

Alcohol consumption as a cause of cancer

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ABSTRACT

Background and aims There is increasing research evidence about the causal role of alcohol in cancer, accompanied by unclear and conflicting messages in the media. This paper aimed to clarify the strength of the evidence for alcohol as a cause of cancer, and the meaning of cause in this context. **Methods** Recent epidemiological and biological research on alcohol and cancer was reviewed and summarized, drawing upon published meta-analyses identified from the Medline database and the archives of the International Agency for Research on Cancer. More recent epidemiological studies not included in these publications were also reviewed. A brief description of the nature of causal inference in epidemiology was used to frame discussion of the strength of the evidence that alcohol causes cancer, and contrast this with the case for a protective association of alcohol with cardiovascular disease. **Results** The usual epidemiological understanding of a cause is a factor that increases the incidence of a condition in the population. In the context of a body of epidemiological evidence of an association of alcohol consumption with a disease, the inference that it is a causal association requires alternative explanations of the observed finding to be judged unlikely. Even without complete knowledge of biological mechanisms, the epidemiological evidence can support the judgement that alcohol causes cancer of the oropharynx, larynx, oesophagus, liver, colon, rectum and breast. The measured associations exhibit gradients of effect that are biologically plausible, and there is some evidence of reversibility of risk in laryngeal, pharyngeal and liver cancers when consumption ceases. The limitations of cohort studies mean that the true effects may be somewhat weaker or stronger than estimated currently, but are unlikely to be qualitatively different. The same, or similar, epidemiological studies also commonly report protection from cardiovascular disease associated with drinking but a high level of scepticism regarding these findings is now warranted. **Conclusions** There is strong evidence that alcohol causes cancer at seven sites in the body and probably others. Current estimates suggest that alcohol-attributable cancers at these sites make up 5.8% of all cancer deaths worldwide. Confirmation of specific biological mechanisms by which alcohol increases the incidence of each type of cancer is not required to infer that alcohol is a cause.

Keywords Alcohol, cancer, cardiovascular disease, causal inference, cohort studies, epidemiology, evidence-based policy.

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INTRODUCTION

In the last decade there has been a proliferation of research literature, reviews and comment on the association of alcohol consumption with cancer. In some parts of the world the scientific consensus that alcohol causes cancer has already led to more explicit consideration of cancer risk in policy-making [1,2], and programmes to increase public knowledge of the risks [3].

The use of causal language in scientific and public discussions is patchy, with titles of papers and newspaper headlines often choosing to describe a causal association as a 'link' between alcohol and cancer. Expressions such

as 'alcohol-related cancer', 'alcohol-attributable cancer' and the effect of alcohol on 'the risk of cancer' incorporate an implicit causal association, but are easily interpreted as something less than cancer being caused by drinking.

Among health professionals, journalists and the wider public there seems to be particular confusion about two aspects of 'alcohol causes cancer', the first being the meaning of 'cause' and the second being the quality of the evidence. For example, incomplete understanding of biological mechanisms may be raised as an objection to calling alcohol a cause of cancer, and knowledge that there are other causes of the same cancers also seems to challenge acceptance of alcohol as a cause. The analogy with smoking

causing lung cancer is not sufficiently close to aid understanding. Currently, alcohol's causal role is perceived to be more complex than tobacco's, and the solution suggested by the smoking analogy—that we should all reduce and eventually give up drinking alcohol—is widely unacceptable.

A central concern of epidemiology is assessment of the validity of individual studies and of the collective quality of the body of evidence supporting the view that a particular association is causal. The re-assessment of previous studies in light of new research or new insights is not uncommon, and the establishment of the epidemiological basis for causal inference is an iterative process that is never completed fully. In the study of alcohol and specific cancers, most evidence is derived from a large pool of observational epidemiological studies, particularly cohort studies, to which new and sometimes improved examples are being added. The well-recognized limitations of these designs means there is discussion, debate and new research under way that challenges and refines published estimates of risk, and explores threats to validity. There is also new evidence emerging regularly about the association of drinking with further cancer types [4].

In this context, some confusion and scepticism about whether alcohol causes cancer may seem understandable, but in some cases doubt is also being generated by dissemination of misinformation, which undermines research findings and contradicts evidence-based public health messages.

A recent example in New Zealand followed from an Alcohol and Cancer symposium that had been covered by national television news and the press. An opinion piece in the capital's daily newspaper, disputing the evidence reported from the conference, was entitled: 'To say moderate alcohol use causes cancer is wrong' [5]. It included the statement: 'While chronic abusive alcohol consumption is associated with a plethora of health problems including cancer, attributing cancer to social moderate drinking is simply incorrect and is not supported by the body of scientific literature'. The article was attributed to a former senior scientist in the United States now employed by an alcohol industry body, while continuing to publish on alcohol in the scientific literature [6,7].

EVIDENCE THAT ALCOHOL CAUSES CANCER

Put very briefly, existing epidemiological evidence supports a causal association of alcohol consumption with cancers at seven sites: oropharynx, larynx, oesophagus, liver, colon, rectum and female breast. For all these there is a dose-response relationship, where the increase in cancer risk with increased average consumption is monotonic, either linear or exponential, without evidence of threshold of effect. There does not appear to be any variation by

beverage type. These conclusions are based on comprehensive reviews undertaken in the last 10 years by the World Cancer Research Fund and American Institute for Cancer Research [8], the International Agency for Research on Cancer [9,10], the Global Burden of Disease Alcohol Group [11] and the most recent comprehensive meta-analysis undertaken by Bagnardi and colleagues [4], building on meta-analyses of the effect of alcohol on single cancers.

The meta-analyses have not been able to describe the influence of pattern of drinking on cancer risk, e.g. whether frequency of heavy drinking occasions is influential in addition to the effect of average volume, due to insufficient data in the component studies. However, recent analyses from two large cohort studies in the United States do not suggest a significant impact of drinking pattern on risk of total cancer in light to moderate drinkers [12].

The strength of the association with alcohol varies by site of the cancer, being particularly strong for mouth, pharynx and oesophagus (relative risk in the range of 4–7 for ≥ 50 g of alcohol per day compared with no drinking) and less so for colorectal cancer, liver and breast cancer (relative risk approximately 1.5 for ≥ 50 g/day) [13]. For cancers of the mouth, pharynx, larynx and oesophagus there is a well-recognized interaction of alcohol with smoking, resulting a multiplicative effect on risk. Biological evidence is supportive of the carcinogenic potential of drinking alcohol and the interaction with smoking, but mechanisms are not understood fully [13].

Further supporting the causal association is evidence that, for some cancers, the risk associated with alcohol attenuates when drinking ceases. Pooled analyses of studies of drinking cessation from 2007 [14] suggested that the risk of oesophageal cancer and cancers of the head and neck increased for a period of years before declining, and was similar to never drinkers after 20 years. A recent systematic review of the risk of laryngeal and pharyngeal cancers after quitting [15] also found that the risk was reversible, with a reduction of approximately 15% of the excess risk in 5 years, and equivalence with never drinkers after more than 30 years. A meta-analysis of effect of drinking cessation on the liver also found evidence of reversibility, with a decrease in risk of hepatocellular carcinoma of 6–7% per year and equivalence with never drinkers after 23 years [16].

The effects of light to moderate drinking on cancer risk have had special attention recently. The United Kingdom's Million Women cohort study found that during 7 years of follow-up, women who drank between 70 and 140 g of alcohol per week had a 5% increase in total cancer compared with those drinking less than 20 g per week, and a 13% increase in breast cancer. In this study, alcohol-related risk of aerodigestive cancers was limited to women who smoked [17], reflecting the multiplicative interaction between these two causes [13]. A meta-analysis in 2013 found that light drinkers were at increased risk of cancers of the

mouth, pharynx, oesophagus and breast, but not colorectal, liver or laryngeal cancers [18]. Recently published analyses of data from two large US cohort studies by Cao and colleagues found that light to moderate consumption in women was associated with an increased total risk of cancers known to be associated with alcohol. This was due largely to the effect on breast cancer, where a significant increase in risk was seen from the first drink per day. Similar overall findings were seen for men who had ever smoked, but no significant association was seen for male light drinkers who had never smoked [12].

There is accumulating research supporting a causal contribution of alcohol to cancer at sites other than those already mentioned, particularly for pancreas, prostate and skin (melanoma) [4], and for pancreatic cancer risk being associated with heavy drinking occasions as well as average consumption [19]. It also seems reasonably clear that some cancers are not affected (adenocarcinoma of oesophagus, gastric cardia, endometrium, bladder [4]) or have a negative association with alcohol consumption (thyroid cancer, Hodgkin's and non-Hodgkin's lymphomas and renal cell cancer [4,17,20]).

This raises the question of why alcohol affects some cancers and not others, and whether this undermines the conclusion that 'alcohol causes cancer'. The explanation seems to lie in the heterogeneity of probable mechanisms for the effect of alcohol on cancer at different sites [13].

The mechanisms by which alcohol causes cancer are not well understood, but are thought to depend upon the target organ [13]. Pure ethanol does not act as a carcinogen in animal studies, and evidence that it causes mutations directly in humans is weak [21]. For cancers of the mouth, pharynx, larynx, oesophagus and liver there is strong evidence that DNA damage is due to acetaldehyde, the carcinogenic metabolite of ethanol oxidation [22]. Most ethanol will be metabolized to acetaldehyde in the liver, but salivary acetaldehyde has been found to reach high levels when drinking, as further metabolism to acetate is limited at the site [18]. There is some evidence of another causal pathway through alcohol facilitating access for other carcinogens, such as tobacco constituents, by enabling the penetration of the mucosa in the upper aerodigestive tract [18]. This would go some way towards explaining the interaction between alcohol and smoking for head and neck cancers [22]. Stronger associations and more susceptibility at low doses is seen for the cancers where alcohol and acetaldehyde come into direct contact with the tissues [18].

The actions of alcohol are thought to be modulated by genetic factors, particularly polymorphisms affecting alcohol metabolism, folate and methionine metabolism and DNA repair [21]. Mechanisms for breast cancer appear to involve interference with oestrogen metabolism, and even moderate drinking increases circulating levels of sex hormones which activate cellular proliferation [17,23].

Oestrogen may exert its carcinogenic effect directly or via oestrogen receptors [24]. Although other mechanisms are likely to be involved, it appears that breast cancer may result from very different pathways than other cancers, and breast tissue may be more susceptible to alcohol than other sites [12].

Plausible biological mechanisms, even with supporting experimental evidence, do not provide very strong evidence about what causes increases in incidence of disease in populations and what could reduce incidence [25]. Plausible biological mechanisms did not prevent evidence about the apparent beneficial effects of hormone replacement therapy on cardiovascular disease (CVD) or beta-carotene on both CVD and cancer being overturned by subsequent randomized trials [26,27]. Reasoned and reasonable conclusions about causation draw upon the whole body of evidence available, and put most faith in the most rigorous epidemiological research.

WHAT IS MEANT BY CAUSE IN EPIDEMIOLOGY AND HOW DO WE REACH A JUDGEMENT?

Rothman provides a useful model for causes of disease in populations [28]. Each individual instance of disease has a singular mechanism, which can be thought of as a combination of component causes making up a 'sufficient cause'. The component causes can act simultaneously or sequentially. In a population there are multiple possible mechanisms for any type of disease, and these mechanisms may have some component causes in common. Thus, removal of one of the component causes will alter the incidence of disease in the population, but is unlikely to prevent it entirely.

Proof is impossible in epidemiology, as in all other science. Randomized controlled trials (RCTs) are well known to have advantages over cohort and case-control studies in terms of causal inference, but they are nevertheless subject to error. When considering exposures such as alcohol consumption which are potentially harmful or have a long period of latency or cumulative effect, RCTs are not appropriate or feasible and most evidence will necessarily come from observational studies.

In making judgements about causation, there are principles that can provide guidance if a body of good quality epidemiological evidence is available, but there is no checklist or statistical method for inferring causation. Judgement largely employs inductive reasoning, conjecture and refutation. Induction is informed by consideration of the whole body of evidence, including its consistency, and by the investigation of heterogeneity and threats to validity of the studies. Conjecture based on induction provides a target for refutation, or testing of competing hypotheses. The best-known list of properties of the evidence to consider

when assessing causation is Sir Austin Bradford Hill's set of 'viewpoints' laid out in 1965 [29], which owe much to the US Surgeon-General's report of 1964 [30] and to philosophers of earlier centuries. Hill's considerations were strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy. It is common for these to be presented erroneously as 'causal criteria', although the author made it clear that this was not his intention. As discussed by Rothman [28], none of the nine viewpoints outlined by Bradford Hill is either a necessary or sufficient property to support causal inference, apart from the temporal association between the exposure and the outcome (the cause must precede the effect). As summarized by Szklo & Nieto, 'The implicit questions that these guidelines seek to address are whether confounding and bias are reasonable alternative explanations for an observed associations and, if not, whether a cause-effect relationship can be inferred' [31].

In the large review of evidence for causal associations of food, nutrition and physical activity with cancer, published by the World Cancer Research Fund and American Institute for Cancer Research in 2007 [8], causality was described as 'that a factor decreases or increases the risk of cancer' and 'causal relationships... can be confidently inferred when epidemiological evidence, and experimental and other biological findings, are consistent, unbiased, strong, graded, coherent, repeated and plausible. Individually none of these factors is likely to be sufficient to infer a causal relationship with confidence. Also, individual relationships may be deficient in various respects but collectively can still be judged as causal because of their cumulative weight.'

ALCOHOL CAUSES CANCER BUT DOES NOT PREVENT CVD: CAN YOU HAVE IT BOTH WAYS?

Commentators ask how we can say that alcohol causes cancer while doubting the benefits of alcohol for CVD. Even though the evidence may come from the same cohort studies, many epidemiologists will accept that the higher risk of cancer from higher consumption is causal, while remaining sceptical of the J-shaped curve that proposes benefit for light to moderate drinkers compared with abstainers and an increase in risk for heavier drinkers. Critics say you cannot have it both ways: are the studies right or not?

In judging whether the associations are likely to be causal, we need to consider the alternative explanations. Theoretically, non-causal explanations come in the form of biases, confounding and chance, but here chance can be excluded due to the size and number of the studies. Conversely, biases arise from the way in which the cohort studies have been conducted, and the same biases may affect all or many of the studies. Several potential sources of bias

have been documented, particularly measurement of alcohol consumption and the make-up of the reference group [32,33]. In addition, confounding occurs in non-randomized studies where other contributing causes are not distributed evenly between the exposure groups. For example, when heavy drinkers are more likely to smoke than light drinkers, the effects of heavy drinking on cancer are exaggerated by the heavy drinkers' smoking. Within studies, confounders are identified, measured and controlled with varying rigour. However, all cohort studies are affected by residual confounding from unidentified confounders, from the imperfect measurement of known confounders, from misclassification of confounders and from the way in which continuous measures are categorized [31]. Combining studies in meta-analyses only improves precision of estimates, and does nothing to mitigate bias and confounding.

When we compare the effect of these limitations on the association of alcohol with CVD and with cancer, measured in the same cohort studies, it is possible to see why different levels of scepticism about the findings are appropriate.

- *Measurement of average consumption.* Self-reported alcohol consumption commonly underestimates actual consumption, and this will bias the effects seen in cohort studies. If underestimation of drinking was uniform across the population we could move the risk curves to the right, and the observed effects, both benefits and harms, would be attributed to heavier drinking. This means the risk of cancer would be less than thought currently, and the putative benefits for CVD would also be weaker, with maximal benefit at a level of drinking that is unacceptable due to other harms [33]. However, research on under-reporting suggests that it is common but not uniform, and has been seen to vary by how much people usually drink, as well as by gender, socioeconomic status, and country [34,35]. Underestimation in whole populations can be modelled and adjusted for [36], but we cannot predict the effect of individual-level under-reporting on measures of effect.
- *Lack of pattern measurement.* Few cohort studies have collected data on frequency of heavy drinking occasions or other dimensions of drinking pattern. Therefore, seven drinks on Friday night becomes average consumption of one drink a day. However, cancers develop over a long period and the little evidence available suggests that pattern of drinking may not alter risk greatly in low to moderate volume drinkers [12], which is consistent with proposed mechanisms for most cancers [19]. The mechanisms suggested for cardioprotection are sensitive to regularity of drinking, and epidemiological studies across populations show that the benefits are not observed in groups with heavy drinking occasions, even if average consumption is moderate [37].

- *Misclassification of abstainer reference group.* Inclusion of former drinkers and occasional drinkers in the abstainer category would be expected to raise the risk of cancer in this group. When used as a reference group, this would result in underestimation of cancer risk in other drinker groups, so the findings would be conservative estimates of harm. A meta-analysis of studies of breast cancer found that the misclassification of occasional drinkers as abstainers biased cancer risk towards the null for other categories of drinkers, but that inclusion of former drinkers was not influential [38]. For CVD, this misclassification would also be expected to result in underestimation of harm due to higher CVD risk in the former drinkers, and this would exaggerate the observed beneficial effect. A recent meta-analysis provides evidence that correcting for this particular weakness substantially reduces the observed CVD benefit among drinkers [39].
- *Residual confounding.* Contributing causes other than alcohol will vary by cancer type, and so confounding that remains after adjustment for measured confounders will also vary. To provide a non-causal explanation for the consistent monotonic relation between alcohol and cancer across at least seven cancer sites, there would need to be a set of confounders for each cancer that were associated strongly with average level of consumption and the specific cancer outcome in a dose–response manner. These strong confounders would need to be novel, not already adequately controlled, and not associated with cancer types that have no demonstrated harmful association with alcohol.

For residual confounding to explain some or all of the J-shaped associations between alcohol and CVD, there would need to be a set of confounders that are associated strongly with low to moderate drinking, but not with heavier drinking, that are protective for cardiovascular disease and not already controlled adequately in the cohort studies. In this case there is evidence that suggests that this is not only possible, but probable. It has long been demonstrated that the CVD benefit is reduced in studies which control for more confounders [40]. Confounders include a range of ‘life-style’ factors, particularly healthier behaviours and socio-demographic characteristics that are associated with moderate drinking. In a large US survey in 2005, 27 of 30 CVD risk factors were shown to be more prevalent in abstainers than moderate drinkers [41]. This means that confounding by many factors needs to be controlled in non-randomized studies, and suggests that residual confounding by similar unmeasured characteristics is likely. Findings of a recent Mendelian randomization study designed to provide unconfounded estimates of CVD risk associated with drinking supported the hypothesis that the observed beneficial effect was due to confounding [42].

While residual confounding of the alcohol and cancer associations may reduce or increase the magnitude of the

harmful effect, residual confounding of the CVD association is plausibly responsible for the whole of the observed protective effect [42], and particularly in combination with the bias caused by misclassification of former drinkers as abstainers [39].

CONCLUSIONS

There is strong evidence that alcohol causes cancer at seven sites, and probably others. The measured associations exhibit gradients of effect that are biologically plausible, and there is some evidence of reversibility of risk in laryngeal, pharyngeal and liver cancers when consumption ceases. The limitations of cohort studies mean that the true effects may be somewhat weaker or stronger than estimated currently, but unlikely to be qualitatively different (e.g. to not exist or to be J-shaped).

Ongoing research will elucidate mechanisms more clearly and increase confidence in the epidemiology. At the same time there will be orchestrated attempts to discredit the science and the researchers, and to confuse the public. The stakes are high for alcohol industries when there is no argument, on current evidence, for a safe level of drinking with respect to cancer. Promotion of health benefits from drinking at moderate levels is seen increasingly as disingenuous or irrelevant in comparison to the increase in risk of a range of cancers. Breast cancer poses a particular challenge for the industries’ marketing efforts, being a leading cause of cancer death in women with an identified causal factor that is amenable to change. It has also had a high profile with the public as a tragic, mutilating, blameless condition, a reputation which is due largely to large-scale emotive fund-raising campaigns.

Recent active discussion of cancer risk, along with increasing attention to fetal alcohol spectrum disorder, provides more support for population-level control of alcohol consumption, weakening the industry arguments that making better individual choices is the answer. However, the large multi-national alcohol corporations have virtually unlimited resources available to tackle commercial threats, and cannot be expected to step back from this challenge.

Some individualized approaches to prevention and treatment may depend upon more detailed understanding of the mechanisms by which alcohol causes cancer, but population approaches to reducing incidence and mortality from cancer caused by alcohol are clear enough and are consistent with strategies to reduce other forms of alcohol-related harm [43].

From a public health perspective, alcohol is estimated to have caused approximately half a million deaths from cancer in 2012; 5.8% of cancer deaths world-wide [21]. The highest risks are associated with the heaviest drinking, but a considerable burden is experienced by drinkers with

low to moderate consumption, due to the distribution of drinking in the population [44]. Thus, population-wide reduction in alcohol consumption will have an important effect on the incidence of these conditions, while targeting the heaviest drinkers alone has limited potential.

Declaration of interests

None.

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