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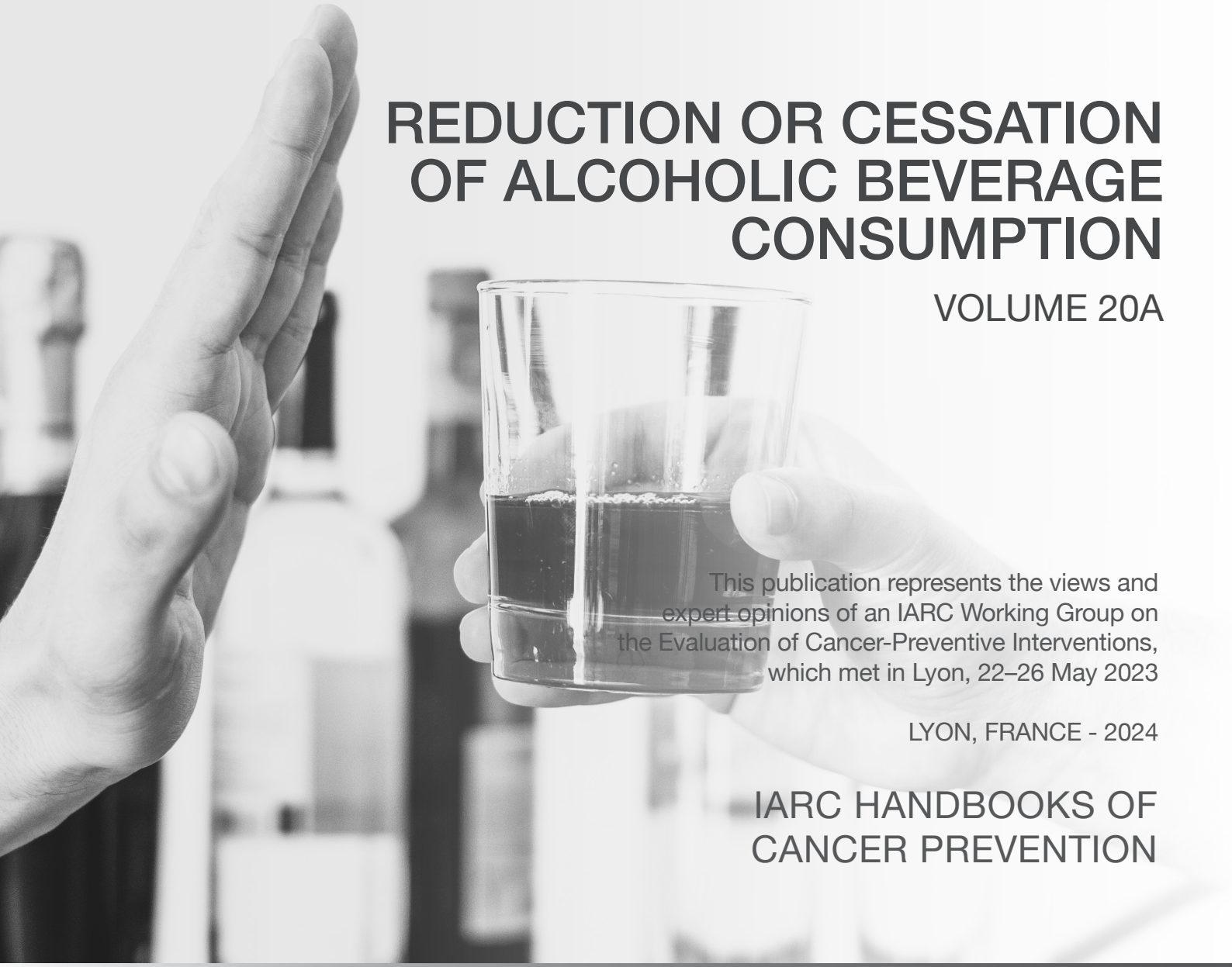

REDUCTION OR CESSATION OF ALCOHOLIC BEVERAGE CONSUMPTION

VOLUME 20A

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

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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 post-menopausal 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 Never Current Past Never Current Past	Cases 61 52 21 Deaths 43 34 14	 1.0 (ref) 1.49 (1.01–2.21) 1.90 (1.13–3.18) P_{trend} = 0.006 1.0 (ref) 1.76 (1.08–2.86) 2.04 (1.08–3.86) P_{trend} = 0.008	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
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 Abstain Ex-regular Occasional Current regular	 23 12 39 66	 1.00 (0.65–1.53) 1.06 (0.60–1.87) 1.33 (0.96–1.86) 1.89 (1.46–2.45)	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

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 Never Former Current	 34 91 210	 1.0 (ref) 3.0 (1.9–4.7) 3.4 (2.3–5.2)	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

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 Non [drinking] Former Current Duration of cessation ≥ 10 yr < 10 yr	 27 56 44 20 36	 1.0 (ref) 2.73 (1.73–4.31) 1.07 (0.69–1.68) 1.0 (ref) 4.61 (2.08–10.22)		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
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 Never/ occasional Former regular Current regular	 195 61 253	 1.0 (ref) 0.77 (0.51–1.17) 1.29 (0.97–1.73)	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

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 Never Former Current	 23 9 20	 1.0 (ref) 1.2 (0.6–2.6) 1.3 (0.7–2.4)	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	Pharynx (excluding nasopharynx)	Drinking status Abstain Ex-regular Occasional Current regular	 10 9 15 33	 1.00 (0.53–1.89) 1.81 (0.93–3.50) 1.18 (0.69–2.00) 2.05 (1.42–2.96)	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

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 Non Ex Current	 28 22 98	 1.0 (ref) 7.4 (2.8–20.3) 6.4 (3.3–13.9)	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
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 Never Former Current	 33 116 292	 1.0 (ref) 3.9 (2.5–6.1) 4.5 (3.0–6.8)	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

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 Never/occasional Former regular Current regular Never/occasional Former regular Current regular	Oropharynx 29 20 69 Hypopharynx 4 19 66	 1.0 (ref) 2.83 (1.39–5.76) 4.23 (2.38–7.52) 1.0 (ref) 14.02 (4.38–44.85) 21.55 (7.36–63.15)	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
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 Never Former Current	 295 106 280	 1.0 (ref) 1.40 (0.95–2.06) 1.02 (0.78–1.34) P_{trend} = 0.98	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

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 None/none None/mild None/moderate None/heavy Mild/none Mild/mild Mild/moderate Mild/heavy Moderate/none Moderate/mild Moderate/moderate Moderate/heavy Heavy/none Heavy/mild Heavy/moderate Heavy/heavy	1642 total	 1.0 (ref) 1.01 (0.79–1.29) 1.10 (0.76–1.60) 1.31 (0.88–1.95) 1.10 (0.86–1.41) 1.0 (ref) 0.73 (0.55–0.95) 1.10 (0.80–1.53) 1.65 (1.12–2.41) 1.11 (0.85–1.45) 1.0 (ref) 0.93 (0.69–1.24) 1.51 (0.95–2.41) 2.10 (1.55–2.85) 0.75 (0.54–1.03) 1.0 (ref)	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

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 Non Ex Current	 56 12 60	 1.0 (ref) 3.0 (0.2–3.4) 4.1 (2.5–8.8)	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
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 Never/occasional Former regular Current regular	 35 11 49	 1.0 (ref) 0.86 (0.40–1.85) 1.84 (1.09–3.11)	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

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 Never/occasional Former Daily	 16 5 57	 1.0 (ref) 1.55 (0.58–4.14) 2.73 (1.55–4.81) P_{trend} = 0.0002	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
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 Non-drinking Ex-drinking Drinking Duration of cessation Rare/none < 5 yr 5–15 yr ≥ 15 yr	Deaths 18 12 166 14 4 3 1	 1.0 (ref) 2.10 (0.99–4.42) 2.28 (1.40–3.72) 1.0 (ref) 3.75 (1.16–12.1) 2.76 (0.76–10.0) 1.03 (0.13–8.12)	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

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 Never Former Current Drinking status Never Former Current	All 65 24 69 OSCC 32 12 45	 1.0 (ref) 1.2 (0.7–1.9) 1.6 (1.1–2.3) 1 (ref) 1.2 (0.6–2.4) 2.0 (1.3–3.2)	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
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 Abstain Ex-regular Occasional Current regular Abstain Ex-regular Occasional Current regular	Men 243 152 558 655 Women 340 8 377 15	 1.00 (0.88–1.14) 1.23 (1.05–1.44) 1.05 (0.96–1.15) 1.80 (1.66–1.96) 1.00 (0.89–1.13) 1.17 (0.57–2.41) 0.99 (0.88–1.12) 1.23 (0.73–2.06)	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

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)	Oesophagus (ICD-10 code C15; histology not specified)	Alcohol intake in 2009/2011 None/none None/mild None/moderate None/heavy Mild/none Mild/mild Mild/moderate Mild/heavy Moderate/none Moderate/mild Moderate/moderate Moderate/heavy Heavy/none Heavy/mild Heavy/moderate Heavy/heavy	3009 total	 1.0 (ref) 0.92 (0.76–1.12) 1.07 (0.81–1.41) 1.01 (0.79–1.29) 1.13 (0.92–1.38) 1.0 (ref) 0.80 (0.66–0.98) 0.74 (0.59–0.92) 2.38 (1.79–3.17) 1.38 (1.13–1.70) 1.0 (ref) 0.73 (0.61–0.88) 3.66 (2.77–4.83) 2.23 (1.74–2.86) 1.03 (0.83–1.29) 1.0 (ref)	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

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 Current Never Duration of cessation > 0–2 yr 2–5 yr 5–10 yr 10–15 yr > 15 yr	 1.0 (ref) 0.37 (0.35–0.39) 2.50 (2.23–2.80) 1.10 (1.03–1.18) 0.85 (0.79–0.92) 0.85 (0.79–0.92) 0.35 (0.31–0.39)	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)

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 Almost never Former Current Duration of cessation Almost never 1–9 yr ≥ 10 yr	 31 31 284 NR	 1.0 (ref) 4.4 (2.5–7.9) 4.4 (2.9–6.7) 1.0 (ref) 5.1 (2.6–10.0) 3.5 (1.4–9.1)	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
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 Never/rare Ex Current Light Moderate Heavy	 5 13 24 86 106	 0.17 (0.05–0.56) 9.44 (3.29–27.08) 1.0 (ref) 8.22 (4.42–15.28) 13.74 (7.18–26.29)	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

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 ≥ –7 –6.9 to –1 –0.9 to +0.9 +1 to +6.9 +7 to +14 > +14	 2 22 14 20 12 35	 0.5 (0.1–2.5) 1.2 (0.5–2.7) 1.0 (ref) 1.3 (0.6–2.7) 1.4 (0.6–3.3) 2.5 (1.1–5.3) P_{trend} < 0.0001	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
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), hypopharynx (ICD-O-2 codes C13–C14), oesophagus (ICD-O-2 code C15), and larynx (ICD-O-2 code C32)	Lifetime intake Never Former Current (g/day) > 0.1–≤ 6 > 6–≤ 18 > 18–≤ 30 > 30–≤ 60 > 60–≤ 96 > 96	Men 1 36 23 44 46 70 30 32	 0.51 (0.07–3.80) 4.14 (2.38–7.19) 1.0 (ref) 0.78 (0.47–1.31) 1.10 (0.65–1.86) 1.65 (1.00–2.71) 2.20 (1.23–3.95) 4.63 (2.52–8.48) P_{trend} < 0.0001	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

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 None/none None/mild None/moderate None/heavy Mild/none Mild/mild Mild/moderate Mild/heavy Moderate/none Moderate/mild Moderate/moderate Moderate/heavy Heavy/none Heavy/mild Heavy/moderate Heavy/heavy	3884 total	1.0 (ref) 0.94 (0.80–1.11) 1.00 (0.74–1.35) 1.13 (0.83–1.55) 1.20 (1.04–1.38) 1.0 (ref) 0.98 (0.81–1.19) 1.11 (0.87–1.42) 1.21 (0.90–1.63) 1.15 (0.96–1.38) 1.0 (ref) 0.96 (0.77–1.20) 1.47 (1.06–2.05) 1.22 (0.92–1.61) 0.93 (0.73–1.18) 1.0 (ref)	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

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 Never Ex Current < 1 drink/day 1–2 drinks/day ≥ 3 drinks/day	 30 6 98 49 20	 1.0 (ref) 0.84 (0.34–2.08) 1.16 (0.75–1.79) 1.59 (0.95–2.64) 1.71 (0.92–3.19)	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
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 Abstain Casual Initiate Quit Drinking	 55 10 23 7 16	 1.0 (ref) 1.14 (0.58–2.22) 1.50 (0.89–2.53) 1.10 (0.50–2.41) 1.80 (1.00–3.23)	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

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 Never Ex Current	 11 10 85	 1.0 (ref) 1.6 (0.7–3.8) 1.7 (0.9–3.3)	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
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 Drinking status/ duration of cessation Rare/none Drinking Ex-drinking < 5 yr 5–15 yr ≥ 15 yr Rectum Drinking status/duration of cessation Rare/none Drinking Ex-drinking	Deaths Men 36 148 19 6 4 3 25 120 15	 1.0 (ref) 1.16 (0.80–1.68) 1.57 (0.90–2.75) 2.36 (0.97–5.74) 1.29 (0.45–3.70) 1.30 (0.39–4.32) 1.0 (ref) 1.33 (0.86–2.06) 1.89 (0.99–3.60)	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

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 5–15 yr ≥ 15 yr Drinking status Colon Non Ex Current Rectum Non Ex Current Colon Non Ex Current	6 2 2 Incidence Men 24 19 177 30 14 106 Women 149 6 43	3.46 (1.37–8.70) 0.85 (0.19–3.67) 1.17 (0.27–5.06) 1.0 (ref) 2.01 (1.09–3.68) 1.97 (1.28–3.03) 1.0 (ref) 1.25 (0.66–2.38) 1.01 (0.67–1.52) 1.0 (ref) 1.56 (0.68–3.60) 1.03 (0.72–1.45)		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
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)	Drinking status Never Former Lifetime infrequent Current Light Moderate Heavier	Deaths All 229 152 162 163 102 42	 1.0 (ref) 1.25 (0.97–1.60) 1.06 (0.86–1.32) 0.86 (0.67–1.10) 1.04 (0.78–1.39) 1.01 (0.70–1.47)	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

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 Colorectum None/none Low/low High/low Low/high High/high Current amount (g/day)/past status Colon 0 < 10 10–19 ≥ 20 Past Rectum 0 < 10 10–19 ≥ 20 Past	NHS/ NHSII/ HPFS 532 1544 44 478 26 NHS/ HPFS 237 430 204 180 88 67 134 63 52 23	 1.0 (ref) 1.11 (1.00–1.23) 1.39 (1.01–1.92) 1.32 (1.14–1.53) 1.39 (0.91–2.13) 1.0 (ref) 0.97 (0.82–1.14) 1.04 (0.85–1.26) 1.27 (1.03–1.56) 1.02 (0.79–1.32) P_{trend} = 0.003 1.0 (ref) 1.04 (0.77–1.40) 1.07 (0.75–1.55) 1.26 (0.85–1.87) 0.93 (0.56–1.54) P_{trend} = 0.20	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-inflammatory 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

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 None/none None/mild None/moderate None/heavy Mild/none Mild/mild Mild/moderate Mild/heavy Moderate/none Moderate/mild Moderate/moderate Moderate/heavy Heavy/none Heavy/mild Heavy/moderate Heavy/heavy	41 102 total	1.0 (ref) 0.96 (0.92–1.01) 1.01 (0.92–1.12) 1.02 (0.92–1.14) 1.08 (1.03–1.12) 1.0 (ref) 0.97 (0.91–1.04) 0.94 (0.86–1.03) 1.09 (0.99–1.20) 1.12 (1.06–1.19) 1.0 (ref) 0.96 (0.89–1.04) 1.31 (1.17–1.46) 1.12 (1.03–1.23) 1.04 (0.96–1.13) 1.0 (ref)	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

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 Decrease 12 g/day	1530	0.86 (0.78–0.95)	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
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	Colo-rectum (ICD-10 codes C18–C20)	Change in alcohol HLI score between Q1 and Q2 1-unit increase (i.e. reduction in alcohol consumption)	839	0.97 (0.86–1.08)	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

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 Colon Non Ex Current Rectum Non Ex Current Colon Non Ex Current	 Men 248 41 173 255 34 174 Women 448 6 15	 1.0 (ref) 2.3 (1.4–3.7) 1.0 (0.8–1.3) 1.0 (ref) 1.1 (0.9–1.4) 0.6 (0.4–1.0) 1.0 (ref) 1.4 (0.4–4.3) 0.7 (0.4–1.3)	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

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 Colorectum Non Former Current Colon Non Former Current Rectum: Non Former Current	 307 26 373 348 total 358 total 	 1.0 (ref) 2.30 (1.27–4.17) 8.61 (6.15–12.05) P_{trend} < 0.0001 1.0 (ref) 2.51 (1.24–5.07) 7.60 (5.13–11.25) 1.0 (ref) 1.71 (0.80–3.65) 7.52 (5.13–11.01)	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
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 Colorectum Never Ex Current Proximal colon Never Ex Current Distal colon Never Ex Current Rectum Never Ex Current	Men 107 103 416 19 22 85 31 26 122 57 55 209	 1.0 (ref) 1.62 (1.11–2.37) 1.05 (0.78–1.40) 1.0 (ref) 2.10 (1.07–4.14) 1.25 (0.73–2.15) 1.0 (ref) 1.36 (0.75–2.47) 1.04 (0.67–1.62) 1.0 (ref) 1.63 (1.02–2.59) 0.99 (0.69–1.42)	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.]

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 Never Current Ex-drinking Duration of cessation ≤ 10 yr 11–15 yr ≥ 16 yr	 25 100 25 12 8 4	 1.0 (ref) 0.98 (0.63–1.52) 2.33 (1.34–4.07) 7.87 (3.89–16.0) 2.08 (0.93–4.67) 0.96 (0.33–2.77)	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
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 Never Ex-drinking Current	 3 10 35	 1.0 (ref) 6.6 (1.8–24.2) 2.7 (0.8–8.9)	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

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 Abstain Ex-regular Occasional Current regular Abstain Ex-regular Occasional Current regular	Men 365 203 477 547 Women 679 13 227 20	 1.00 (0.90–1.12) 1.24 (1.08–1.43) 0.86 (0.78–0.94) 1.07 (0.98–1.17) 1.00 (0.90–1.11) 1.04 (0.59–1.81) 0.78 (0.68–0.90) 0.84 (0.54–1.31)	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
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 None/none None/mild None/moderate None/heavy Mild/none Mild/mild Mild/moderate Mild/heavy	15 333 total	 1.0 (ref) 1.12 (1.04–1.21) 1.26 (1.09–1.46) 1.15 (1.00–1.33) 0.99 (0.92–1.06) 1.0 (ref) 1.03 (0.93–1.14) 0.91 (0.80–1.03)	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

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 Non-drinking Current ≥ 80 g/day Current < 80 g/day Former ≥ 80 g/day Former < 80 g/day Occasional	54 total	 1.0 (ref) 1.15 (0.35–3.78) 1.10 (0.39–3.07) 1.66 (0.69–3.96) 1.46 (0.56–3.79) 0.77 (0.20–2.99)	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
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 Never Past Current < 2.4 drinks/day ≥ 2.4 drinks/day	 16 17 1 3	 1.0 (ref) 0.59 (0.20–1.73) 0.06 (0.01–0.57) 0.17 (0.02–1.42)	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

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 decompensated cirrhosis No adjustment 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 measurements, 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	Histologically confirmed 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 multivitamins confounded associations 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. (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 Ductal Never Former Current Lobular Never Former Current ER+PR+ 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 < 7 to < 7 drinks/week < 7 to 7–13 drinks/week < 7 to ≥ 14 drinks/week 7–13 to < 7 drinks/week 7–13 to 7–13 drinks/week 7–13 to ≥ 14 drinks/week ≥ 14 to < 7 drinks/week ≥ 14 to 7–13 drinks/week ≥ 14 to ≥ 14 drinks/week	 496 90 32 66 99 69 26 40 136	 1.0 (ref) 1.38 (1.10–1.73) 1.16 (0.81–1.67) 0.88 (0.64–1.20) 1.0 (ref) 1.18 (0.87–1.62) 1.23 (0.81–1.88) 1.16 (0.81–1.66) 1.0 (ref)	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
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 Never Former Current < 1 drink/day 1–1.9 drinks/day ≥ 2 drinks/day Duration of cessation ≤ 5 yr 6–14 yr ≥ 15 yr	 65 277 1219 170 110 89 43 139	 1.0 (ref) 1.04 (0.79–1.37) 1.06 (0.82–1.36) 1.10 (0.82–1.48) 1.22 (0.89–1.68) 1.0 (ref) 0.72 (0.49–1.04) 1.03 (0.79–1.36)	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

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 Abstain Ex-regular Occasional Current regular	 1280 19 934 56	 1.00 (0.93–1.08) 1.46 (0.79–1.95) 1.12 (1.05–1.20) 1.16 (0.89–1.52)	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
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 Stable > 12 g/day Stable < 12 g/day Decrease to ≤ 12 g/day Increase to ≥ 12 g/day	685 total	 1.0 (ref) 0.73 (0.49–1.10) 1.27 (0.71–2.29) 0.81 (0.52–1.26)	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

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 None/none None/mild None/moderate None/heavy Mild/none Mild/mild Mild/moderate Mild/heavy Moderate/none Moderate/mild Moderate/moderate Moderate/heavy Heavy/none Heavy/mild Heavy/moderate Heavy/heavy	20 532 total	 1.0 (ref) 0.97 (0.91–1.04) 0.83 (0.63–1.10) 1.07 (0.69–1.67) 0.94 (0.88–0.99) 1.0 (ref) 0.83 (0.66–1.03) 0.69 (0.45–1.06) 0.92 (0.74–1.16) 1.02 (0.87–1.19) 1.0 (ref) 1.15 (0.77–1.71) 0.76 (0.49–1.17) 0.95 (0.68–1.32) 0.64 (0.43–0.97) 1.0 (ref)	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

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 1-unit increase (i.e. reduction in alcohol consumption)	2384	0.94 (0.88–1.00)	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, breast-feeding, 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

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 Never Ex Current ≥ 4 days/week < 4 days/week vs non-cancer controls Never Ex Current ≥ 4 days/week < 4 days/week	 188 71 198 689 188 71 198 689	 1.0 (ref) 1.3 (0.7–2.3) 2.0 (1.3–2.0) 1.5 (1.1–2.1) 1.0 (ref) 1.6 (1.1–2.4) 2.5 (1.9–3.4) 1.9 (1.5–2.4)	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
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 Never Ex Current < 3 drinks/month 3–8 drinks/month 9–25 drinks/month ≥ 26 drinks/month	 393 17 247 201 140 315	 1.0 (ref) 0.59 (P = 0.16) 1.11 (P = 0.45) 1.02 (P = 0.93) 1.09 (P = 0.62) 1.13 (P = 0.35)	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

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			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
				Age > 50 yr				
				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 Never Ex Current tertile 1 Current tertile 2 Current tertile 3	 44 66 (all current n = 103)	 1.0 (ref) 1.61 (0.90–2.90) 0.87 (0.45–1.70) 0.90 (0.44–1.82) 0.99 (0.48–2.01)	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

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 Non Ex Current Non Ex Current Non Ex Current	All 233 11 130 Premenopausal 100 5 85 Postmenopausal 130 6 44	 1.0 (ref) 0.42 (0.19–0.95) 0.86 (0.61–1.22) 1.0 (ref) 1.09 (0.22–5.36) 0.73 (0.41–1.25) 1.0 (ref) 0.43 (0.15–1.26) 1.14 (0.68–1.88)	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
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	Non-drinking Ex Current 1–12 g/week 13–36 g/week > 36 g/week Non-drinking Ex Current 1–12 g/week 13–36 g/week > 36 g/week	Premenopausal 29 5 23 25 31 Postmenopausal 105 8 27 20 28	 1.0 (ref) 1.4 (0.3–6.2) 0.8 (0.4–1.9) 0.9 (0.4–1.9) 1.0 (0.4–2.2) 1.0 (ref) 0.6 (0.2–1.7) 0.9 (0.5–1.6) 0.6 (0.3–1.2) 0.8 (0.4–1.6)	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

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 Never Former Current Light Moderate Heavy	 286 8 73 50 36	 1.0 (ref) 1.17 (0.48–2.83) 0.92 (0.67–1.26) 0.95 (0.65–1.39) 1.33 (0.84–2.11)	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
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 Abstain Ex Current Premenopausal Abstain Ex Current Postmenopausal Abstain Ex Current	All 660 15 334 416 10 246 224 5 88	 1.0 (ref) 1.34 (0.56–3.22) 0.63 (0.52–0.76) 1.0 (ref) 2.44 (0.71–8.39) 0.66 (0.53–0.84) 1.0 (ref) 0.68 (0.17–2.67) 0.55 (0.38–0.78)	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

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 postmenopausal 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

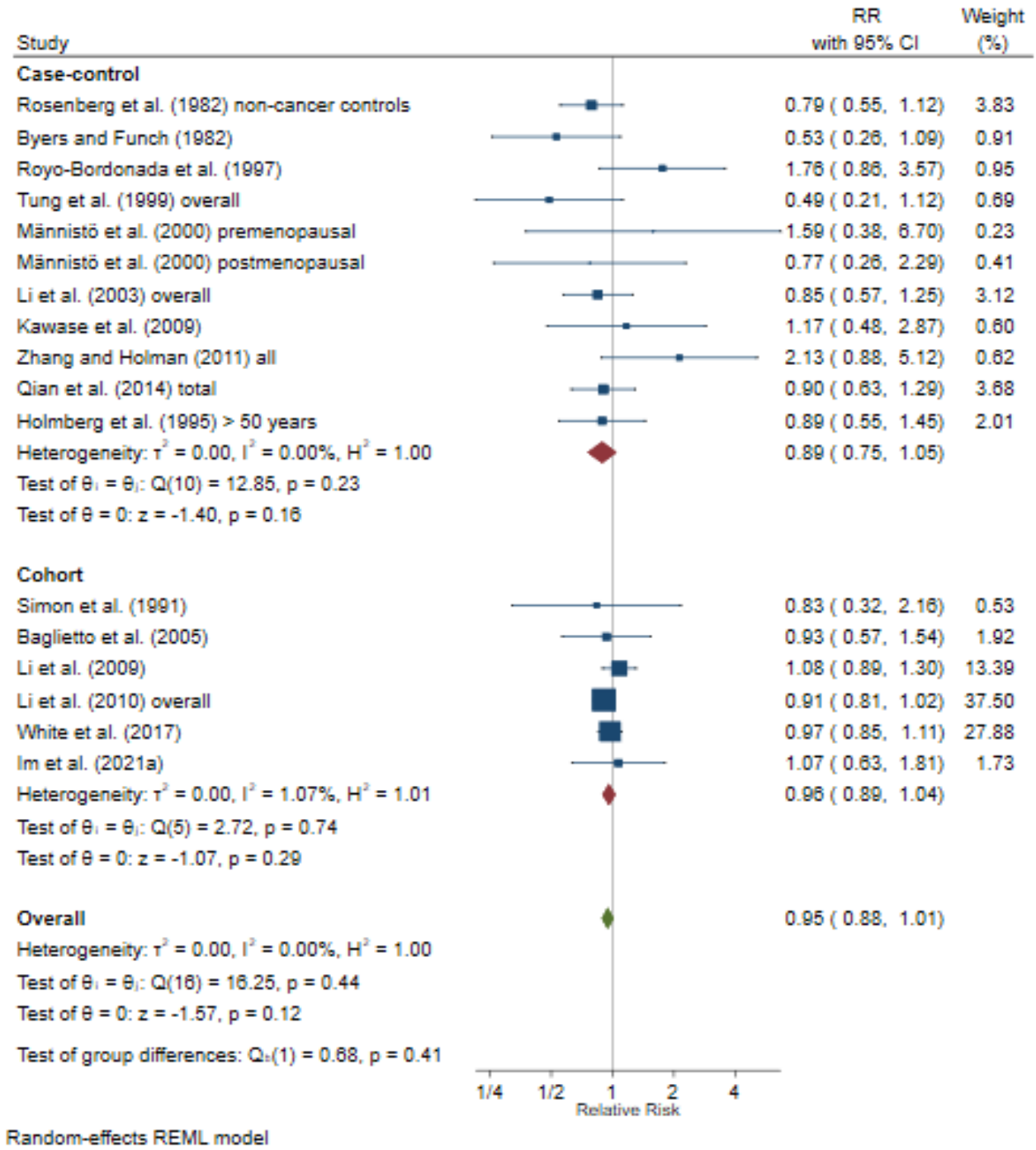
[Using a random-effects model and meta-analytic techniques, the Working Group assessed the association between cessation of alcoholic beverage consumption compared with continuing consumption and risk of breast cancer; the summary relative risks were 0.89 (95% CI, 0.75–1.05) for 10 case–control studies, 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* Never Former Light Moderate Heavy P_{trend} *ALDH2* Never Former Light Moderate Heavy P_{trend}	**2/*2* 1.0 (ref) 1.78 (0.59–5.34) 0.93 (0.61–1.43) 1.06 (0.66–1.72) 1.61 (0.85–3.02) 0.418 **1/*1* 1.0 (ref) 1.03 (0.34–3.16) 0.88 (0.57–1.36) 0.98 (0.61–1.59) 1.21 (0.7–2.11) 0.887	**1/*2* 1.0 (ref) 0.91 (0.16–5.11) 0.85 (0.5–1.45) 0.88 (0.45–1.71) 1.12 (0.52–2.4) 0.832 **1/*2* 1.0 (ref) 1.94 (0.4–9.27) 0.97 (0.57–1.67) 0.85 (0.41–1.76) 1.82 (0.52–6.36) 0.892	**1/*1* 1.0 (ref) [no cases] 0.82 (0.21–3.25) 0.59 (0.09–3.93) 1.7 (0.16–17.69) 0.887 **2/*2* [no cases] – – – – –	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

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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