 (TLR2) (lipoteichoic acid, from Gram-positive bacteria) and TLR4 (LPS, from Gram-negative bacteria). The levels of these ligands were significantly higher among the participants with heavy alcohol consumption and decreased significantly after 1 week of abstinence, although they remained significantly higher than those among the controls.

Yang et al. (2021) conducted a longitudinal study of 79 individuals with ARH, 66 individuals with heavy alcohol consumption and without overt liver disease at baseline, and 46 healthy controls. The levels of regenerating islet-derived protein 3α (REG3α) and trefoil factor 3 (TFF3) (identified as biomarkers for intestinal injury) at baseline were significantly higher only among the individuals with ARH compared with the controls, and the elevated levels persisted at 6 months and 12 months of follow-up upon abstinence.

(b) Mucosal immune cells in the gastrointestinal environment

A potential consequence of the changes in the microbiome, increased permeability, and microbial translocation is intestinal inflammation (Bishehsari et al., 2017), which is modulated by the effects of alcohol on mucosal immune cells.

In the study of Maccioni et al. (2020), there were no overt histological features of inflammation in duodenal biopsies from the participants with AUD; in fact, there were fewer haematopoietic cells (CD45+), macrophages (CD68+), and T cells (CD3+) compared with controls. Assays of mRNA levels of interleukin-17 (IL-17), IL-1β, interferon γ (IFN-γ), and IL-22 showed increases only in the IL-1β transcripts.

A small study (Maier et al., 1999) compared duodenum samples from participants who consumed ≥ 80 g of alcohol per day for > 2 years and healthy controls. In the samples taken within 5 days of abstinence from the individuals with heavy alcohol consumption, increased numbers of B lymphocytes and decreased numbers of common leukocyte antigen (CLA)-positive inter-epithelial lymphocytes and of macrophages were seen compared with controls. These changes were no longer seen after 5–10 days of abstinence among a small subset of the cohort. [The Working Group noted that this was a very small study, with a very short abstinence period and little control for other variables.]

(c) *Effects on circulating markers of immune activation*

Translocation of microbial products to the liver via the portal vein is thought to play a central role in the pathogenesis of ALD. The resident macrophages (Kupffer cells) are activated (especially via TLR4-mediated pathways), causing the release of numerous cytokines and increasing the generation of reactive chemical species. Microbial LPS levels also are increased in peripheral circulation, potentially stimulating immune responses in distant organs (Liangpunsakul et al., 2017). The understanding of the extent and time course for resolution of these effects is based largely on measuring changes in circulating cytokines and the properties of cells obtained from individuals who have heavy alcohol consumption and are entering a treatment programme for AUD or ALD, or from comparisons of individuals who have heavy alcohol consumption with individuals who are abstinent. These results are discussed below and summarized in Table 3.5.

(i) *Cytokines and chemokines and circulating markers of inflammation*

The immune system is sensitive to even short-term exposure to alcohol. Acute administration of 60 g of alcohol to 5 healthy volunteers caused an increase in IL-8 concentrations (González-Quintela et al., 2000). Among 221 individuals who never consumed alcohol, 140 who had light alcohol consumption, 53 who had moderate alcohol consumption, and 45 who had heavy alcohol consumption, the percentage of individuals with high IL-8 concentrations (defined as > 10 pg/mL) increased from 5.9% in those who never consumed alcohol to 10.7% in those with light alcohol consumption, 13.2% in those with moderate alcohol consumption, and 17.8% in those with heavy alcohol consumption (Gonzalez-Quintela et al., 2007). Increases in concentrations of IL-2, IL-4, IL-10, and IFN-γ were reported after 30 days of consumption of moderate amounts of beer by a group of 57 healthy adults who abstained for 30 days before this exposure period (Romeo et al., 2007). Walline et al. (2018) compared cytokine concentrations among 22 individuals who had heavy alcohol consumption with those among 20 individuals who had lower alcohol consumption and found increased LPS levels but no difference in IL-6 or IL-10 levels. Elevations in levels of the inflammatory cytokines IFN-γ-induced protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP1) (Manzardo et al., 2016; Bjørkhaug et al., 2020), and IL-17 (Xu et al., 2020) have been observed among individuals with heavy alcohol consumption compared with individuals who are abstinent. [The effect of abstinence on these cytokines was not reported.]

One approach to understanding the effect of abstinence on alcohol-induced inflammation

is to compare cytokine concentrations among individuals who recently abstained with those in controls. In one study (García-Marchena et al., 2017), the concentrations of the chemokines CXCL12 and CX3CL1 were found to be reduced among 85 individuals who formerly had heavy alcohol consumption and had abstained for ≥ 4 weeks (average, 9 months) compared with 55 healthy controls. [The wide range of duration of abstinence is somewhat problematic, and it is not understood why the chemokine levels would remain persistently low or whether they would increase with even longer abstinence. The presence of other disease was not discussed.]

García-Marchena et al. (2020) also reported higher levels of inflammatory cytokines (IL-1β, IL-6, and tumour necrosis factor α [TNF-α]) and decreased levels of potentially anti-inflammatory cytokines (IL-4 and IL-17) among 85 individuals who formerly had heavy alcohol consumption and were now abstinent compared with 55 healthy controls [probably the same participants as in the study of García-Marchena et al. (2017)]. [Among the participants who formerly had heavy alcohol consumption and abstained, those with liver and pancreatic disease had higher IL-6 levels and lower IL-17 levels than the other participants who abstained, underscoring the importance of recognizing the presence of co-existing alcohol-related organ injury in any such studies.]

A more informative way of determining the effect of abstinence has been to measure cytokine concentrations at admission for rehabilitation treatment and at various durations of abstinence thereafter. [A common confounder in these studies is the stress of withdrawal on the markers under investigation, and the presence or absence of liver disease among the participants undergoing treatment.] González-Quintela et al. (2000) studied cytokine levels among 29 participants hospitalized for rehabilitation treatment and reported higher IL-6 and IL-10 concentrations at admission, which decreased after 6 days of abstinence but remained substantially higher than those among the controls. The levels of IL-8 and IL-12 did not differ from those among the controls and they did not change significantly with abstinence. [The Working Group noted that 6 days is a short duration of abstinence and that the control group was only 5 individuals.]

In the study of Leclercq et al. (2012) described previously, plasma levels of IL-6, TNF-α, and C-reactive protein (CRP) were significantly increased at the initial and final measurements among individuals with alcohol dependence compared with controls. Half of the participants had a decrease in IL-6 levels and two thirds had a decrease in TNF-α levels after 19 days of abstinence. IL-10 levels were higher at entry compared with controls and decreased significantly with abstinence. Compared with controls, the participants with alcohol dependence had significantly higher concentrations of high-sensitivity CRP (hsCRP) and LPS at entry; hsCRP levels remained significantly higher after abstinence.

In the subsequent study (Leclercq et al., 2014), plasma levels of TNF-α, IL-8, and IL-10 were increased (and there was a non-significant increase in IL-6 levels) among individuals with or without high intestinal permeability at baseline; after 19 days of abstinence, the levels remained elevated compared with controls. Also, IL-1β levels were slightly elevated at both time points. Plasma hsCRP concentrations were increased after abstinence only among the subset of participants with high intestinal permeability.

Girard et al. (2019) followed up a cohort of 115 individuals with AUD after admission for detoxification for up to 6 months. The degree of abstinence was assessed at each time point using the timeline follow-back method, and the participants served as their own controls. Of the participants, 26% abstained completely for 6 months, 38% had at least one relapse, and 23% were not abstinent at any time during follow-up. The concentrations of TNF-α, IL-6, IL-8, IL-12, and IL-1β decreased after 1 month; levels of MCP1 decreased and then plateaued at a lower

concentration at 2 months of abstinence. There were no changes in levels of IL-10, IL-12, or IFN-γ. Otherwise, there was no difference in cytokine concentration at the later time points between the individuals who abstained and those who did not abstain. [There was no control group, only the cytokine levels at the beginning of detoxification, and the data were combined for individuals who were abstinent, who were not abstinent, and who had a relapse. Not all cytokines were detectable in all participants at admission, except for MCP1 and IL-8, and they became detectable or undetectable at various time points, leading to large standard deviations.]

Yen et al. (2017) studied 78 men with AUD, at entry into detoxification treatment and 4 weeks later, for a panel of cytokines (IL-2, IFN-γ, TNF-α, IL-4, IL-5, IL-6, IL-10, IL-1β, IL-8, and granulocyte macrophage colony-stimulating factor [GM-CSF]). The control group was 86 healthy individuals. All cytokine concentrations were higher at admission among the individuals with AUD than among the controls. Within 4 weeks, all of the concentrations had decreased significantly in the 48 participants who abstained; the level of GM-CSF decreased to the control levels, whereas levels of the other cytokines were still significantly higher than the control levels [although, in most cases, quite close to the control levels].

Liangpunsakul et al. (2017) studied 97 individuals with excessive alcohol consumption and 51 individuals without excessive alcohol consumption. They found that the individuals with excessive alcohol consumption had higher concentrations of LPS, sCD14, and sCD163 (a marker of macrophage activation) than those without excessive alcohol consumption, and the concentrations correlated with the quantity of alcohol consumed in the previous 30 days. In a separate cohort, 31 individuals in rehabilitation treatment were studied for changes in these immune markers over 12 weeks. The concentrations decreased to normal after 4 weeks and remained low for 12 weeks.

A consortium evaluating the pathogenesis of ARH (Li et al., 2017) studied an array of 38 cytokines among 20 healthy controls, 65 individuals with heavy alcohol consumption but without liver disease (ascertained by serum liver tests), and 68 individuals with ARH. There was no difference in cytokine concentrations between the participants with heavy alcohol consumption and the controls. There was an increase in 11 inflammatory cytokines, anti-inflammatory cytokines, and growth factors, including TNF-α, IL-6, IL-8, IP-10, IL-10, IL-7, IL-15, and tumour growth factor α (TGF-α), among the individuals with ARH compared with the individuals with heavy alcohol consumption but without liver disease, and some of the changes persisted for 12 months (Li et al., 2017). [This study reinforces the caveat that studies of the effect of alcohol among individuals with heavy alcohol consumption must consider the possibility that there is occult liver disease confounding the conclusions, because histological alcohol-related steatohepatitis can be present among individuals who have only mild abnormalities in aminotransferases (Seitz et al., 2018).]

Voican et al. (2015) studied 47 individuals with ALD at baseline and at 1 week after withdrawal of alcohol. They measured mRNA expression levels in blood samples and subcutaneous fat biopsies for a host of adipokines and cytokines, including IL-1β, IL-18, caspase-1, C–C motif chemokine ligand 2 (CCL2), osteopontin, and semaphorin 7A. The levels of these chemokines and inflammasome components were correlated with liver damage at baseline. After 1 week of abstinence, macrophage infiltration of subcutaneous fat decreased and the macrophages were reoriented towards an anti-inflammatory M2 phenotype.

Chaturvedi et al. (2020) examined the effect of alcohol consumption on the concentration of neuroimmune regulators (molecules in the

nervous system that can silence innate immune responses and suppress inflammation). The concentration of the neuroimmune regulator CD200 was lower among the individuals with AUD at baseline compared with the controls, and no significant improvement was reported at 1 month of abstinence.

(ii) Circulating immune cells

Donnadieu-Rigole et al. (2016) studied flow cytometric characteristics of peripheral blood mononuclear cells among individuals with AUD at admission for detoxification and after 2 weeks of abstinence. At admission, an altered distribution of circulating monocytes was found among the participants with AUD, with a decrease in the classical $CD14^{+}/CD16^{-}$ monocyte subset and an increase in the non-classical $CD14^{dim}/CD16^{+}$ subset compared with healthy controls. These changes improved partially during abstinence.

In another study (Li et al., 2019), individuals with heavy alcohol consumption had reduced numbers of MAIT cells (expressed as a percentage of T cells) of 0.56% compared with individuals who were abstinent (1.25%), and individuals with ARH had even lower levels (0.16%). Among the individuals with ARH, the cells were hyperactivated, which was associated with increased plasma levels of IL-7, IL-15, IL-17, IL-18, IL-23, IFN-γ, and TNF-α. No changes were observed in the levels of other circulating innate T cells, including natural killer (NK) T cells, invariant NK T cells, and γδ T cells. The numbers of MAIT cells increased among individuals with heavy alcohol consumption and among individuals with ARH after 6 months and 12 months of abstinence but remained significantly lower than those among healthy controls. [The activation of the MAIT cells may have resulted from the changes in the intestinal mucosa discussed previously, ultimately leading to activation-induced cell death.]

Shiba et al. (2021) studied 72 men with alcohol dependence who were admitted to the hospital for inpatient treatment for 4 weeks. They examined changes in levels of LPS and responsiveness to LPS stimulation of circulating blood monocytes, and the interaction between these changes and the genotypes of the individuals at the *ADH1B* and *ALDH2* loci. The control group consisted of 13 healthy men. There were lower percentages of $CD14^{+}CD16^{-}$ cells at entry among the participants with alcohol dependence compared with the controls; these increased at 4 weeks but not to control levels. There was no difference in the levels of $CD14^{int}CD16^{+}$ or $CD14^{-}CD16^{+}$ subtypes, nor were there changes in the levels of other circulating cells (plasmacytoid dendritic cells, NK cells, or NK T cells). When the $CD14^{+}CD16^{-}$ cells were incubated with LPS overnight, they produced less TNF-α and IL-6 than control cells, and this difference partially reverted at 4 weeks. $CD14^{+}CD16^{-}$ cells from individuals with alcohol dependence who were heterozygous for *ALDH2*2* had an even more suppressed response to LPS, which was potentiated by the presence of an *ADH1B*2* allele, compared with cells from participants who were homozygous for *ADH1B*1*. [This suggests that the concentrations of acetaldehyde reached during heavy alcohol consumption contributed to this effect.] Incubation of the $CD14^{+}CD16^{-}$ cells with malondialdehyde–acetaldehyde–albumin adducts attenuated the response of the cells to a second stimulation with LPS after an initial 24-hour exposure, again supporting a role for acetaldehyde in this effect on the circulating monocytes. The mechanism for this effect was suggested to involve induction of IL-1 receptor-associated kinase M, which regulates the response to LPS, in the cells from the individuals with alcohol dependence.

Shiba et al. (2021) extended their study to mice that were fed ethanol by gavage for 42 days, mice that were fed ethanol and then had ethanol withdrawn for 21 days, and control mice. Hepatic macrophages ($CD11b^{+}$ cells) were isolated and stimulated with LPS. Intracellular

TNF-α expression was reduced in the cells from the ethanol-fed animals and returned to normal 21 days after withdrawal of ethanol. Finally, the authors compared the responses of hepatic $CD11b^+$ cells from wild-type and *ALDH2*2* transgenic mice that were fed ethanol and found that the *ALDH2*2* mice had lower levels of LPS-stimulated TNF-α.

3.2.7 Oxidative stress

Ethanol oxidation, especially via CYP2E1, is associated with the generation of reactive oxygen species. CYP2E1 is considered a "leaky" enzyme, which can readily transfer electrons from NAD phosphate to oxygen rather than to ethanol, generating hydroxyl radicals, superoxide anions, and hydrogen peroxide (IARC, 2010); in addition, the activity of CYP2E1 is induced by alcohol consumption. Reactive oxygen species are detoxified by superoxide dismutase, the selenoprotein glutathione peroxidase (GPx), glutathione reductase, and catalase, and by reaction with retinol, carotene, and vitamin E. Increased production of reactive oxygen species can lead to increased breakdown products of lipid peroxides. Evidence of oxidative stress and of impaired ability to detoxify reactive oxygen species has been found among individuals with chronic heavy alcohol consumption; five studies have assessed the time course for resolution of these effects (Table 3.6).

D'Antonio et al. (1986) measured carotene, retinol, and α-tocopherol on day 0 and day 5 among 192 men with AUD admitted for detoxification. Plasma carotene levels were somewhat low at admission (94 μg/dL among 149 participants) and increased by 30% by day 5. Dietary history suggested an intake of carotene ~1 unit lower than that considered normal. Retinol and α-tocopherol levels were normal at admission and on day 5. Among a subset of 19 participants, carotene levels increased after 33 days of abstinence to 190 μg/dL. [The increase in carotene levels could have resulted from abstinence or improved dietary intake.]

Girre et al. (1990) assessed selenium, vitamin E (α-tocopherol measurement), and GPx levels among 25 individuals with AUD and 25 age- and sex-matched controls. The plasma and erythrocyte levels of GPx and α-tocopherol and the plasma and whole-blood levels of selenium were reduced among the participants with AUD compared with the controls. After 14 days of abstinence in hospital (and no dietary supplementation), plasma levels of selenium remained low but whole-blood levels increased. Plasma levels of GPx were unchanged after abstinence, whereas erythrocyte enzyme activity increased significantly (not reaching the normal level). Plasma and erythrocyte levels of α-tocopherol remained low with abstinence.

Lettéron et al. (1993) measured exhaled ethane as a measure of oxidative stress among 42 healthy individuals who were controls, 52 participants with liver disease other than ALD who were controls, and 89 participants who had heavy alcohol consumption and were admitted to the hospital for alcohol withdrawal and liver disease assessment. Among the participants with heavy alcohol consumption, 73 had advanced liver disease (ARH, cirrhosis, or both). Samples of breath were obtained from the participants at various times after admission to the hospital. The level of exhaled ethane was 5 times as high among the individuals with heavy alcohol consumption and ALD as among the controls or the participants without ALD. The participants without ALD served as a control for the effect of liver disease. In a small subset of that group (9 participants followed up over time), there was a slow resolution towards normal with abstinence, over a period of weeks. The level of exhaled ethane was positively but weakly correlated with levels of daily alcohol consumption before admission.

In Taiwan (China), Peng et al. (2005) investigated the activity of antioxidant enzymes and malondialdehyde in plasma from 29 participants

Table 3.6 Effects of cessation of alcohol consumption on oxidative stress

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
D'Antonio et al. (1986) USA	192 participants (men) with AUD (126 White, 66 Black; average age, 40 years) entering a 4-day inpatient treatment followed by a 28-day outpatient detoxification programme	No control group (population data) Dietary survey done at admission	Total pure alcohol per day (mL), mean ± SD: 341 ± 353 149 participants (96 White, 53 Black) completed the 4-day inpatient programme. Among them, 19 patients (16 White, 3 Black) completed the 28-day outpatient programme	Blood Plasma concentration of carotene (colorimetry); serum retinol and α-tocopherol (HPLC)	**Carotene (µg/dL)** At baseline: 94 After 4-day abstinence: 145 (comparable to "non-alcoholic population") After 33-day abstinence: 190 (within normal range) **Retinol (µg/dL) and α-tocopherol (µg/10 mL)** At baseline: within normal range After 4-day abstinence: no change After 33-day abstinence: no change [Levels were estimated from figures]
Girre et al. (1990) France	25 participants (20 men, 5 women; mean age, 40 years) entering a 14-day inpatient detoxification programme Controls: 25 healthy hospital staff members (mean age, 39 years) who consumed alcohol occasionally (weekly consumption < 100 g)	Sex and age No patients with cirrhosis; no dietary supplements	Alcohol consumption: mean, 253 g per day for a duration (mean ± SD) of 11.8 ± 8.1 years 14 days of inpatient abstinence	Blood Plasma and whole-blood selenium (atomic absorption spectrometry), GPx (enzyme assay), α-tocopherol (HPLC)	Values are mean ± SD **Plasma selenium (µmol/L)** Baseline: 0.92 ± 0.20 Abstinence: 0.88 ± 0.21 Controls: 1.15 ± 0.20 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs baseline}} < 0.001$ **Whole-body selenium (µmol/L)** Baseline: 0.90 ± 0.26 Abstinence: 1.09 ± 0.31 Controls: 1.33 ± 0.29 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs baseline}} < 0.025$ $P_{\text{abstinence vs controls}} < 0.001$ **Plasma GPx (U/L)** Baseline: 292.1 ± 102.2 Abstinence: 281.2 ± 63.9 Controls: 328.3 ± 51.4 $P_{\text{baseline vs controls}} < 0.05$ $P_{\text{abstinence vs baseline}}$: NS **Erythrocyte GPx (U/g Hb)** Baseline: 28.2 ± 4.7 Abstinence: 31.09 ± 5.62 Controls: 34.1 ± 3.1

Table 3.6 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
Girre et al. (1990) (cont.)					$P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs baseline}} < 0.001$ **Plasma α-tocopherol (mg/L)** Baseline: 10.36 ± 3.06 Abstinence: 10.86 ± 3.29 Controls: 14.63 ± 4.21 $P_{\text{baseline vs controls}} < 0.005$ $P_{\text{abstinence vs baseline}}$: NS **Erythrocyte α-tocopherol (mg/L)** Baseline: 2.29 ± 0.69 Abstinence: 2.38 ± 0.69 Controls: 3.25 ± 0.95 $P_{\text{baseline vs controls}} < 0.001$ $P_{\text{abstinence vs baseline}}$: NS
Lettéron et al. (1993) France	89 HD participants (45 men, 44 women; average age, 49 years) admitted to a hospital for alcohol withdrawal and assessment of liver disease Control group 1: 42 healthy laboratory or clinical staff members (22 men, 20 women; average age, 40 years) Control group 2: 52 patients with liver disease other than ALD (29 men, 23 women; average age, 49 years)	Liver conditions in HD participants and controls: HD participants: 10 with hepatic steatosis, 6 with ARH, 29 with cirrhosis without ARH, 34 with hepatic cirrhosis and ARH, and 4 with alcohol-related cirrhosis and hepatocellular carcinoma Control group 2: 2 with liver transplants, 6 with acute hepatitis, 11 with chronic hepatitis, 17 with viral cirrhosis, 1 with liver polyadenomatosis, 5 with non-alcohol-related hepatocellular carcinoma, 2 with liver metastases, 5 with sclerosing cholangitis, 1 with biliary cirrhosis, and 2 with extrahepatic bile duct obstruction	Varying times after admission; 9 HD participants studied serially	Exhaled breath Ethane (gas-liquid chromatography)	**Exhaled ethane (pmol/L)** HD: ~800 Control group 1: ~200 Control group 2: ~200 $P < 0.0001$ [Levels were estimated from figures] Positively correlated with previous daily alcohol consumption ($r = 0.275$; $P = 0.009$) Inversely correlated with duration of abstinence ($r = 0.235$; $P = 0.026$) Serially studied HD participants had variable rates of normalization

Table 3.6 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
Peng et al. (2005) Taiwan (China)	29 participants with AUD (28 men, 1 woman; average age, 43.81 years) admitted for detoxification Controls: 19 healthy participants (11 men, 8 women; average age, 30.33 years)	Participants with AUD: HBsAg-negative and no liver cirrhosis	Alcohol consumption (mean ± SD): 271.2 ± 123.6 g per day for a duration (mean ± SD) of 22.2 ± 10.5 years 14 days of abstinence	Blood (serum) MDA (thiobarbituric acid assay); CAT, GPx, and GR (enzyme assay); SOD (ELISA)	Values are mean ± SD **MDA (μM)** 24 hours after admission AUD: 6.50 ± 2.14 Controls: 3.96 ± 0.86 $P < 0.05$ Normalized after 7 days and 14 days of abstinence **SOD (ng/mL)** 24 hours after admission AUD: 0.10 ± 0.05 Controls: 0.80 ± 0.53 $P < 0.05$ Remained low during up to 14 days of abstinence $P < 0.05$ **GPx (nmol/min/mL)** 24 hours after admission AUD: 156.46 ± 73.79 Controls: 205.08 ± 44.71 $P < 0.05$ Remained low after 7 days and 14 days of abstinence $P < 0.05$ **CAT (U/mL)** 24 hours after admission: no significant difference between AUD and controls Lower after 14 days of abstinence vs controls and baseline $P < 0.05$ **GR (nmol/min/mL)** 24 hours after admission: no significant difference between AUD and controls Higher after 7 days of abstinence vs controls and baseline $P < 0.05$ Lower after 14 days of abstinence (similar to controls)

Table 3.6 (continued)

Reference Study location	Setting, study design, number, age, sex, ethnicity, and health status of exposed and control groups	Matching factors Covariates controlled for	Alcohol exposure and duration of abstinence	Sampling matrix End-point biomarker (test used)	Results
Varella Morandi Junqueira-Franco et al. (2006) Brazil	10 participants (men) with alcohol-related pellagra (average age, 35 years) entering a 27-day inpatient detoxification programme Exclusion criteria: not previously treated with vitamins	Not reported	Alcohol consumption: > 90 g of ethanol per day Patients entered inpatient treatment (abstinence) for 27 days and were given 100 mg of niacin per day	Urine and blood NMN (HPLC); vitamin E (HPLC); GPx (enzyme assay); MDA (thiobarbituric acid and quantified by HPLC); protein carbonyl levels (colorimetric assay)	Values are mean ± SD **NMN (mg/24 hours)** Baseline: 0.82 ± 1.21 Treatment: 9.97 ± 9.89 $P < 0.05$ **MDA (µmol/L)** Baseline: 1.19 ± 0.40 Treatment: 0.89 ± 0.27 $P < 0.05$ **Protein carbonyls (nmol/mg protein)** Baseline: 2.22 ± 0.36 Treatment: 1.84 ± 0.40 $P < 0.05$ **Plasma vitamin E (µmol/L)** Baseline: 12.66 ± 4.23 Treatment: 20.49 ± 7.74 $P < 0.05$ **GPx (U/g Hb)** Baseline: 21.70 ± 7.46 Treatment: 29.54 ± 8.72 $P < 0.05$

ALD, alcohol-related liver disease; ARH, alcohol-related hepatitis; AUD, alcohol use disorder; CAT, catalase; ELISA, enzyme-linked immunosorbent assay; GPx, glutathione peroxidase; GR, glutathione reductase; Hb, haemoglobin; HBsAg, hepatitis B surface antigen; HD, heavy drinking; HPLC, high-performance liquid chromatography; MDA, malondialdehyde; NMN, N^1-methylnicotinamide; NS, not significant; SD, standard deviation; SOD, superoxide dismutase.

with AUD (28 men and 1 woman) and 19 healthy controls. None of them were reported to carry the *ALDH2*2* allele. Concentrations of malondialdehyde were 2-fold higher and levels of GPx and superoxide dismutase were lower among the participants with AUD at entry compared with the controls. Levels of catalase and glutathione reductase were not affected. With 14 days of abstinence, malondialdehyde levels decreased to control levels, whereas superoxide dismutase and GPx levels remained low.

In a study in Brazil (Varella Morandi Junqueira-Franco et al., 2006), participants with AUD who had pellagra were treated with niacin for 27 days (niacin is a non-traditional antioxidant that affects macrophage function; Montserrat-de la Paz et al., 2017). There was an expected large (10-fold) increase in the urinary concentration of the niacin metabolite N^1-methylnicotinamide, an increase of ~40% in erythrocyte GPx activity, an increase of ~60% in vitamin E levels (both GPx activity and vitamin E level were below reference values before treatment), a decrease of ~20% in plasma carbonyl groups (a marker of protein oxidation), and a decrease of ~25% in plasma malondialdehyde levels. [This study did not have any comparison with samples from a control group, and any positive effects resulting from abstinence remain unclear because the participants experienced it together with administration of daily doses of niacin and, no doubt, an improved diet.]

Kang et al. (2022) examined the effect of 3 weeks of abstinence on hepatic markers of oxidative stress in a mouse model of ARH. The model entailed a ramp-up in alcohol administration over 5 days, 10 days on the Lieber–DeCarli liquid diet, and bolus gavage of ethanol on day 11, followed by a return to an alcohol-free diet. [The number of animals studied was small, but this was a unique assessment of the time course of alcohol withdrawal.] The ethanol treatment protocol caused an increase in serum and liver triglycerides, serum malondialdehyde levels, and CYP2E1 mRNA levels, and a 2–3-fold increase in the level of alanine transaminase (ALT), which resolved by 1–2 weeks after the return to an alcohol-free diet. Expression of several genes that encode enzymes involved in antioxidant responses was decreased with alcohol feeding and increased again during abstinence: Nfe2/2, which encodes the NRF2 protein; Sod1, which encodes superoxide dismutase; and GSHPx, which encodes GPx. The mRNA level of Hmox1, which encodes haem oxygenase, increased with alcohol feeding and decreased during abstinence. mRNA levels reflective of macrophage numbers (Adgre1 and Cd68 mRNA) and inflammatory cytokine levels (Tnf for TNF and Ccl2 for CCL2) increased with alcohol feeding and then decreased to normal over 3 weeks. [The relevance of these data to humans without overt liver disease is unknown.]

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4. SUMMARY

4.1 Alcoholic beverages

4.1.1 Definitions and types of products

Alcoholic beverages are liquids containing ethanol that are intended for consumption. The main categories of alcoholic beverages are beer, wine, and spirits. The ethanol content varies by type of beverage and by country, typically ranging from 5–15% volume for fermented beverages to 50% volume or higher for distilled beverages. Various types of homemade, artisanal, or locally produced alcoholic beverages are relatively more common in low- and middle-income countries. Alcohol also may be consumed in other products, including surrogate alcohol, which is non-beverage alcohol that is not intended for human consumption.

In addition to ethanol and acetaldehyde, alcoholic beverages may contain several toxicants that are derived from the raw materials used or that may arise during the production process, some of which are carcinogenic. Because alcohol provides more energy per gram than carbohydrates or proteins and almost as much as pure fat, alcoholic beverages can contribute significantly to total energy intake.

4.1.2 Surveillance, prevalence, trends, and determinants of consumption

(a) Monitoring of consumption at the population level

Alcohol consumption is monitored in many countries, and globally by the World Health Organization (WHO). The most important indicator of the level of alcohol consumption in a country is adult alcohol per capita (individuals aged ≥ 15 years) consumption (APC), which is defined as the total (sum of recorded and unrecorded alcohol) amount of alcohol consumed per person over a calendar year in litres of pure alcohol, adjusted for tourist consumption, and which is indicative of the overall level of alcohol consumption in a population. This indicator is supplemented by information from surveys, which enable assessment of the level of alcohol consumption among different groups, such as adult APC per drinker, or by sex or age. In addition, surveys usually contain information about abstention (lifetime abstention and former alcohol consumption) and about occasions of heavy alcohol consumption.

(b) Prevalence of and trends in alcohol consumption by WHO region

Overall, the global level of alcohol consumption as measured in adult APC was stable over the past two decades, although there are different

regional and country-level trends. Often, changes in the level of alcohol consumption are associated with the implementation of alcohol control policies. One example is the decrease in alcohol consumption in the WHO European Region, which was largely a result of tax increases and other measures in the eastern part of the region.

Globally in 2019, 44% of adults had consumed alcohol in the previous year. In the WHO European Region, the WHO Region of the Americas, and the WHO Western Pacific Region, more than 60% of adults consume alcohol. In contrast, in the WHO African Region and the WHO South-East Asia Region, less than 30% of adults consume alcohol, and in the WHO Eastern Mediterranean Region, 4% of adults consume alcohol. Adult APC has the same rank order as the prevalence of current alcohol consumption.

The adult APC per drinker shows less regional variation. However, the APC per drinker is relatively high in the WHO African Region (17 L) and the WHO South-East Asia Region (14 L); this is much higher than the APC in the population for the WHO African Region (4.5 L) and the WHO South-East Asia Region (3.8 L). The reason is the high prevalence of abstention in these two regions.

(c) Determinants of consumption

The prevalence and patterns of alcohol consumption vary across subgroups defined by sex, age, race, ethnicity, culture, religion, tobacco smoking, and socioeconomic status.

Globally, men are more likely than women to consume alcohol, to consume greater quantities of alcohol, and to have an alcohol use disorder. The difference between sexes in alcohol consumption is less pronounced in higher-income countries than in low- and middle-income countries and has narrowed over time. In addition to other factors, gendered roles and norms contribute to sex differences in alcohol consumption. There is currently an evidence gap about alcohol consumption among gender-diverse populations.

Among individuals who consume alcohol, consumption often begins in adolescence or in the early 20s, with a peak in the early to mid-20s, followed by a decrease and plateau in middle age and a further decrease at older ages. In the past two decades, younger cohorts in several high-income countries have shown a decrease in alcohol consumption relative to older cohorts.

In addition to sex and age, there is substantial variation in alcohol consumption across and within races, ethnicities, and cultures. These concepts are largely social constructs and are dynamic, which precludes a straightforward summary of their influence on alcohol consumption behaviours. In general, higher socioeconomic status is associated with a higher prevalence of and more frequent alcohol consumption, although individuals who are comparatively disadvantaged are at a greater risk of alcohol-related harm per litre of alcohol consumed. Consumption of counterfeit and surrogate alcohol also is associated with lower socioeconomic status. Social role transitions such as to full-time work, separation or divorce, and retirement also are associated with an increase in alcohol consumption. Alcohol consumption is associated with tobacco smoking, but the extent to which the two behaviours overlap differs between populations.

(d) Determinants of reduction or cessation

Several factors may contribute to a reduction or cessation of alcohol consumption among individuals or across a population. Alcohol consumption among adolescents and young adults has decreased, particularly in high-income countries, and there is a tendency for alcohol consumption to decrease at older ages. Health-related reasons for reducing alcohol consumption fall into two broad categories: preserving or improving health, and being ill (the "sick quitter" effect). Individuals who do not smoke may be more

likely to reduce or cease alcohol consumption or abstain than individuals who smoke. Social role transitions such as getting married, entering into a cohabiting relationship, and becoming a parent are associated with a decrease in alcohol consumption. Social networks also play an important role in alcohol consumption behaviours; shared norms about alcohol consumption and abstention and informal social control can influence individuals to reduce their alcohol consumption. Periods of religious significance or fasting have been linked to a temporary reduction in alcohol consumption, which sometimes leads to abstinence. Unfavourable economic conditions have been associated with a shift from heavier to lighter consumption of alcohol at a population level, although during such times certain subpopulations, particularly men, are at risk of increased consumption. Survey data also confirm that alcohol affordability and availability can be factors in the decision to reduce or cease alcohol consumption.

When considering alcohol consumption in relation to all of the above-mentioned factors, it is important to also consider other issues, such as the historical, social, and policy context, globalization and migration, and public health crises such as the COVID-19 pandemic.

4.1.3 Population attributable fraction

Globally in 2020, an estimated 741 300 new cancer cases were attributable to alcohol consumption (4.1% of all new cancer cases and 11.7% of all cases of the seven cancer types associated with alcohol consumption). About three quarters of those cancers occurred among males, resulting in a larger proportion of alcohol-attributable new cancer cases among males (6.1%) than among females (2.0%). The largest proportions of alcohol-attributable cancer cases among males were in eastern Asia (8.6%), central and eastern Europe (7.8%), and parts of sub-Saharan Africa. The population attributable fractions among females were largest in central and eastern Europe, Australia and New Zealand, western Europe, and northern Europe (ranging from 3.0% to 3.4%). Variations in population attributable fractions by sex and region largely reflected variations in alcohol consumption.

Globally in 2020, an estimated 31.6% of all new cases of oesophageal cancer were attributable to alcohol consumption. This proportion was 20.2% for lip and oral cavity cancer, 22.0% for pharyngeal cancer, 17.3% for liver cancer, 15.0% for laryngeal cancer, 8.4% for colorectal cancer, and 4.4% for female breast cancer. Among the seven cancer types associated with alcohol consumption combined, oesophageal cancer contributed the most alcohol-attributable cases globally in 2020 (189 700 cases, accounting for 25.6% of all cancer cases attributable to alcohol consumption), followed by colorectal cancer (156 700 cases; 21.1%), liver cancer (154 700 cases; 20.9%), female breast cancer (98 300 cases; 13.3%), lip and oral cavity cancer (74 900 cases; 10.1%), pharyngeal cancer (39 400 cases; 5.3%), and laryngeal cancer (27 600 cases; 3.7%).

4.2 Associations of cancer risk in humans

4.2.1 Methodological considerations

There is a limited body of research about reduction of alcoholic beverage consumption and risk of alcohol-related cancers, but more research about cessation. There are no randomized controlled trials of reduction or cessation of alcohol consumption and cancer incidence or mortality. The Working Group reviewed and evaluated all informative individual cohort studies and case–control studies and pooled analyses and meta-analyses with available data to assess associations of reduction, duration of cessation, or cessation and continuing consumption with alcohol-related cancer risk. Individual studies included in meta-analyses or pooled

analyses, meta-analyses or pooled analyses with overlapping studies, studies with fewer than 5 cancer cases in the cessation category (overall or within subgroups), and studies of precursor lesions were excluded.

To assess whether cessation of alcohol consumption can reduce alcohol-related cancer risk requires comparing risks for cessation with continuing consumption. However, most studies compared risks for cessation with abstention. Therefore, when necessary, hazard ratios, relative risks, odds ratios, and confidence intervals were recalculated to compare risks for alcohol cessation with continuing consumption (referred to below as "calculated" relative risks).

Potential biases must be carefully considered when evaluating epidemiological studies about reduction or cessation of alcoholic beverage consumption and cancer risk. The amount of alcohol consumed is a risk factor for alcohol-related cancers, and individuals who ceased consumption may not have consumed the same amount of alcohol as individuals who did not cease consumption. Therefore, in observational studies comparing cessation with continuing consumption and cancer risk, the adjustment for or stratification on amount consumed can reduce potential confounding. Another concern is confounding due to smoking cessation, because smoking cessation reverses smoking-related risk of cancers of the upper aerodigestive tract (i.e. oral cavity, pharyngeal, laryngeal, and oesophageal cancers) and could result in the appearance of a lower risk of cancer associated with reduction or cessation of alcohol consumption. Reverse causation could result in the appearance of a higher risk of cancer associated with cessation of alcohol consumption if symptoms of undiagnosed cancer led to alcohol cessation. Reverse causation is a concern in case–control studies if alcohol consumption at the time of diagnosis is assessed, and in cohort studies that did not determine whether to begin follow-up time at least 1 year after the measurement of alcohol consumption. Assessment of risk reduction after long-term alcohol cessation is less prone to bias due to reverse causation; however, few studies assessed associations for duration of cessation and even fewer for long-term cessation. In cohort studies with long follow-up time, it is important to collect repeated measures of alcohol consumption, as well as information about confounders such as tobacco use, to avoid potential bias due to misclassification of exposure over time. In hospital-based case–control studies, some controls, even those with illnesses unrelated to alcohol consumption, may have ceased consuming alcohol due to illness, which could also result in the appearance of a lower risk for cessation. When examining the available epidemiological evidence, the Working Group acknowledged these, and other, methodological considerations.

4.2.2 Associations of reduction, duration of cessation, or cessation of alcoholic beverage consumption with cancer risk

(a) Oral cancer

Eight informative studies were available to assess associations of duration of cessation and cessation of alcohol consumption with risk of oral cancer. These studies included two cohort studies (one in India and one in China), a large international pooled analysis of 12 case–control studies (n = 8 hospital-based and n = 4 population-based), and five individual hospital-based case–control studies in Brazil, China, Taiwan (China) (n = 2), and Uruguay. No informative studies of reduction of alcohol consumption were identified.

The international pooled analysis was the only study with data about duration of cessation. After adjustment for the number of alcoholic drinks per day, pack-years of tobacco smoking, and other risk factors compared with continuing consumption, long-term alcohol cessation (≥ 20 years) was associated with a 55% lower

relative risk of oral cancer (relative risk [RR], 0.45; 95% confidence interval [CI], 0.26–0.78). The risks for long-term alcohol cessation were substantially lower in the 1–2 drinks per day stratum (RR, 0.59; 95% CI, 0.22–1.57) and in the ≥ 3 drinks per day stratum (RR, 0.43; 95% CI, 0.28–0.67) than in the < 1 drink per day stratum (RR, 0.98; 95% CI, 0.54–1.77). The risk for long-term alcohol cessation compared with continuing consumption was lower in the current-smoking stratum (RR, 0.40; 95% CI, 0.18–0.88) than in all the strata of duration of smoking cessation. In a subset of participants with detailed alcohol consumption and smoking history data, after meta-analytic adjustment for smoking status and duration of smoking cessation, the calculated relative risks were 0.75 (95% CI, 0.57–0.98) for 5–19 years of cessation and 0.75 (95% CI, 0.43–1.33) for long-term cessation.

The risk of oral cancer associated with alcohol cessation compared with continuing consumption was assessed in all eight studies. In the international pooled analysis, the relative risk for cessation was 0.60 (95% CI, 0.43–0.84). Relative risks ranged from 0.46 to 0.88 among one cohort study and four individual case–control studies. In the other cohort study of cancer incidence, the relative risk for cessation was 1.28, and in the fifth case–control study, the relative risk for cessation was 2.55.

(b) Pharyngeal cancer

Nine informative studies were available to assess associations of duration of cessation and cessation of alcohol consumption with risk of pharyngeal cancer (i.e. seven studies of oropharyngeal and/or hypopharyngeal cancer and two studies of nasopharyngeal cancer). These studies included two cohort studies (one in India and one in China), a large international pooled analysis of 13 case–control studies ($n = 9$ hospital-based and $n = 4$ population-based), and one friend- or family-based, one population-based, and four hospital-based case–control studies in China, Japan, Taiwan (China) ($n = 2$), Thailand, and Uruguay. No informative studies of reduction of alcohol consumption were identified.

Duration of alcohol cessation and risk of pharyngeal cancer were assessed in two studies. In the international pooled analysis, compared with continuing consumption, the relative risk for long-term alcohol cessation (≥ 20 years) and risk of oropharyngeal and hypopharyngeal cancer (combined) was 0.74 (95% CI, 0.50–1.09). There were no consistent patterns of association for long-term alcohol cessation across strata of higher amounts of consumption, or across strata of smoking status and duration of smoking cessation. In a subset of participants with detailed alcohol consumption and smoking history data, after meta-analytic adjustment for smoking status and duration of smoking cessation, the calculated relative risk for long-term cessation was 0.95 (95% CI, 0.56–1.61). In an individual case–control study of hypopharyngeal cancer, the relative risk for ≥ 10 years of cessation compared with continuing consumption was 2.13 (95% CI, 0.30–15.12).

In the two cohort studies, compared with continuing consumption, the calculated relative risk of hypopharyngeal cancer associated with alcohol cessation was 0.92 (95% CI, 0.42–2.04) and the calculated relative risk of pharyngeal cancer associated with alcohol cessation was 0.88 (95% CI, 0.41–1.88). In the pooled analysis and four individual case–control studies of oropharyngeal and/or hypopharyngeal cancer, the calculated relative risks for cessation compared with continuing consumption ranged from 0.65 to 1.68. In the two individual case–control studies of nasopharyngeal cancer, which is less strongly associated with alcohol consumption, the calculated relative risks for cessation were 1.21 (95% CI, 0.90–1.64) and 1.37 (95% CI, 0.92–2.06).

(c) Laryngeal cancer

Seven informative studies were available to assess associations of reduction, duration of cessation, and/or cessation of alcohol consumption with risk of laryngeal cancer. These studies included three cohort studies in China, India, and the Republic of Korea, a large international pooled analysis of nine case–control studies (*n* = 7 hospital-based and *n* = 2 population-based), and three hospital-based case–control studies in Taiwan (China) (*n* = 2) and Uruguay.

Reduction of alcohol consumption and risk of laryngeal cancer were assessed in a large cohort study with a median follow-up time of 6.4 years. Compared with stable moderate consumption (15–29.9 g of ethanol per day) or stable heavy consumption (≥ 30 g of ethanol per day), reduction in consumption to a lower level over 2 years was not consistently associated with a reduced risk of laryngeal cancer. In the international pooled analysis, compared with continuing consumption, long-term alcohol cessation (≥ 20 years) was associated with a 31% lower relative risk of laryngeal cancer (RR, 0.69; 95% CI, 0.52–0.91); the reduction in risk was greater across strata of higher amounts of consumption (RR, 0.99; 95% CI, 0.56–1.74 for < 1 drink per day, and RR, 0.28; 95% CI, 0.09–0.86 for ≥ 3 drinks per day). In a subset of participants with detailed alcohol consumption and smoking history data, the relative risk for long-term alcohol cessation in the current-smoking stratum was 0.74 (95% CI, 0.46–1.20), and lower risks were also observed in most strata of duration of smoking cessation. After meta-analytic adjustment for smoking status and duration of smoking cessation, the association for long-term alcohol cessation was weaker (calculated RR, 0.80; 95% CI, 0.56–1.13).

Cessation of alcohol consumption and risk of laryngeal cancer were assessed in all seven studies. In the pooled analysis, two of the cohort studies, and three individual case–control studies, the calculated relative risks for cessation compared with continuing consumption ranged from 0.31 to 0.95. In the large cohort study with a median follow-up time of 6.4 years, across strata of baseline consumption, the relative risks for cessation ranged from 1.10 to 1.65 compared with stable consumption.

(d) Oesophageal cancer

Seventeen informative studies were available to assess associations of reduction, duration of cessation, and/or cessation of alcohol consumption and risk of oesophageal cancer. These studies included five cohort studies, one meta-analysis (*n* = 4 hospital-based case–control studies), and 11 other individual case–control studies (*n* = 3 population-based and *n* = 8 hospital-based) and were conducted primarily in eastern Asia, with some studies in south America, western Europe, and the USA. Although alcohol consumption is an established risk factor for the more commonly occurring squamous cell carcinoma of the oesophagus but not for oesophageal adenocarcinoma, the few studies of both subtypes combined were included in this review when the histological type was not clearly defined.

Reduction of alcohol consumption and risk of oesophageal cancer were assessed in the cohort study with a median follow-up time of 6.4 years. Compared with stable moderate consumption (15–29.9 g of ethanol per day) or stable heavy consumption (≥ 30 g of ethanol per day), reduction in consumption to a lower level over 2 years was associated with a higher risk.

Duration of alcohol cessation and risk of oesophageal cancer were assessed in nine studies (the meta-analysis, a cohort study of mortality, and *n* = 7 individual case–control studies). In the smoking-adjusted meta-analysis of four case–control studies, two of which also adjusted for the amount of alcohol consumed, there was a higher risk for < 5 years of cessation compared with continuing consumption. In contrast, there was a 15% lower relative risk for 5–10 years of cessation (RR, 0.85; 95% CI, 0.79–0.92) and 10–15 years of

cessation (RR, 0.85; 95% CI, 0.79–0.92), and a 65% lower relative risk for ≥ 15 years of cessation (RR, 0.35; 95% CI, 0.31–0.39). A similar pattern was observed in a multicentre case–control study, which also adjusted for cumulative alcohol consumption and cumulative tobacco consumption; the relative risk for ≥ 20 years of cessation was 0.46 (95% CI, 0.19–1.16). In the cohort study of oesophageal cancer mortality, compared with continuing consumption, the relative risk for ≥ 15 years of cessation was 0.46 (95% CI, 0.15–1.37). Among three of the other six individual case–control studies, compared with continuing consumption, the calculated relative risks were lower in the longest-term cessation category (range, 0.30–0.80).

Among the five cohort studies and 10 case–control studies of alcohol cessation and risk of oesophageal cancer, the calculated relative risks for cessation compared with continuing consumption were < 1 (range, 0.23–0.92) in four cohort studies and four case–control studies and ≥ 1 (range, 1.00–5.49) in the other cohort studies and case–control studies.

(e) Combined cancers of the upper aerodigestive tract

Seven informative studies were available to assess associations of reduction, duration of cessation, and/or cessation of alcohol consumption and risk of combined cancers of the head and neck or of all upper aerodigestive tract cancers combined (i.e. head and neck and oesophageal cancers). These studies included four cohort studies in China, Europe ($n = 2$), and the Republic of Korea, a large international pooled analysis of 13 case–control studies ($n = 9$ hospital-based and $n = 4$ population-based), and two individual hospital-based case–control studies in Japan and Taiwan (China).

Two cohort studies assessed reduction and risk. In the cohort study with a median follow-up time of 6.4 years, compared with stable moderate consumption (15–29.9 g of ethanol per day) or stable heavy consumption (≥ 30 g of ethanol per day), reduction in consumption to a lower level over 2 years was not consistently associated with a lower risk of oral and pharyngeal cancer combined. In a cohort study in Denmark with a follow-up time of up to 21 years, the relative risk of all upper aerodigestive tract cancers associated with reducing consumption by ≥ 7 drinks per week compared with stable consumption (change of −0.9 to +0.9 drinks per week) was 0.5 (95% CI, 0.1–2.5).

Duration of cessation and risk were assessed in three studies. In the international pooled analysis, compared with continuing consumption, long-term alcohol cessation (≥ 20 years) was associated with a 40% lower relative risk of oral cavity, pharyngeal, and laryngeal cancer combined (RR, 0.60; 95% CI, 0.40–0.89). In that analysis, the relative risks for long-term cessation were 0.45 (95% CI, 0.25–0.81) in the hospital-based studies and 0.89 (95% CI, 0.54–1.45) in the population-based studies. In a subset of participants with detailed alcohol consumption and smoking history data, the reduction in risk for long-term cessation was greater in the current-smoking stratum (RR, 0.53; 95% CI, 0.32–0.88) than in the strata of duration of smoking cessation. After meta-analytic adjustment for smoking status and duration of smoking cessation, there was a 26% lower relative risk of head and neck cancer (calculated RR, 0.74; 95% CI, 0.56–0.98). In one individual case–control study, ≥ 10 years of cessation was associated with a lower risk of head and neck cancer (RR, 0.46; 95% CI, 0.27–0.79), but these results were not adjusted for detailed smoking history. In contrast, there were consistently higher risks of head and neck cancer across three categories of increasing duration of cessation (range of calculated RR, 1.42–2.83) in another case–control study.

Associations for cessation of alcohol consumption were assessed in six studies. Compared with continuing consumption, alcohol cessation was associated with a lower risk of head and neck

cancer in one cohort study (calculated RR, 0.84), in the pooled analysis (calculated RR, 0.85), and in one individual case–control study (calculated RR, 0.63). Alcohol cessation was associated with a higher risk of head and neck cancer or all upper aerodigestive tract cancers in the other studies.

(f) Colorectal cancer

Seventeen informative studies were available to assess associations of reduction, duration of cessation, and/or cessation of alcohol consumption with risk of colorectal cancer, colon cancer, and/or rectal cancer. These studies included a pooled analysis of three cohort studies, 10 individual cohort studies, and six case–control studies (n = 3 hospital-based and n = 3 population-based), which were conducted in eastern Asia, Europe, and North America.

Reduction of alcohol consumption and risk of colorectal cancer were assessed in three individual cohort studies and the pooled analysis. In one study, a reduction of 12 g of ethanol per day was associated with a 14% lower relative risk of colorectal cancer (RR, 0.86; 95% CI, 0.78–0.95). In another cohort study with a median follow-up time of 14.2 years, the relative risk associated with a one-category reduction in consumption was 0.97 (95% CI, 0.86–1.08). Reduction of alcohol consumption was not associated with a lower risk of colorectal cancer in the two other studies.

Duration of cessation and risk were assessed in two studies. In a hospital-based case–control study, compared with continuing consumption, duration of cessation was inversely associated with risk (RR, 1.37; 95% CI, 0.91–2.06 for < 66 months; RR, 0.66; 95% CI, 0.42–1.06 for 66–180 months, and RR, 0.52; 95% CI, 0.31–0.86 for > 180 months of cessation); results were similar for colon cancer and rectal cancer. In a cohort study of cancer mortality, there were no clear patterns of reduced risk with longer duration of cessation for colon cancer or rectal cancer.

Alcohol cessation and risk were assessed in 15 studies. Among the eight individual cohort studies and one pooled analysis, the calculated relative risks for alcohol cessation compared with continuing consumption and colorectal cancer ranged from 0.54 to 1.34 and were < 1 in four of five studies of colon cancer and in two of four studies of rectal cancer. Among the six case–control studies of alcohol cessation compared with continuing consumption, the calculated relative risks were < 1 in three of four studies of colorectal cancer (range, 0.27–0.99), two of six studies of colon cancer (0.33 and 0.64), and three of six studies of rectal cancer (range, 0.23–0.93).

(g) Liver cancer

Twelve informative studies were available to assess associations of reduction, duration of cessation, and/or cessation of alcohol consumption with risk of liver cancer. These studies included nine cohort studies and three hospital-based case–control studies. Most of the studies were conducted in Japan (n = 7), and other studies were conducted in China (n = 1), Italy (n = 2), the Republic of Korea (n = 1), and Spain (n = 1). Four studies included only populations with underlying liver disease, either specifically related to alcohol (n = 1) or not specifically related to alcohol (n = 3).

In the only study of reduction of alcohol consumption, compared with stable moderate consumption (15–29.9 g of ethanol per day) or stable heavy consumption (≥ 30 g of ethanol per day), reduction in consumption to a lower level over 2 years was not associated with a reduced risk of liver cancer. In the four general population studies that assessed duration of cessation and risk of liver cancer, relative risks were > 1 (range, 3.0–8.03) for the shortest durations of cessation, which ranged from < 5 years to ≤ 10 years, and remained near to or greater than 1 (range, 0.98–8.6) for the longest durations, which ranged from > 5 years to ≥ 16 years.

Among the 12 studies of alcohol cessation and risk of liver cancer, the relative risk was 0.80 (95% CI, 0.53–1.19) for the study limited

to individuals with alcohol-related liver disease. In all other studies, which included individuals without alcohol-related liver disease, the calculated relative risks for cessation were near to or greater than 1 (range, 0.99–6.00).

(h) Female breast cancer

Twenty-one informative studies were available to assess associations of reduction or cessation of alcohol consumption with risk of breast cancer. The 11 cohort studies included data from 7 countries over a period from 1959 to 2018, and the 10 case–control studies ($n = 5$ hospital-based, $n = 3$ population-based, and $n = 2$ mixed hospital-based and population-based) included data from 13 countries over a period from 1957 to 2013. No informative studies were available to assess duration of cessation compared with continuing consumption and risk of breast cancer.

Reduction of alcohol consumption and risk of breast cancer were assessed in four cohort studies. In the study with the longest follow-up time (median, 14.2 years), alcohol reduction was associated with a lower risk of breast cancer. However, no consistent patterns of association for alcohol reduction were observed in three other cohort studies, in which the follow-up time ranged from 6.4 years to 10.8 years.

The Working Group used meta-analytic techniques to assess the association of alcohol cessation compared with continuing consumption and risk of breast cancer; the summary relative risks were 0.89 (95% CI, 0.75–1.05) for 10 case–control studies, 0.96 (95% CI, 0.89–1.04) for six cohort studies of cancer incidence (the cohort study of cancer mortality was not included), and 0.95 (95% CI, 0.88–1.01) for all studies combined. In analyses stratified on hormone receptor status, the calculated hazard ratios for cessation were 0.90 (95% CI, 0.77–1.04) for estrogen and progesterone receptor-positive breast cancer and 1.18 (95% CI, 0.88–1.58) for estrogen and progesterone receptor-negative breast cancer in one cohort study among postmenopausal women. In a population-based case–control study, the calculated relative risks were 0.85 (95% CI, 0.58–1.23) for estrogen receptor-positive breast cancer and 1.00 (95% CI: 0.44–2.28) for estrogen receptor-negative breast cancer.

(i) Gene-by-environment interactions

The joint associations of alcohol cessation and polymorphisms in the *ADH1B*, *ADH1C*, or *ALDH2* genes with cancer risk were assessed in three studies – one study each for oral cavity and pharyngeal cancer, oesophageal cancer, and breast cancer. In all three studies there were methodological limitations, and there were too few cases in the alcohol cessation category within each genotype strata (range, 0–11) to provide reliable estimates of association. Therefore, the Working Group did not evaluate the modifying effects of genetic variability on the association between alcohol cessation and cancer risk.

4.3 Mechanistic data

4.3.1 Absorption, distribution, and metabolism of ethanol and alcohol-related mechanisms of carcinogenesis

Upon alcohol consumption, ethanol is oxidized to acetaldehyde by alcohol dehydrogenase (ADH) and then to acetate by aldehyde dehydrogenase (ALDH). The local oxidation of ethanol to acetaldehyde is catalysed mostly by various ADH enzymes present in the microbiome. In contrast, the capacity of the oral or intestinal microbiome and mucosa to eliminate acetaldehyde is limited because of reduced ALDH activity, which results in accumulation of acetaldehyde at genotoxic concentrations in body fluids of the oral cavity, stomach, and colon (i.e. saliva, gastric juices, and colonic contents). This exposure to acetaldehyde is markedly enhanced by two other major risk factors for alcohol-related cancers: (i) genetic polymorphism of human ADH and ALDH2 enzymes, and (ii) tobacco smoking. Among

individuals with reduced ALDH2 activity (individuals who are heterozygous for *ALDH2*2*), ethanol metabolism results in double the concentration of salivary acetaldehyde as long as ethanol stays in the body. Chronic smoking combined with chronic heavy alcohol consumption induces changes in the oral microbiome, which may contribute to the observed synergistic effect of alcohol consumption and tobacco smoking on oral cancer risk. Also, after an ethanol challenge, salivary acetaldehyde concentrations during concomitant smoking among individuals who are currently smoking are 7 times those among individuals who do not smoke.

Genotoxicity is the best-described mechanism by which alcohol consumption causes cancer. Exposure to high concentrations of acetaldehyde, a potent genotoxic metabolite of ethanol, is a major determinant of alcohol-related carcinogenesis, particularly in the upper aerodigestive tract. Acetaldehyde – even at low concentrations – reacts with DNA, resulting in DNA damage, including chromosomal aberrations and DNA adducts, which may in turn lead to mutations. DNA damage may also result from other genotoxic pathways deriving from the ethanol-inducible CYP2E1 enzyme producing various reactive oxygen species. These reactive oxygen species can lead to lipid peroxidation, oxidative stress, and perturbation of DNA repair. Other mechanisms have been proposed, some of which may apply to the breast or liver, where local acetaldehyde concentrations are unlikely to be high. Alcohol consumption alters the composition of the intestinal microbiome and leads to epithelial barrier dysfunction and increased intestinal permeability, resulting in increased translocation of microbiota and microbial products across the mucosa. Microbial translocation and endotoxaemia trigger systemic inflammation, with the potential to increase cancer risk through oxidative stress, changes in cytokine levels, and impaired immune responses. Alcohol consumption also decreases folate absorption and inhibits enzymes that are critical for one-carbon metabolism and DNA methylation. Among women, alcohol consumption increases circulating concentrations of estradiol, testosterone, and other sex hormones and decreases the concentration of sex hormone-binding globulin; these changes may play a role in alcohol-related breast carcinogenesis.

4.3.2 Cancer-related mechanistic changes after cessation of alcohol consumption

(a) Genotoxicity

The effects of cessation of alcohol consumption on DNA damage have been evaluated mostly by measuring and quantifying chromosomal aberrations and micronuclei in peripheral blood cells. The samples analysed may have a different exposure, cell turnover, and efficiency of DNA damage repair mechanisms compared with the cells in the target organs relevant to alcohol carcinogenesis. Seven studies compared the frequency of chromosomal aberrations among groups of individuals with alcohol use disorder, individuals with alcohol use disorder who abstained from alcohol consumption for periods from a few months to several years, and controls without alcohol use disorder. Four of these studies found that frequencies were lower among individuals with alcohol use disorder who abstained than among individuals with alcohol use disorder, and that these were comparable to those among controls. Two other studies did not find a significant difference between individuals with alcohol use disorder and abstainers but had limitations. In the first study, the frequencies of chromosomal aberrations were measured only at a very early stage (1 week) of a detoxification programme and baseline levels were not provided; the second study included only a small number of participants. One study, in which most individuals smoked, observed an increase in the frequencies of chromosomal aberrations at later time points (after 1 year) of the alcohol

abstinence programme, which resulted from an increase in smoking intensity.

Among the studies considered, four investigated the effects of duration of abstinence – short-term (1–12 months) and long-term (more than several years) – on DNA damage and found no correlation. Another study quantified the levels of the acetaldehyde-derived DNA adduct N^2-ethylidenedeoxyguanosine in oral cells, before and after specific increasing doses of alcohol, and observed a return to baseline levels within 24 hours upon alcohol cessation. In one study, mitochondrial DNA damage measured in peripheral blood samples of healthy volunteers exposed to a known dose of alcohol was induced by alcohol consumption but did not persist after 4 weeks.

(b) Epigenetics

Regular alcohol consumption induces epigenetic modifications. One study examined the effect of alcohol cessation on the methylation of *ALDH2* and methylenetetrahydrofolate reductase (*MTHFR*), two genes thought to be important for alcohol metabolism and carcinogenesis. The significantly higher methylation in these genes observed at baseline was still evident after 3 months of rehabilitation; however, some individuals in the group were not abstinent. The study also showed that abstinence was associated with significantly lower global DNA methylation of long interspersed element 1 (*LINE-1*), a surrogate marker for overall DNA methylation. One study, which was an epigenome-wide methylation analysis to examine the effects of 2 weeks of acute withdrawal compared with controls, reported changes in methylation patterns both at individual CpG sites and in differentially methylated regions. The small study size (< 200 participants) may affect the robustness of the findings.

(c) Endocrine system

Among women, alcohol consumption increases the concentrations of estradiol, testosterone, and other sex hormones. All the available studies among humans were performed among men. Two studies among individuals entering a treatment programme for alcohol use disorder examined the effects of 1–2 weeks of alcohol withdrawal. One reported that serum testosterone levels increased compared with baseline, whereas the other reported that they did not. The latter study also reported no change in estradiol levels but found a significant decrease in levels of sex hormone-binding globulin. Two studies examined changes in insulin or insulin resistance among individuals with moderate alcohol consumption who stopped consuming alcohol for 4 weeks or 6 weeks. The results were not concordant; one study showed improvement through a decrease in peripheral insulin resistance, and another showed that hepatic insulin resistance increased. The three available studies on the thyroid hormone system were methodologically too different to assess replication of effects. However, there is some evidence that alcohol withdrawal leads to decreased levels of triiodothyronine, thyroxine, and related thyroid hormones among individuals with alcohol use disorder who stop consuming alcohol, but these hormones may be sensitive to the acute effects of physical dependence. A single study showed that 6 months of cessation led to increased vitamin D levels, no significant increase in parathyroid hormone concentrations, and no change in insulin-like growth factor 1 (IGF-1) concentrations. The relevance of cortisol to cancer risk is unclear, but one study using a time-course analysis of concentrations in hair showed that cortisol concentrations decrease rapidly after alcohol cessation.

(d) Microbiome

Chronic heavy alcohol consumption induces changes in the composition and abundance of both the oral and the intestinal microbiome.

Two studies assessed the variations in the composition of the oral microbiome of individuals with alcohol use disorder after a period of alcohol abstinence. This approach is based on evidence showing that the acetaldehyde production capacity of the oral microbiome is elevated among individuals with heavy alcohol consumption. Therefore, these studies relied on an indirect measurement of the microbiome activity by assessing the ability of the bacteria in saliva samples to metabolize ethanol ex vivo. One study found that the capacity of the oral microbiome to produce acetaldehyde from ethanol decreased after 3 weeks of abstinence, whereas no difference was observed in the other study, which considered 18 days of abstinence.

The effects of alcohol abstinence on the intestinal microbiota were analysed in six studies; four resulted from the analysis of samples from the same cohort of individuals with alcohol use disorder entering a treatment programme. All of these studies focused on the analysis of samples collected over a period of abstinence of only a few weeks. These studies indicate variations in the abundance and composition in the virome and in the fungal microbiome upon abstinence.

These studies have major limitations, mostly related to small sample sizes, resulting in the inability to consider proper adjustments when multiple comparisons are performed. In addition, the effects of abstaining from alcohol consumption cannot easily be disentangled from the effects that may result from inpatient treatments and changes in lifestyle and diet during the abstinence periods considered.

(e) Inflammatory and immune responses

Chronic heavy alcohol consumption increases intestinal permeability, and hence microbial translocation across the gastrointestinal tract, and creates an inflammatory state characterized by increased levels of circulating cytokines and altered levels of certain immune cells. These changes are more pronounced among individuals with alcohol-related hepatitis and cirrhosis.

Cessation of alcohol consumption for 3–4 weeks resulted in reduced intestinal permeability, towards normal. Heavy alcohol consumption causes intestinal mucosal cell injury; the increased levels of intestinal fatty acid binding protein remained elevated after 6 weeks of abstinence, and levels of regenerating islet-derived protein 3α and trefoil factor 3 also remained elevated for at least 12 months of abstinence among individuals with alcohol-related hepatitis. Microbial translocation results in increased circulating bacterial components such as lipopolysaccharides, lipopolysaccharide binding protein, and peptidoglycan recognition proteins. After cessation of alcohol consumption, levels of lipopolysaccharide binding protein remained elevated for 3–6 weeks, and levels of peptidoglycan recognition proteins and lipopolysaccharide remained elevated for 2–3 weeks.

With long-term heavy alcohol consumption, the translocation of microbial products activates the immune system. Elevated levels of soluble CD14, a marker of macrophage activation, decrease over 10 days to 6 weeks of abstinence.

Levels of cytokines are elevated among individuals with alcohol use disorder and through varying durations of abstinence, including the pro-inflammatory cytokines interleukin 6, tumour necrosis factor α, and interleukin 1β and the anti-inflammatory cytokines interleukin 10 and interleukin 4. The source of the cytokines is not known, but the liver is thought to be a major contributor, and one study implicated adipose tissue as well. An important confounder of these

studies is the presence, known or unknown, of alcohol-related liver disease.

Circulating immune cells are altered by heavy alcohol consumption. In one study, reduction in the levels of $CD14^{+}/CD16^{-}$ monocytes and their responsiveness to lipopolysaccharide was more pronounced among individuals who were heterozygous for *ALDH2*2* and had the *ADH1B*2* allele, implicating acetaldehyde in this effect; the changes improved after 4 weeks of abstinence. In another study, a shift in the characteristics of circulating monocytes was observed within 2 weeks of abstinence, suggesting a less inflammatory and more anti-inflammatory state. Circulating levels of mucosal-associated invariant T cells ($CD8^{+}$ T cells enriched in the intestinal mucosa and liver) were markedly decreased among individuals with alcohol-related hepatitis and somewhat decreased among individuals with heavy alcohol consumption. Over 6–12 months of abstinence, these levels increased among both groups but did not return to normal.

(f) Oxidative stress

Ethanol oxidation is associated with the generation of reactive oxygen species, resulting in lipid peroxidation, which is reflected by elevated levels of malondialdehyde and increased exhalation of ethane. Individuals with chronic heavy alcohol consumption show evidence of oxidative stress and impaired ability to detoxify the reactive oxygen species. The time course of resolution has been assessed in five studies among individuals with alcohol use disorder entering a treatment programme. In two studies, the elevated malondialdehyde levels decreased to normal levels over 2–4 weeks of abstinence. In another study among individuals with alcohol use disorder, most of whom had advanced liver disease, increased exhalation of ethane appeared to decrease over a period of several weeks of abstinence, although not returning to normal among all participants. Other studies examined the plasma levels of enzymes and vitamins that detoxify the products of oxidative stress (superoxide dismutase, the selenoprotein glutathione peroxidase, glutathione reductase, catalase, retinol, carotene, and vitamin E). Vitamin E levels were low at entry into treatment in two studies; the levels increased over 27 days in a study in which niacin supplementation was given to the participants, but they did not increase in a second study of 14 days' duration without niacin treatment. Three studies examined serum glutathione peroxidase activity, which was low at the beginning of abstinence and increased only among the participants in the study with niacin supplementation. It was not possible to distinguish the effects of niacin, abstinence, improved diet, or simply a longer period of abstinence in these studies. In three different studies, levels of carotene, selenium, and superoxide dismutase were low at the beginning of abstinence and only carotene levels increased during abstinence.

5. EVALUATIONS

5.1 Associations of reduction or cessation of alcoholic beverage consumption with cancer risk in humans

5.1.1 Oral cancer

There is *sufficient evidence* that reduction or cessation of alcoholic beverage consumption reduces the risk of oral cancer.

Rationale. In the most influential study, the large international pooled analysis, long-term cessation was associated with a lower risk of oral cancer compared with continuing consumption even after adjustment for the amount of alcohol consumed, pack-years of smoking, and other risk factors. There was consistent evidence of a reduced risk for long-term cessation in strata of higher amounts of consumption. Furthermore, consistent with smoking modifying the carcinogenic effect of alcohol, the risk for long-term alcohol cessation was lower in the current-smoking stratum than in the other smoking strata. The reduced risk for long-term cessation overall was weaker but remained after adjustment for duration of smoking cessation. Moreover, in most other studies reviewed, alcohol cessation was associated with a lower risk compared with continuing consumption.

5.1.2 Pharyngeal cancer

There is *inadequate evidence* that reduction or cessation of alcoholic beverage consumption reduces the risk of pharyngeal cancer.

Rationale. In the most influential study, the large international pooled analysis, long-term cessation was not associated with a lower risk of oropharyngeal and hypopharyngeal cancer combined after adjusting for alcohol consumption, smoking status, duration of smoking cessation, and other risk factors. These findings contrast with that for oral cancer, for which the risk was lower. Results from studies of cessation and risk of pharyngeal cancer were inconsistent within and between pharynx subsites.

5.1.3 Laryngeal cancer

There is *limited evidence* that reduction or cessation of alcoholic beverage consumption reduces the risk of laryngeal cancer.

Rationale. Long-term alcohol cessation was associated with a lower risk of laryngeal cancer in the large international pooled analysis; however, this association was not as strong as that observed for oral cancer. There was a lower risk of laryngeal cancer associated with alcohol cessation compared with continuing consumption in the three individual hospital-based case–control studies and in two cohort studies, but not with alcohol reduction or cessation in

another large cohort study. Furthermore, given the strength of the association between smoking and risk of laryngeal cancer, bias due to smoking cessation could not be ruled out with reasonable confidence.

5.1.4 Oesophageal cancer

There is *sufficient evidence* that reduction or cessation of alcoholic beverage consumption reduces the risk of oesophageal cancer.

Rationale. In the only study of reduction of alcohol consumption, the median follow-up time was only 6.4 years, which may not be adequate for observing reduced cancer risks. Among six of nine studies of duration of cessation, including an influential meta-analysis, long-term cessation was associated with a substantially lower risk of oesophageal cancer. The large number of studies supporting an inverse association helps to rule out chance. Similarly, consistent results across study designs help to rule out selection bias and information bias. Furthermore, confounding due to smoking and the amount of alcohol consumed also could be ruled out with reasonable confidence.

5.1.5 Colorectal cancer

There is *limited evidence* that reduction or cessation of alcoholic beverage consumption reduces the risk of colorectal cancer.

Rationale. In the most influential study, a large cohort study in multiple European countries with two prospective measurements of alcohol consumption, reduction of alcohol consumption was associated with a lower risk of colorectal cancer. Other cohort studies of reduction of alcohol consumption, one of which used retrospective assessment of alcohol consumption and one that had assessment only 2 years apart, did not show reduced risks. In one case–control study, the relative risks of colorectal cancer decreased with longer duration of cessation, whereas in a cohort study of colon cancer and rectal cancer mortality, there was no consistent evidence of reduced risk. Overall, there are inconsistencies among studies of alcohol reduction and cessation, and few studies of duration of cessation.

5.1.6 Liver cancer

There is *inadequate evidence* that reduction or cessation of alcoholic beverage consumption reduces the risk of liver cancer.

Rationale. In the only study of reduction of alcohol consumption, no evidence of a lower risk of liver cancer was observed. In a cohort study of individuals with alcohol-related liver disease, compared with continuing consumption, cessation was associated with a lower risk of liver cancer. In contrast, relative risks for duration of cessation and cessation were near to or greater than 1 in all other studies comprising participants without alcohol-related liver disease. For most of the studies, bias due to reverse causation or competing risk could not be ruled out.

5.1.7 Breast cancer

There is *limited evidence* that reduction or cessation of alcoholic beverage consumption reduces the risk of breast cancer.

Rationale. The body of evidence suggests that cessation of alcohol consumption may be associated with a lower risk of breast cancer compared with continuing consumption, and a lower risk was observed in the Working Group meta-analysis. This association may be limited to hormone receptor-positive tumours. Given the consistent, but modest and imprecise, inverse associations between alcohol cessation and risk of breast cancer observed, and the few studies with analyses by hormone receptor status, chance and bias could not be ruled out with reasonable confidence.

5.2 Mechanistic data

There is *sufficient evidence* from mechanistic studies that alcohol cessation reduces alcohol-related carcinogenesis.

This evaluation is based on evidence for the three mechanisms listed here.

5.2.1 Local exposure to genotoxic concentrations of acetaldehyde after ethanol ingestion

There is *strong evidence* that cessation of alcoholic beverage consumption results in an immediate reduction or elimination of the ingested ethanol and its conversion to acetaldehyde in the oral cavity, and subsequent local exposure to this carcinogenic metabolite in the upper aerodigestive tract and colon. It also reduces or eliminates the systemic distribution of ethanol and later conversion to acetaldehyde throughout the body; this is particularly relevant in the oral cavity among individuals with reduced ALDH2 enzyme activity.

5.2.2 DNA damage

There is *strong evidence* that cessation of alcoholic beverage consumption results in a decrease in acetaldehyde-induced DNA damage – although this has only been validated in blood and in the context of chronic heavy consumption; a reduction or elimination of acetaldehyde–DNA adduct formation in the oral cavity has also been observed.

5.2.3 Intestinal permeability and microbial translocation

There is *strong evidence* that cessation of alcoholic beverage consumption reverses changes in intestinal permeability and microbial translocation in the intestine. However, these data were limited to studies among individuals with chronic heavy consumption, and the role of these changes in alcohol-induced carcinogenesis remains unclear.

Worldwide, in 2020, an estimated 741 300 new cancer cases were attributable to alcohol consumption. This represents 4.1% of all new cancer cases, 6.1% among men and 2.0% among women.

A Working Group of 15 independent international experts, convened by the International Agency for Research on Cancer (IARC) from February to May 2023, evaluated the body of literature assessing the effectiveness of reduction or cessation of alcoholic beverage consumption in reducing risk of alcohol-related cancers.

The Working Group reviewed and summarized the available epidemiological evidence and provided evidence-based evaluations of the effectiveness of reduction or cessation of alcohol consumption in reducing risk of cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver, and female breast. The Working Group also identified and evaluated the mechanisms of alcohol-related carcinogenesis that may be reversed upon cessation.

To complement the evaluations, this publication presents background information on the alcohol-related cancer burden worldwide, the population attributable fraction of alcohol-related cancers, and determinants of cessation.

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