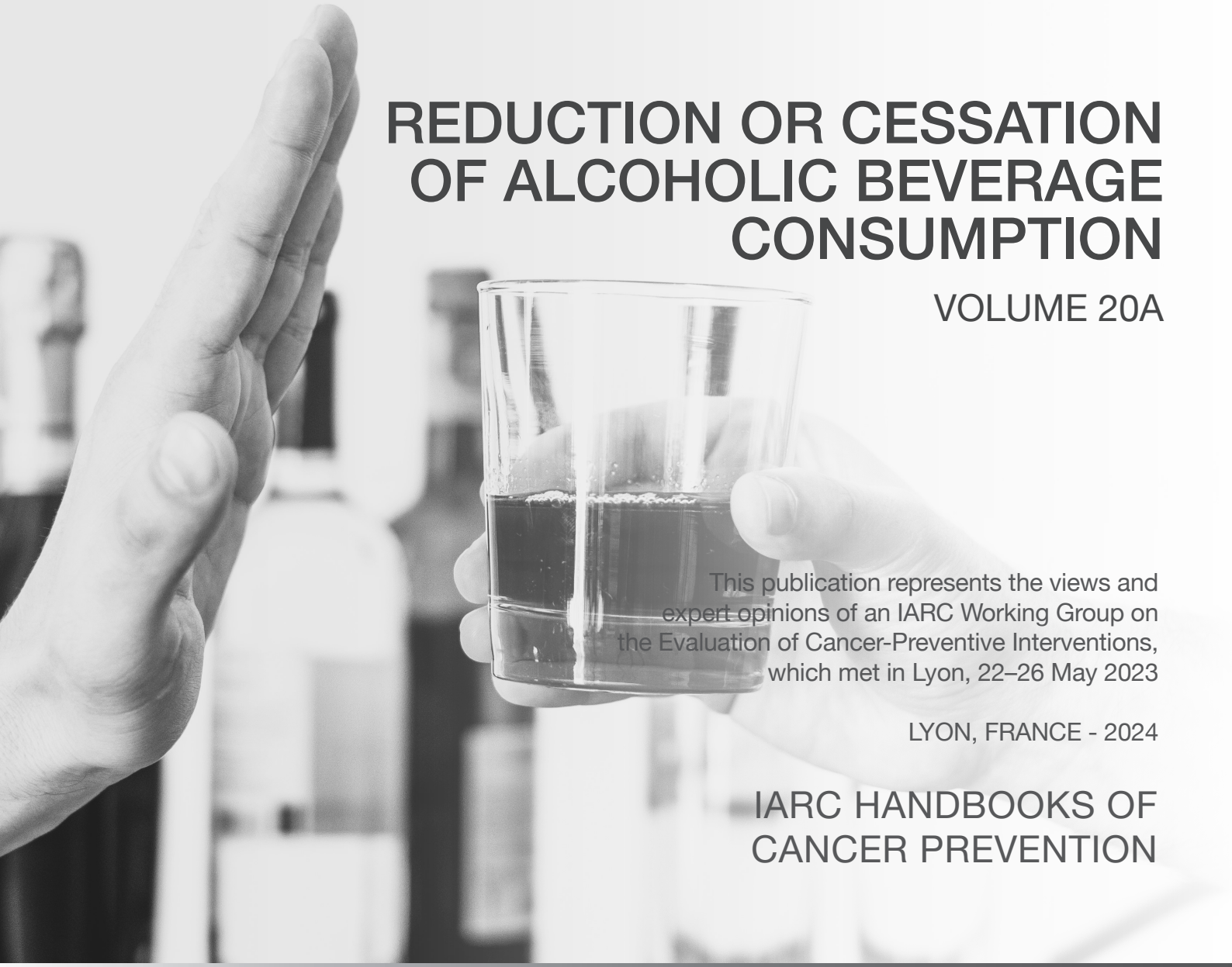
IARC HANDBOOKS



# 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

LYON, FRANCE - 2024

IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

# 4. SUMMARY

## 4.1 Alcoholic beverages

### *4.1.1 Definitions and types of products*

Alcoholic beverages are liquids containing ethanol that are intended for consumption. The main categories of alcoholic beverages are beer, wine, and spirits. The ethanol content varies by type of beverage and by country, typically ranging from 5–15% volume for fermented beverages to 50% volume or higher for distilled beverages. Various types of homemade, artisanal, or locally produced alcoholic beverages are relatively more common in low- and middle-income countries. Alcohol also may be consumed in other products, including surrogate alcohol, which is non-beverage alcohol that is not intended for human consumption.

In addition to ethanol and acetaldehyde, alcoholic beverages may contain several toxicants that are derived from the raw materials used or that may arise during the production process, some of which are carcinogenic. Because alcohol provides more energy per gram than carbohydrates or proteins and almost as much as pure fat, alcoholic beverages can contribute significantly to total energy intake.

### *4.1.2 Surveillance, prevalence, trends, and determinants of consumption*

#### *(a) Monitoring of consumption at the population level*

Alcohol consumption is monitored in many countries, and globally by the World Health Organization (WHO). The most important indicator of the level of alcohol consumption in a country is adult alcohol per capita (individuals aged ≥ 15 years) consumption (APC), which is defined as the total (sum of recorded and unrecorded alcohol) amount of alcohol consumed per person over a calendar year in litres of pure alcohol, adjusted for tourist consumption, and which is indicative of the overall level of alcohol consumption in a population. This indicator is supplemented by information from surveys, which enable assessment of the level of alcohol consumption among different groups, such as adult APC per drinker, or by sex or age. In addition, surveys usually contain information about abstention (lifetime abstention and former alcohol consumption) and about occasions of heavy alcohol consumption.

#### *(b) Prevalence of and trends in alcohol consumption by WHO region*

Overall, the global level of alcohol consumption as measured in adult APC was stable over the past two decades, although there are different

regional and country-level trends. Often, changes in the level of alcohol consumption are associated with the implementation of alcohol control policies. One example is the decrease in alcohol consumption in the WHO European Region, which was largely a result of tax increases and other measures in the eastern part of the region.

Globally in 2019, 44% of adults had consumed alcohol in the previous year. In the WHO European Region, the WHO Region of the Americas, and the WHO Western Pacific Region, more than 60% of adults consume alcohol. In contrast, in the WHO African Region and the WHO South-East Asia Region, less than 30% of adults consume alcohol, and in the WHO Eastern Mediterranean Region, 4% of adults consume alcohol. Adult APC has the same rank order as the prevalence of current alcohol consumption.

The adult APC per drinker shows less regional variation. However, the APC per drinker is relatively high in the WHO African Region (17 L) and the WHO South-East Asia Region (14 L); this is much higher than the APC in the population for the WHO African Region (4.5 L) and the WHO South-East Asia Region (3.8 L). The reason is the high prevalence of abstention in these two regions.

### *(c) Determinants of consumption*

The prevalence and patterns of alcohol consumption vary across subgroups defined by sex, age, race, ethnicity, culture, religion, tobacco smoking, and socioeconomic status.

Globally, men are more likely than women to consume alcohol, to consume greater quantities of alcohol, and to have an alcohol use disorder. The difference between sexes in alcohol consumption is less pronounced in higher-income countries than in low- and middle-income countries and has narrowed over time. In addition to other factors, gendered roles and norms contribute to sex differences in alcohol consumption. There is currently an evidence gap about alcohol consumption among gender-diverse populations.

Among individuals who consume alcohol, consumption often begins in adolescence or in the early 20s, with a peak in the early to mid-20s, followed by a decrease and plateau in middle age and a further decrease at older ages. In the past two decades, younger cohorts in several high-income countries have shown a decrease in alcohol consumption relative to older cohorts.

In addition to sex and age, there is substantial variation in alcohol consumption across and within races, ethnicities, and cultures. These concepts are largely social constructs and are dynamic, which precludes a straightforward summary of their influence on alcohol consumption behaviours. In general, higher socioeconomic status is associated with a higher prevalence of and more frequent alcohol consumption, although individuals who are comparatively disadvantaged are at a greater risk of alcohol-related harm per litre of alcohol consumed. Consumption of counterfeit and surrogate alcohol also is associated with lower socioeconomic status. Social role transitions such as to full-time work, separation or divorce, and retirement also are associated with an increase in alcohol consumption. Alcohol consumption is associated with tobacco smoking, but the extent to which the two behaviours overlap differs between populations.

### *(d) Determinants of reduction or cessation*

Several factors may contribute to a reduction or cessation of alcohol consumption among individuals or across a population. Alcohol consumption among adolescents and young adults has decreased, particularly in high-income countries, and there is a tendency for alcohol consumption to decrease at older ages. Health-related reasons for reducing alcohol consumption fall into two broad categories: preserving or improving health, and being ill (the "sick quitter" effect). Individuals who do not smoke may be more

likely to reduce or cease alcohol consumption or abstain than individuals who smoke. Social role transitions such as getting married, entering into a cohabiting relationship, and becoming a parent are associated with a decrease in alcohol consumption. Social networks also play an important role in alcohol consumption behaviours; shared norms about alcohol consumption and abstention and informal social control can influence individuals to reduce their alcohol consumption. Periods of religious significance or fasting have been linked to a temporary reduction in alcohol consumption, which sometimes leads to abstinence. Unfavourable economic conditions have been associated with a shift from heavier to lighter consumption of alcohol at a population level, although during such times certain subpopulations, particularly men, are at risk of increased consumption. Survey data also confirm that alcohol affordability and availability can be factors in the decision to reduce or cease alcohol consumption.

When considering alcohol consumption in relation to all of the above-mentioned factors, it is important to also consider other issues, such as the historical, social, and policy context, globalization and migration, and public health crises such as the COVID-19 pandemic.

### *4.1.3 Population attributable fraction*

Globally in 2020, an estimated 741 300 new cancer cases were attributable to alcohol consumption (4.1% of all new cancer cases and 11.7% of all cases of the seven cancer types associated with alcohol consumption). About three quarters of those cancers occurred among males, resulting in a larger proportion of alcohol-attributable new cancer cases among males (6.1%) than among females (2.0%). The largest proportions of alcohol-attributable cancer cases among males were in eastern Asia (8.6%), central and eastern Europe (7.8%), and parts of sub-Saharan Africa. The population attributable fractions among females were largest in central and eastern Europe, Australia and New Zealand, western Europe, and northern Europe (ranging from 3.0% to 3.4%). Variations in population attributable fractions by sex and region largely reflected variations in alcohol consumption.

Globally in 2020, an estimated 31.6% of all new cases of oesophageal cancer were attributable to alcohol consumption. This proportion was 20.2% for lip and oral cavity cancer, 22.0% for pharyngeal cancer, 17.3% for liver cancer, 15.0% for laryngeal cancer, 8.4% for colorectal cancer, and 4.4% for female breast cancer. Among the seven cancer types associated with alcohol consumption combined, oesophageal cancer contributed the most alcohol-attributable cases globally in 2020 (189 700 cases, accounting for 25.6% of all cancer cases attributable to alcohol consumption), followed by colorectal cancer (156 700 cases; 21.1%), liver cancer (154 700 cases; 20.9%), female breast cancer (98 300 cases; 13.3%), lip and oral cavity cancer (74 900 cases; 10.1%), pharyngeal cancer (39 400 cases; 5.3%), and laryngeal cancer (27 600 cases; 3.7%).

## 4.2 Associations of cancer risk in humans

### *4.2.1 Methodological considerations*

There is a limited body of research about reduction of alcoholic beverage consumption and risk of alcohol-related cancers, but more research about cessation. There are no randomized controlled trials of reduction or cessation of alcohol consumption and cancer incidence or mortality. The Working Group reviewed and evaluated all informative individual cohort studies and case–control studies and pooled analyses and meta-analyses with available data to assess associations of reduction, duration of cessation, or cessation and continuing consumption with alcohol-related cancer risk. Individual studies included in meta-analyses or pooled

analyses, meta-analyses or pooled analyses with overlapping studies, studies with fewer than 5 cancer cases in the cessation category (overall or within subgroups), and studies of precursor lesions were excluded.

To assess whether cessation of alcohol consumption can reduce alcohol-related cancer risk requires comparing risks for cessation with continuing consumption. However, most studies compared risks for cessation with abstention. Therefore, when necessary, hazard ratios, relative risks, odds ratios, and confidence intervals were recalculated to compare risks for alcohol cessation with continuing consumption (referred to below as "calculated" relative risks).

Potential biases must be carefully considered when evaluating epidemiological studies about reduction or cessation of alcoholic beverage consumption and cancer risk. The amount of alcohol consumed is a risk factor for alcohol-related cancers, and individuals who ceased consumption may not have consumed the same amount of alcohol as individuals who did not cease consumption. Therefore, in observational studies comparing cessation with continuing consumption and cancer risk, the adjustment for or stratification on amount consumed can reduce potential confounding. Another concern is confounding due to smoking cessation, because smoking cessation reverses smoking-related risk of cancers of the upper aerodigestive tract (i.e. oral cavity, pharyngeal, laryngeal, and oesophageal cancers) and could result in the appearance of a lower risk of cancer associated with reduction or cessation of alcohol consumption. Reverse causation could result in the appearance of a higher risk of cancer associated with cessation of alcohol consumption if symptoms of undiagnosed cancer led to alcohol cessation. Reverse causation is a concern in case–control studies if alcohol consumption at the time of diagnosis is assessed, and in cohort studies that did not determine whether to begin follow-up time at least 1 year after the measurement of alcohol consumption. Assessment of risk reduction after long-term alcohol cessation is less prone to bias due to reverse causation; however, few studies assessed associations for duration of cessation and even fewer for long-term cessation. In cohort studies with long follow-up time, it is important to collect repeated measures of alcohol consumption, as well as information about confounders such as tobacco use, to avoid potential bias due to misclassification of exposure over time. In hospital-based case–control studies, some controls, even those with illnesses unrelated to alcohol consumption, may have ceased consuming alcohol due to illness, which could also result in the appearance of a lower risk for cessation. When examining the available epidemiological evidence, the Working Group acknowledged these, and other, methodological considerations.

### *4.2.2 Associations of reduction, duration of cessation, or cessation of alcoholic beverage consumption with cancer risk*

#### *(a) Oral cancer*

Eight informative studies were available to assess associations of duration of cessation and cessation of alcohol consumption with risk of oral cancer. These studies included two cohort studies (one in India and one in China), a large international pooled analysis of 12 case–control studies ($n$ = 8 hospital-based and $n$ = 4 population-based), and five individual hospital-based case–control studies in Brazil, China, Taiwan (China) ($n$ = 2), and Uruguay. No informative studies of reduction of alcohol consumption were identified.

The international pooled analysis was the only study with data about duration of cessation. After adjustment for the number of alcoholic drinks per day, pack-years of tobacco smoking, and other risk factors compared with continuing consumption, long-term alcohol cessation (≥ 20 years) was associated with a 55% lower

relative risk of oral cancer (relative risk [RR], 0.45; 95% confidence interval [CI], 0.26–0.78). The risks for long-term alcohol cessation were substantially lower in the 1–2 drinks per day stratum (RR, 0.59; 95% CI, 0.22–1.57) and in the ≥ 3 drinks per day stratum (RR, 0.43; 95% CI, 0.28–0.67) than in the < 1 drink per day stratum (RR, 0.98; 95% CI, 0.54–1.77). The risk for long-term alcohol cessation compared with continuing consumption was lower in the current-smoking stratum (RR, 0.40; 95% CI, 0.18–0.88) than in all the strata of duration of smoking cessation. In a subset of participants with detailed alcohol consumption and smoking history data, after meta-analytic adjustment for smoking status and duration of smoking cessation, the calculated relative risks were 0.75 (95% CI, 0.57–0.98) for 5–19 years of cessation and 0.75 (95% CI, 0.43–1.33) for long-term cessation.

The risk of oral cancer associated with alcohol cessation compared with continuing consumption was assessed in all eight studies. In the international pooled analysis, the relative risk for cessation was 0.60 (95% CI, 0.43–0.84). Relative risks ranged from 0.46 to 0.88 among one cohort study and four individual case–control studies. In the other cohort study of cancer incidence, the relative risk for cessation was 1.28, and in the fifth case–control study, the relative risk for cessation was 2.55.

### *(b) Pharyngeal cancer*

Nine informative studies were available to assess associations of duration of cessation and cessation of alcohol consumption with risk of pharyngeal cancer (i.e. seven studies of oropharyngeal and/or hypopharyngeal cancer and two studies of nasopharyngeal cancer). These studies included two cohort studies (one in India and one in China), a large international pooled analysis of 13 case–control studies ($n$ = 9 hospital-based and $n$ = 4 population-based), and one friend- or family-based, one population-based, and four hospital-based case–control studies in China, Japan, Taiwan (China) ($n$ = 2), Thailand, and Uruguay. No informative studies of reduction of alcohol consumption were identified.

Duration of alcohol cessation and risk of pharyngeal cancer were assessed in two studies. In the international pooled analysis, compared with continuing consumption, the relative risk for long-term alcohol cessation (≥ 20 years) and risk of oropharyngeal and hypopharyngeal cancer (combined) was 0.74 (95% CI, 0.50–1.09). There were no consistent patterns of association for long-term alcohol cessation across strata of higher amounts of consumption, or across strata of smoking status and duration of smoking cessation. In a subset of participants with detailed alcohol consumption and smoking history data, after meta-analytic adjustment for smoking status and duration of smoking cessation, the calculated relative risk for long-term cessation was 0.95 (95% CI, 0.56–1.61). In an individual case–control study of hypopharyngeal cancer, the relative risk for ≥ 10 years of cessation compared with continuing consumption was 2.13 (95% CI, 0.30–15.12).

In the two cohort studies, compared with continuing consumption, the calculated relative risk of hypopharyngeal cancer associated with alcohol cessation was 0.92 (95% CI, 0.42–2.04) and the calculated relative risk of pharyngeal cancer associated with alcohol cessation was 0.88 (95% CI, 0.41–1.88). In the pooled analysis and four individual case–control studies of oropharyngeal and/or hypopharyngeal cancer, the calculated relative risks for cessation compared with continuing consumption ranged from 0.65 to 1.68. In the two individual case–control studies of nasopharyngeal cancer, which is less strongly associated with alcohol consumption, the calculated relative risks for cessation were 1.21 (95% CI, 0.90–1.64) and 1.37 (95% CI, 0.92–2.06).

*(c) Laryngeal cancer*

Seven informative studies were available to assess associations of reduction, duration of cessation, and/or cessation of alcohol consumption with risk of laryngeal cancer. These studies included three cohort studies in China, India, and the Republic of Korea, a large international pooled analysis of nine case–control studies ($n = 7$ hospital-based and $n = 2$ population-based), and three hospital-based case–control studies in Taiwan (China) ($n = 2$) and Uruguay.

Reduction of alcohol consumption and risk of laryngeal cancer were assessed in a large cohort study with a median follow-up time of 6.4 years. Compared with stable moderate consumption (15–29.9 g of ethanol per day) or stable heavy consumption (≥ 30 g of ethanol per day), reduction in consumption to a lower level over 2 years was not consistently associated with a reduced risk of laryngeal cancer. In the international pooled analysis, compared with continuing consumption, long-term alcohol cessation (≥ 20 years) was associated with a 31% lower relative risk of laryngeal cancer (RR, 0.69; 95% CI, 0.52–0.91); the reduction in risk was greater across strata of higher amounts of consumption (RR, 0.99; 95% CI, 0.56–1.74 for < 1 drink per day, and RR, 0.28; 95% CI, 0.09–0.86 for ≥ 3 drinks per day). In a subset of participants with detailed alcohol consumption and smoking history data, the relative risk for long-term alcohol cessation in the current-smoking stratum was 0.74 (95% CI, 0.46–1.20), and lower risks were also observed in most strata of duration of smoking cessation. After meta-analytic adjustment for smoking status and duration of smoking cessation, the association for long-term alcohol cessation was weaker (calculated RR, 0.80; 95% CI, 0.56–1.13).

Cessation of alcohol consumption and risk of laryngeal cancer were assessed in all seven studies. In the pooled analysis, two of the cohort studies, and three individual case–control studies, the calculated relative risks for cessation compared with continuing consumption ranged from 0.31 to 0.95. In the large cohort study with a median follow-up time of 6.4 years, across strata of baseline consumption, the relative risks for cessation ranged from 1.10 to 1.65 compared with stable consumption.

*(d) Oesophageal cancer*

Seventeen informative studies were available to assess associations of reduction, duration of cessation, and/or cessation of alcohol consumption and risk of oesophageal cancer. These studies included five cohort studies, one meta-analysis ($n = 4$ hospital-based case–control studies), and 11 other individual case–control studies ($n = 3$ population-based and $n = 8$ hospital-based) and were conducted primarily in eastern Asia, with some studies in south America, western Europe, and the USA. Although alcohol consumption is an established risk factor for the more commonly occurring squamous cell carcinoma of the oesophagus but not for oesophageal adenocarcinoma, the few studies of both subtypes combined were included in this review when the histological type was not clearly defined.

Reduction of alcohol consumption and risk of oesophageal cancer were assessed in the cohort study with a median follow-up time of 6.4 years. Compared with stable moderate consumption (15–29.9 g of ethanol per day) or stable heavy consumption (≥ 30 g of ethanol per day), reduction in consumption to a lower level over 2 years was associated with a higher risk.

Duration of alcohol cessation and risk of oesophageal cancer were assessed in nine studies (the meta-analysis, a cohort study of mortality, and $n = 7$ individual case–control studies). In the smoking-adjusted meta-analysis of four case–control studies, two of which also adjusted for the amount of alcohol consumed, there was a higher risk for < 5 years of cessation compared with continuing consumption. In contrast, there was a 15% lower relative risk for 5–10 years of cessation (RR, 0.85; 95% CI, 0.79–0.92) and 10–15 years of

cessation (RR, 0.85; 95% CI, 0.79–0.92), and a 65% lower relative risk for ≥ 15 years of cessation (RR, 0.35; 95% CI, 0.31–0.39). A similar pattern was observed in a multicentre case–control study, which also adjusted for cumulative alcohol consumption and cumulative tobacco consumption; the relative risk for ≥ 20 years of cessation was 0.46 (95% CI, 0.19–1.16). In the cohort study of oesophageal cancer mortality, compared with continuing consumption, the relative risk for ≥ 15 years of cessation was 0.46 (95% CI, 0.15–1.37). Among three of the other six individual case–control studies, compared with continuing consumption, the calculated relative risks were lower in the longest-term cessation category (range, 0.30–0.80).

Among the five cohort studies and 10 case–control studies of alcohol cessation and risk of oesophageal cancer, the calculated relative risks for cessation compared with continuing consumption were < 1 (range, 0.23–0.92) in four cohort studies and four case–control studies and ≥ 1 (range, 1.00–5.49) in the other cohort studies and case–control studies.

### *(e) Combined cancers of the upper aerodigestive tract*

Seven informative studies were available to assess associations of reduction, duration of cessation, and/or cessation of alcohol consumption and risk of combined cancers of the head and neck or of all upper aerodigestive tract cancers combined (i.e. head and neck and oesophageal cancers). These studies included four cohort studies in China, Europe ($n = 2$), and the Republic of Korea, a large international pooled analysis of 13 case–control studies ($n = 9$ hospital-based and $n = 4$ population-based), and two individual hospital-based case–control studies in Japan and Taiwan (China).

Two cohort studies assessed reduction and risk. In the cohort study with a median follow-up time of 6.4 years, compared with stable moderate consumption (15–29.9 g of ethanol per day) or stable heavy consumption (≥ 30 g of ethanol per day), reduction in consumption to a lower level over 2 years was not consistently associated with a lower risk of oral and pharyngeal cancer combined. In a cohort study in Denmark with a follow-up time of up to 21 years, the relative risk of all upper aerodigestive tract cancers associated with reducing consumption by ≥ 7 drinks per week compared with stable consumption (change of −0.9 to +0.9 drinks per week) was 0.5 (95% CI, 0.1–2.5).

Duration of cessation and risk were assessed in three studies. In the international pooled analysis, compared with continuing consumption, long-term alcohol cessation (≥ 20 years) was associated with a 40% lower relative risk of oral cavity, pharyngeal, and laryngeal cancer combined (RR, 0.60; 95% CI, 0.40–0.89). In that analysis, the relative risks for long-term cessation were 0.45 (95% CI, 0.25–0.81) in the hospital-based studies and 0.89 (95% CI, 0.54–1.45) in the population-based studies. In a subset of participants with detailed alcohol consumption and smoking history data, the reduction in risk for long-term cessation was greater in the current-smoking stratum (RR, 0.53; 95% CI, 0.32–0.88) than in the strata of duration of smoking cessation. After meta-analytic adjustment for smoking status and duration of smoking cessation, there was a 26% lower relative risk of head and neck cancer (calculated RR, 0.74; 95% CI, 0.56–0.98). In one individual case–control study, ≥ 10 years of cessation was associated with a lower risk of head and neck cancer (RR, 0.46; 95% CI, 0.27–0.79), but these results were not adjusted for detailed smoking history. In contrast, there were consistently higher risks of head and neck cancer across three categories of increasing duration of cessation (range of calculated RR, 1.42–2.83) in another case–control study.

Associations for cessation of alcohol consumption were assessed in six studies. Compared with continuing consumption, alcohol cessation was associated with a lower risk of head and neck

cancer in one cohort study (calculated RR, 0.84), in the pooled analysis (calculated RR, 0.85), and in one individual case–control study (calculated RR, 0.63). Alcohol cessation was associated with a higher risk of head and neck cancer or all upper aerodigestive tract cancers in the other studies.

### *(f) Colorectal cancer*

Seventeen informative studies were available to assess associations of reduction, duration of cessation, and/or cessation of alcohol consumption with risk of colorectal cancer, colon cancer, and/or rectal cancer. These studies included a pooled analysis of three cohort studies, 10 individual cohort studies, and six case–control studies ($n$ = 3 hospital-based and $n$ = 3 population-based), which were conducted in eastern Asia, Europe, and North America.

Reduction of alcohol consumption and risk of colorectal cancer were assessed in three individual cohort studies and the pooled analysis. In one study, a reduction of 12 g of ethanol per day was associated with a 14% lower relative risk of colorectal cancer (RR, 0.86; 95% CI, 0.78–0.95). In another cohort study with a median follow-up time of 14.2 years, the relative risk associated with a one-category reduction in consumption was 0.97 (95% CI, 0.86–1.08). Reduction of alcohol consumption was not associated with a lower risk of colorectal cancer in the two other studies.

Duration of cessation and risk were assessed in two studies. In a hospital-based case–control study, compared with continuing consumption, duration of cessation was inversely associated with risk (RR, 1.37; 95% CI, 0.91–2.06 for < 66 months; RR, 0.66; 95% CI, 0.42–1.06 for 66–180 months, and RR, 0.52; 95% CI, 0.31–0.86 for > 180 months of cessation); results were similar for colon cancer and rectal cancer. In a cohort study of cancer mortality, there were no clear patterns of reduced risk with longer duration of cessation for colon cancer or rectal cancer.

Alcohol cessation and risk were assessed in 15 studies. Among the eight individual cohort studies and one pooled analysis, the calculated relative risks for alcohol cessation compared with continuing consumption and colorectal cancer ranged from 0.54 to 1.34 and were < 1 in four of five studies of colon cancer and in two of four studies of rectal cancer. Among the six case–control studies of alcohol cessation compared with continuing consumption, the calculated relative risks were < 1 in three of four studies of colorectal cancer (range, 0.27–0.99), two of six studies of colon cancer (0.33 and 0.64), and three of six studies of rectal cancer (range, 0.23–0.93).

### *(g) Liver cancer*

Twelve informative studies were available to assess associations of reduction, duration of cessation, and/or cessation of alcohol consumption with risk of liver cancer. These studies included nine cohort studies and three hospital-based case–control studies. Most of the studies were conducted in Japan ($n$ = 7), and other studies were conducted in China ($n$ = 1), Italy ($n$ = 2), the Republic of Korea ($n$ = 1), and Spain ($n$ = 1). Four studies included only populations with underlying liver disease, either specifically related to alcohol ($n$ = 1) or not specifically related to alcohol ($n$ = 3).

In the only study of reduction of alcohol consumption, compared with stable moderate consumption (15–29.9 g of ethanol per day) or stable heavy consumption (≥ 30 g of ethanol per day), reduction in consumption to a lower level over 2 years was not associated with a reduced risk of liver cancer. In the four general population studies that assessed duration of cessation and risk of liver cancer, relative risks were > 1 (range, 3.0–8.03) for the shortest durations of cessation, which ranged from < 5 years to ≤ 10 years, and remained near to or greater than 1 (range, 0.98–8.6) for the longest durations, which ranged from > 5 years to ≥ 16 years.

Among the 12 studies of alcohol cessation and risk of liver cancer, the relative risk was 0.80 (95% CI, 0.53–1.19) for the study limited

to individuals with alcohol-related liver disease. In all other studies, which included individuals without alcohol-related liver disease, the calculated relative risks for cessation were near to or greater than 1 (range, 0.99–6.00).

*(h) Female breast cancer*

Twenty-one informative studies were available to assess associations of reduction or cessation of alcohol consumption with risk of breast cancer. The 11 cohort studies included data from 7 countries over a period from 1959 to 2018, and the 10 case–control studies ($n$ = 5 hospital-based, $n$ = 3 population-based, and $n$ = 2 mixed hospital-based and population-based) included data from 13 countries over a period from 1957 to 2013. No informative studies were available to assess duration of cessation compared with continuing consumption and risk of breast cancer.

Reduction of alcohol consumption and risk of breast cancer were assessed in four cohort studies. In the study with the longest follow-up time (median, 14.2 years), alcohol reduction was associated with a lower risk of breast cancer. However, no consistent patterns of association for alcohol reduction were observed in three other cohort studies, in which the follow-up time ranged from 6.4 years to 10.8 years.

The Working Group used meta-analytic techniques to assess the association of alcohol cessation compared with continuing consumption and risk of breast cancer; the summary relative risks were 0.89 (95% CI, 0.75–1.05) for 10 case–control studies, 0.96 (95% CI, 0.89–1.04) for six cohort studies of cancer incidence (the cohort study of cancer mortality was not included), and 0.95 (95% CI, 0.88–1.01) for all studies combined. In analyses stratified on hormone receptor status, the calculated hazard ratios for cessation were 0.90 (95% CI, 0.77–1.04) for estrogen and progesterone receptor-positive breast cancer and 1.18 (95% CI, 0.88–1.58) for estrogen and progesterone receptor-negative breast cancer in one cohort study among postmenopausal women. In a population-based case–control study, the calculated relative risks were 0.85 (95% CI, 0.58–1.23) for estrogen receptor-positive breast cancer and 1.00 (95% CI: 0.44–2.28) for estrogen receptor-negative breast cancer.

*(i) Gene-by-environment interactions*

The joint associations of alcohol cessation and polymorphisms in the *ADH1B*, *ADH1C*, or *ALDH2* genes with cancer risk were assessed in three studies – one study each for oral cavity and pharyngeal cancer, oesophageal cancer, and breast cancer. In all three studies there were methodological limitations, and there were too few cases in the alcohol cessation category within each genotype strata (range, 0–11) to provide reliable estimates of association. Therefore, the Working Group did not evaluate the modifying effects of genetic variability on the association between alcohol cessation and cancer risk.

## 4.3 Mechanistic data

### *4.3.1 Absorption, distribution, and metabolism of ethanol and alcohol-related mechanisms of carcinogenesis*

Upon alcohol consumption, ethanol is oxidized to acetaldehyde by alcohol dehydrogenase (ADH) and then to acetate by aldehyde dehydrogenase (ALDH). The local oxidation of ethanol to acetaldehyde is catalysed mostly by various ADH enzymes present in the microbiome. In contrast, the capacity of the oral or intestinal microbiome and mucosa to eliminate acetaldehyde is limited because of reduced ALDH activity, which results in accumulation of acetaldehyde at genotoxic concentrations in body fluids of the oral cavity, stomach, and colon (i.e. saliva, gastric juices, and colonic contents). This exposure to acetaldehyde is markedly enhanced by two other major risk factors for alcohol-related cancers: (i) genetic polymorphism of human ADH and ALDH2 enzymes, and (ii) tobacco smoking. Among

individuals with reduced ALDH2 activity (individuals who are heterozygous for *ALDH2*2*), ethanol metabolism results in double the concentration of salivary acetaldehyde as long as ethanol stays in the body. Chronic smoking combined with chronic heavy alcohol consumption induces changes in the oral microbiome, which may contribute to the observed synergistic effect of alcohol consumption and tobacco smoking on oral cancer risk. Also, after an ethanol challenge, salivary acetaldehyde concentrations during concomitant smoking among individuals who are currently smoking are 7 times those among individuals who do not smoke.

Genotoxicity is the best-described mechanism by which alcohol consumption causes cancer. Exposure to high concentrations of acetaldehyde, a potent genotoxic metabolite of ethanol, is a major determinant of alcohol-related carcinogenesis, particularly in the upper aerodigestive tract. Acetaldehyde – even at low concentrations – reacts with DNA, resulting in DNA damage, including chromosomal aberrations and DNA adducts, which may in turn lead to mutations. DNA damage may also result from other genotoxic pathways deriving from the ethanol-inducible CYP2E1 enzyme producing various reactive oxygen species. These reactive oxygen species can lead to lipid peroxidation, oxidative stress, and perturbation of DNA repair. Other mechanisms have been proposed, some of which may apply to the breast or liver, where local acetaldehyde concentrations are unlikely to be high. Alcohol consumption alters the composition of the intestinal microbiome and leads to epithelial barrier dysfunction and increased intestinal permeability, resulting in increased translocation of microbiota and microbial products across the mucosa. Microbial translocation and endotoxaemia trigger systemic inflammation, with the potential to increase cancer risk through oxidative stress, changes in cytokine levels, and impaired immune responses. Alcohol consumption also decreases folate absorption and inhibits enzymes that are critical for one-carbon metabolism and DNA methylation. Among women, alcohol consumption increases circulating concentrations of estradiol, testosterone, and other sex hormones and decreases the concentration of sex hormone-binding globulin; these changes may play a role in alcohol-related breast carcinogenesis.

### *4.3.2 Cancer-related mechanistic changes after cessation of alcohol consumption*

#### *(a) Genotoxicity*

The effects of cessation of alcohol consumption on DNA damage have been evaluated mostly by measuring and quantifying chromosomal aberrations and micronuclei in peripheral blood cells. The samples analysed may have a different exposure, cell turnover, and efficiency of DNA damage repair mechanisms compared with the cells in the target organs relevant to alcohol carcinogenesis. Seven studies compared the frequency of chromosomal aberrations among groups of individuals with alcohol use disorder, individuals with alcohol use disorder who abstained from alcohol consumption for periods from a few months to several years, and controls without alcohol use disorder. Four of these studies found that frequencies were lower among individuals with alcohol use disorder who abstained than among individuals with alcohol use disorder, and that these were comparable to those among controls. Two other studies did not find a significant difference between individuals with alcohol use disorder and abstainers but had limitations. In the first study, the frequencies of chromosomal aberrations were measured only at a very early stage (1 week) of a detoxification programme and baseline levels were not provided; the second study included only a small number of participants. One study, in which most individuals smoked, observed an increase in the frequencies of chromosomal aberrations at later time points (after 1 year) of the alcohol

abstinence programme, which resulted from an increase in smoking intensity.

Among the studies considered, four investigated the effects of duration of abstinence – short-term (1–12 months) and long-term (more than several years) – on DNA damage and found no correlation. Another study quantified the levels of the acetaldehyde-derived DNA adduct $N^2$-ethylidenedeoxyguanosine in oral cells, before and after specific increasing doses of alcohol, and observed a return to baseline levels within 24 hours upon alcohol cessation. In one study, mitochondrial DNA damage measured in peripheral blood samples of healthy volunteers exposed to a known dose of alcohol was induced by alcohol consumption but did not persist after 4 weeks.

### *(b) Epigenetics*

Regular alcohol consumption induces epigenetic modifications. One study examined the effect of alcohol cessation on the methylation of *ALDH2* and methylenetetrahydrofolate reductase (*MTHFR*), two genes thought to be important for alcohol metabolism and carcinogenesis. The significantly higher methylation in these genes observed at baseline was still evident after 3 months of rehabilitation; however, some individuals in the group were not abstinent. The study also showed that abstinence was associated with significantly lower global DNA methylation of long interspersed element 1 (*LINE-1*), a surrogate marker for overall DNA methylation. One study, which was an epigenome-wide methylation analysis to examine the effects of 2 weeks of acute withdrawal compared with controls, reported changes in methylation patterns both at individual CpG sites and in differentially methylated regions. The small study size (< 200 participants) may affect the robustness of the findings.

### *(c) Endocrine system*

Among women, alcohol consumption increases the concentrations of estradiol, testosterone, and other sex hormones. All the available studies among humans were performed among men. Two studies among individuals entering a treatment programme for alcohol use disorder examined the effects of 1–2 weeks of alcohol withdrawal. One reported that serum testosterone levels increased compared with baseline, whereas the other reported that they did not. The latter study also reported no change in estradiol levels but found a significant decrease in levels of sex hormone-binding globulin. Two studies examined changes in insulin or insulin resistance among individuals with moderate alcohol consumption who stopped consuming alcohol for 4 weeks or 6 weeks. The results were not concordant; one study showed improvement through a decrease in peripheral insulin resistance, and another showed that hepatic insulin resistance increased. The three available studies on the thyroid hormone system were methodologically too different to assess replication of effects. However, there is some evidence that alcohol withdrawal leads to decreased levels of triiodothyronine, thyroxine, and related thyroid hormones among individuals with alcohol use disorder who stop consuming alcohol, but these hormones may be sensitive to the acute effects of physical dependence. A single study showed that 6 months of cessation led to increased vitamin D levels, no significant increase in parathyroid hormone concentrations, and no change in insulin-like growth factor 1 (IGF-1) concentrations. The relevance of cortisol to cancer risk is unclear, but one study using a time-course analysis of concentrations in hair showed that cortisol concentrations decrease rapidly after alcohol cessation.

*(d) Microbiome*

Chronic heavy alcohol consumption induces changes in the composition and abundance of both the oral and the intestinal microbiome.

Two studies assessed the variations in the composition of the oral microbiome of individuals with alcohol use disorder after a period of alcohol abstinence. This approach is based on evidence showing that the acetaldehyde production capacity of the oral microbiome is elevated among individuals with heavy alcohol consumption. Therefore, these studies relied on an indirect measurement of the microbiome activity by assessing the ability of the bacteria in saliva samples to metabolize ethanol ex vivo. One study found that the capacity of the oral microbiome to produce acetaldehyde from ethanol decreased after 3 weeks of abstinence, whereas no difference was observed in the other study, which considered 18 days of abstinence.

The effects of alcohol abstinence on the intestinal microbiota were analysed in six studies; four resulted from the analysis of samples from the same cohort of individuals with alcohol use disorder entering a treatment programme. All of these studies focused on the analysis of samples collected over a period of abstinence of only a few weeks. These studies indicate variations in the abundance and composition in the virome and in the fungal microbiome upon abstinence.

These studies have major limitations, mostly related to small sample sizes, resulting in the inability to consider proper adjustments when multiple comparisons are performed. In addition, the effects of abstaining from alcohol consumption cannot easily be disentangled from the effects that may result from inpatient treatments and changes in lifestyle and diet during the abstinence periods considered.

*(e) Inflammatory and immune responses*

Chronic heavy alcohol consumption increases intestinal permeability, and hence microbial translocation across the gastrointestinal tract, and creates an inflammatory state characterized by increased levels of circulating cytokines and altered levels of certain immune cells. These changes are more pronounced among individuals with alcohol-related hepatitis and cirrhosis.

Cessation of alcohol consumption for 3–4 weeks resulted in reduced intestinal permeability, towards normal. Heavy alcohol consumption causes intestinal mucosal cell injury; the increased levels of intestinal fatty acid binding protein remained elevated after 6 weeks of abstinence, and levels of regenerating islet-derived protein 3α and trefoil factor 3 also remained elevated for at least 12 months of abstinence among individuals with alcohol-related hepatitis. Microbial translocation results in increased circulating bacterial components such as lipopolysaccharides, lipopolysaccharide binding protein, and peptidoglycan recognition proteins. After cessation of alcohol consumption, levels of lipopolysaccharide binding protein remained elevated for 3–6 weeks, and levels of peptidoglycan recognition proteins and lipopolysaccharide remained elevated for 2–3 weeks.

With long-term heavy alcohol consumption, the translocation of microbial products activates the immune system. Elevated levels of soluble CD14, a marker of macrophage activation, decrease over 10 days to 6 weeks of abstinence.

Levels of cytokines are elevated among individuals with alcohol use disorder and through varying durations of abstinence, including the pro-inflammatory cytokines interleukin 6, tumour necrosis factor α, and interleukin 1β and the anti-inflammatory cytokines interleukin 10 and interleukin 4. The source of the cytokines is not known, but the liver is thought to be a major contributor, and one study implicated adipose tissue as well. An important confounder of these

studies is the presence, known or unknown, of alcohol-related liver disease.

Circulating immune cells are altered by heavy alcohol consumption. In one study, reduction in the levels of $CD14^+/CD16^-$ monocytes and their responsiveness to lipopolysaccharide was more pronounced among individuals who were heterozygous for *ALDH2*2* and had the *ADH1B*2* allele, implicating acetaldehyde in this effect; the changes improved after 4 weeks of abstinence. In another study, a shift in the characteristics of circulating monocytes was observed within 2 weeks of abstinence, suggesting a less inflammatory and more anti-inflammatory state. Circulating levels of mucosal-associated invariant T cells ($CD8^+$ T cells enriched in the intestinal mucosa and liver) were markedly decreased among individuals with alcohol-related hepatitis and somewhat decreased among individuals with heavy alcohol consumption. Over 6–12 months of abstinence, these levels increased among both groups but did not return to normal.

*(f) Oxidative stress*

Ethanol oxidation is associated with the generation of reactive oxygen species, resulting in lipid peroxidation, which is reflected by elevated levels of malondialdehyde and increased exhalation of ethane. Individuals with chronic heavy alcohol consumption show evidence of oxidative stress and impaired ability to detoxify the reactive oxygen species. The time course of resolution has been assessed in five studies among individuals with alcohol use disorder entering a treatment programme. In two studies, the elevated malondialdehyde levels decreased to normal levels over 2–4 weeks of abstinence. In another study among individuals with alcohol use disorder, most of whom had advanced liver disease, increased exhalation of ethane appeared to decrease over a period of several weeks of abstinence, although not returning to normal among all participants. Other studies examined the plasma levels of enzymes and vitamins that detoxify the products of oxidative stress (superoxide dismutase, the selenoprotein glutathione peroxidase, glutathione reductase, catalase, retinol, carotene, and vitamin E). Vitamin E levels were low at entry into treatment in two studies; the levels increased over 27 days in a study in which niacin supplementation was given to the participants, but they did not increase in a second study of 14 days' duration without niacin treatment. Three studies examined serum glutathione peroxidase activity, which was low at the beginning of abstinence and increased only among the participants in the study with niacin supplementation. It was not possible to distinguish the effects of niacin, abstinence, improved diet, or simply a longer period of abstinence in these studies. In three different studies, levels of carotene, selenium, and superoxide dismutase were low at the beginning of abstinence and only carotene levels increased during abstinence.