International Agency for Research on Cancer

World Health Organization

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IARC Handbooks of Cancer Prevention Volume 20A: Reduction or Cessation of Alcohol Consumption

Questions and Answers (Q&A)

A Working Group of international experts, convened by the International Agency for Research on Cancer (IARC), evaluated the body of literature assessing reduction or cessation of alcoholic beverage consumption, compared with continuing consumption, in relation to the risk of cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver, and breast.

A summary of the findings has been published as a Special Report in *The New England Journal of Medicine*.[1] The findings will be published in full in Volume 20A of the *IARC Handbooks of Cancer Prevention* series.

1. What is the *IARC Handbooks* series?

The *IARC Handbooks of Cancer Prevention* series is published by IARC. The *IARC Handbooks* provide definitive evaluations about which agents and interventions prevent cancer or detect cancer at an early stage. To produce these evaluations, IARC convenes a Working Group of international interdisciplinary experts who collect all the relevant studies published to date, review the data, and determine how sure we can be that such agents and interventions can reduce the risk of cancer or mortality from cancer.

2. What are the key take-home messages from this evaluation?

Based on the evidence reviewed, the Working Group concluded that there is *sufficient evidence* that, compared with continuing consumption, reduction or cessation of alcoholic beverage consumption reduces the incidence of cancers of the oral cavity and the oesophagus. The evidence that reduction or cessation of alcohol consumption reduces risk of the other alcohol-related cancer types was either *limited* or *inadequate*.

The Working Group also concluded that there is *sufficient evidence* from mechanistic studies that cessation of alcohol consumption reduces alcohol-related carcinogenesis. This conclusion is based on *strong evidence* that three alcohol-related mechanistic pathways are reversible upon cessation of alcohol consumption: those involving acetaldehyde metabolism, genotoxicity (such as DNA damage), and the immune and inflammatory systems (intestinal permeability and microbial translocation).

[1] Gapstur SM, Bouvard V, Nethan ST, Freudenheim JL, Abnet CC, English DR, et al. (2023). The IARC perspective on alcohol reduction or cessation and cancer risk. *N Engl J Med*, Published online 28 December 2023; https://doi.org/10.1056/NEJMsr2306723

3. Why did the *IARC Handbooks* programme evaluate the evidence on reduction or cessation of alcoholic beverage consumption in relation to cancer risk?

In 1987, the *IARC Monographs* programme first classified alcoholic beverages as *carcinogenic to humans* (Group 1), based on sufficient evidence of causality for cancers of the oral cavity, pharynx, larynx, oesophagus (squamous cell carcinoma), and liver (hepatocellular carcinoma). Subsequently, in 2007 and in 2009, both colorectal cancer and female breast cancer were added to the list of cancer types caused by alcoholic beverage consumption. In addition, ethanol in alcoholic beverages and acetaldehyde that is associated with consumption of alcoholic beverages were also classified as *carcinogenic to humans* (Group 1).

In 2021, the Working Group for *IARC Handbooks* Volume 19 on oral cancer prevention found *sufficient evidence* that cessation of alcohol consumption decreases the risk of oral cancer. To more fully understand the potential benefit of reduction or cessation of alcoholic beverage consumption in relation to cancer risk, the *IARC Handbooks* programme convened a Working Group to review and evaluate the epidemiological and mechanistic evidence on reduction or cessation of alcoholic beverage consumption for all seven alcohol-related cancer types.

4. Why is alcohol consumption carcinogenic?

Several mechanisms have been proposed to explain the carcinogenicity of alcohol consumption, some of which are well established. The most convincing evidence for the cancer-causing effect is through the metabolism of ethanol to acetaldehyde. Upon ingestion, ethanol – the principal alcohol in alcoholic beverages – is immediately transformed into acetaldehyde. Acetaldehyde is genotoxic and causes DNA damage, particularly in the upper aerodigestive tract (head and neck, and oesophagus), leading to carcinogenic mutations. Alcohol consumption also induces oxidative stress; alters the metabolism of folate; affects sex hormones; and has epigenetic effects, namely by altering DNA methylation. In addition, acetaldehyde alters the composition of the gut microbiome, which leads to intestinal permeability. This, in turn, triggers inflammation, which is known to increase the risk of cancer.

5. If the mechanisms of alcohol-related carcinogenesis can be reversed upon cessation, can we infer that reduction of alcoholic beverage consumption also reverses these mechanisms?

Because the risk of cancer increases with an increasing amount of alcohol consumed, it is reasonable to assume that the risk of cancer decreases with decreasing alcohol consumption. Unfortunately, there are no studies that look into the mechanisms upon reduction of alcohol consumption, and therefore an expert evaluation specifically of alcohol reduction could not be made.

Still, the review of the evidence shows that at least three mechanisms of alcohol-related carcinogenesis are reversible upon cessation of alcohol consumption. First, alcohol cessation leads to a rapid decrease and elimination of alcohol-related acetaldehyde in the upper aerodigestive tract and colon. Second, in the context

of chronic heavy alcohol consumption, alcohol cessation results in a decrease in DNA damage in blood cells within a few months to several years, and in a rapid reduction or elimination of acetaldehyde–DNA adduct formation in the oral cavity. Third, among individuals with alcohol use disorders, alcohol cessation reverses the alcohol-related increase in intestinal permeability and microbial translocation. Hence, one could infer that a reduction in alcohol consumption will reduce alcohol-related biological changes that will eventually lead to cancer.

6. What is new in terms of the evaluation and in terms of the conclusions in this new volume of the *IARC Handbooks*?

Except for the evaluation of the evidence for oral cancer conducted for *IARC Handbooks* Volume 19, there has never been a comprehensive review of the body of scientific evidence on cessation or reduction of consumption of alcoholic beverages and the risk of each of the seven alcohol-related cancer types. Hence, this is a first-time evaluation.

7. There is *sufficient evidence* that reduction or cessation of alcohol consumption reduces the incidence of cancers of the oral cavity and the oesophagus. How did the Working Group reach these conclusions?

These conclusions were based on pooled analyses and meta-analyses of observational epidemiology studies in humans, as well as individual studies, which consistently showed that long-term cessation was associated with a lower risk of cancer of the oral cavity or the oesophagus compared with continuing consumption, even after adjusting for tobacco smoking and for the amount of alcohol consumed.

8. There is *limited evidence* for cancers of the larynx, colorectum, and breast. How did the Working Group reach these conclusions?

For laryngeal cancer, the reduction in risk due to reduction or cessation of alcohol consumption could not be disentangled from that due to smoking cessation with reasonable confidence.

For breast cancer, it is possible that any reduction in risk due to reduction or cessation of alcohol consumption may be limited to hormone receptor-positive breast cancers, which are more strongly related to alcohol consumption. However, few studies assessed reduction or cessation of alcohol consumption and risk by hormone receptor subtype.

For colorectal cancer, the Working Group concluded that the current body of evidence was *limited* because of the inconsistencies among studies of reduction of alcohol consumption and the few studies on duration of cessation of alcohol consumption.

9. There is *inadequate evidence* for cancers of the pharynx and liver. How did the Working Group reach these conclusions?

For pharyngeal cancer, the body of evidence was inconsistent.

For liver cancer, the only study that assessed alcohol reduction showed no evidence of a reduced risk. In addition, *inadequate evidence* from the studies of alcohol cessation could be due, at least in part, to competing risks: heavy alcohol consumption causes liver cirrhosis, which is a precursor to liver cancer. Individuals with advanced cirrhosis who continue to consume alcohol may be 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.

10. Public health campaigns have often stressed that alcohol consumption can cause breast cancer. Is there in fact only *limited evidence* that alcohol consumption causes breast cancer?

No. As stated above, alcoholic beverage consumption is an established cause of breast cancer. Furthermore, the World Cancer Research Fund/American Institute for Cancer Research has shown that even low amounts of alcohol consumption increase the risk of breast cancer. The current review and evaluation assessed the evidence that reduction or cessation of alcohol consumption reduces risk of cancer compared with continuing consumption.

11. What do the evaluations show in terms of the cancer risk associated with low and moderate consumption of alcohol?

The Working Group did not evaluate the evidence on alcohol consumption in relation to cancer risk.

12. Is there a benefit in reducing the consumption of alcohol for low or moderate consumption of alcohol?

The Working Group did not assess whether there was a difference in the reduction in cancer risk due to reduction or cessation of alcohol consumption based on the amount consumed.

13. Based on the results of this review and evaluation, what would you tell your friends and relatives?

First of all, it is important to raise awareness about the fact that alcoholic beverage consumption causes cancer. And now we have evidence that reduction or cessation of alcohol consumption can reduce the risk for some types of cancer caused by consumption for those who currently consume alcohol. In short, less is better.

14. What methodology was used to obtain these results?

The *IARC Handbooks* evaluations follow a rigorous and transparent process:
Step 1: Identify which interventions to review and evaluate.
Step 2: Identify the relevant literature.
Step 3: Screen and select the informative studies.
Step 4: Extract the data, and write study summaries.
Step 5: Evaluate the quality of each study.
Step 6: Perform peer review, by Working Group members and IARC scientists.
Step 7: Synthesize the results and the quality of the studies.
Step 8: Interpret the results, and evaluate the strength of the evidence.

The Working Group reviews and assesses all informative original studies, and pooled analyses or meta-analyses of studies, conducted in a large number of countries around the world. The scientific literature is reviewed according to strict criteria as defined in the Preamble to the *IARC Handbooks*.

15. How does the *IARC Handbooks* classification system work?

The classification system is defined in the Preamble to the *IARC Handbooks* for primary prevention. For epidemiological studies, *sufficient evidence* indicates that a causal preventive association between the intervention and cancer in humans has been established, *limited evidence* indicates that a causal preventive association between the intervention and cancer in humans is plausible, and *inadequate evidence* indicates that the current body of evidence does not enable a conclusion to be drawn about the presence or absence of a preventive association between the intervention and cancer in humans. For mechanistic data, *strong evidence* indicates that there are a substantial number of high-quality studies in humans that consistently link the intervention to a mechanistic pathway by which it could prevent cancer.

16. When will *IARC Handbooks of Cancer Prevention* Volume 20A be available?

The detailed assessments will be published as Volume 20A of the *IARC Handbooks of Cancer Prevention*. Our goal is to publish the full volume online in mid-2024.

17. Why is this evaluation important?

Worldwide, in 2020 an estimated 741 300 new cancer cases (4.1% of all new cancer cases) were attributable to alcohol consumption (6.1% among men and 2.0% among women). Recently, the World Health Organization (WHO) stated that “no safe amount of alcohol consumption for cancers and health can be established”. In 2010, the Sixty-third World Health Assembly endorsed the Global Strategy to Reduce the Harmful Use of Alcohol (Resolution WHA63.13).

Alcohol consumption is a major public health concern, and this was a first-ever evaluation of the body of scientific evidence on the potential benefits of reduction or cessation of alcohol consumption for decreasing alcohol-related cancer risks. This review revealed important research gaps, which, if filled, would further support alcohol control strategies.

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The International Agency for Research on Cancer (IARC) is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer and the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships. If you wish your name to be removed from our press release emailing list, please write to com@iarc.who.int.