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Keywords Alcohol, cancer, causation, health professionals, physicians, public health.

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ALCOHOL'S CONTRIBUTION TO CANCER IS UNDERESTIMATED FOR EXACTLY THE SAME REASON THAT ITS CONTRIBUTION TO CARDIOPROTECTION IS OVERESTIMATED

Connor discusses whether it is consistent to doubt epidemiological studies that low-dose alcohol is cardioprotective while accepting similar evidence that it also causes cancer. We show that misclassification of former and occasional drinkers as abstainers is widespread in alcohol epidemiology. This practice leads to a systematic underestimation of health risks from drinking (e.g. for cancer) and overestimation of health benefits. Correction of this problem in future studies should lead to significantly larger estimates of alcohol's contribution to chronic disease.

We greatly appreciate Dr Connor's thoughtful analysis of the evidence that alcohol consumption can be considered a cause of cancer and not just a possible link or association [1]. She illustrates well how proposed causal associations can, through induction, stimulate new research questions that may help to refute or confirm a causal hypothesis. For example, many observational studies indicate a dose–response relationship between level of prior alcohol consumption and subsequent risk of different cancers. Conversely, there is evidence that cutting down on drinking or abstaining is associated later with a significantly reduced risk of these same cancers. In the same vein, we would add that confirmation of the main causal pathway for cancers of the digestive system via exposure to the alcohol metabolite acetaldehyde [2] has also been provided by genetic studies. These have shown that population subgroups with a genetic propensity to experience a build-up

of acetaldehyde after drinking have a higher risk of such cancers [3].

Connor also addresses a criticism that it may be seen as inconsistent to doubt studies pointing to protection against cardiovascular disease (CVD), while accepting evidence from similar studies as the basis for alcohol causing cancer. Methodological problems with these studies have been highlighted in recent years as a basis for being sceptical of the hypothesis that moderate alcohol use reduces cardiac risk [4–7]. How can the same types of studies be considered dubious for one outcome (CVD) but acceptable for another (cancer)? We would like to add to her discussion of the significance of former and occasional drinker biases in this literature and highlight how they can cause both overestimation of cardioprotection and underestimation of cancer risks across the whole drinking continuum. The underlying theory here is that, as a population ages, a selection bias operates whereby individuals with poorer health are more likely to cut down or stop drinking completely [4]. Such individuals are often still classified as 'abstainers' and used as a reference against which all current drinkers are compared. In simple terms, they make drinkers at all levels of consumption 'look good' by comparison. This, in turn, results in both the appearance of protection at low levels of drinking and reduced risk at higher levels (assuming an underlying dose–response risk relationship applies). It is worth noting that the misclassification of former and occasional drinkers as abstainers is virtually the norm in alcohol epidemiology. In a new meta-analysis on alcohol and prostate cancer, we found that 21 of 27 included studies contained abstainer bias [8]. In a recent meta-analysis of alcohol and all-cause mortality, we reported abstainer biases in 74 of 87 studies [5].

It is thus entirely consistent to be sceptical about cardioprotection at low levels of alcohol intake while accepting evidence of a dose–response risk for cancer from the same or similar studies. What is often not spelt out, however, is how these prevalent biases lead to a substantial underestimation of alcohol's contribution to premature mortality generally, including that from cancer. It is also often overlooked that J-shape (= protective) risk relationships are not specific to CVD, but have been observed for many implausible conditions such as deafness, the common cold, hip fractures, some cancers and even liver cirrhosis [7]. In a recent meta-analysis of alcohol and prostate cancer, we reported a nearly threefold increase in risk for low-volume drinkers when studies with former drinker bias were eliminated: the risk increased from 8% when all studies were included to 23% when only bias-free studies were retained [8].

For the first time, the latest estimates of the global burden of disease from alcohol [9] factor in an increased risk of alcohol-caused mortality among former drinkers [10]. However, there is still no account of the residual underestimation among all current drinkers. The result of correcting for this underestimation is likely to be a substantial increase in the proportion of cancers attributable to alcohol consumption. It is clear that a new generation of alcohol epidemiological studies are required which avoid misclassifying former and occasional drinkers as abstainers and, further, risk estimates based on past meta-analyses need to be adjusted upwards to correct for these past errors. Along with increased understanding of biological pathways, revised estimates of the scale of alcohol's contribution to cancer may eventually cause a seismic shift in cultural attitudes to drinking.

Declaration of interests

T.S. is a recipient of research funds through the University of Victoria from Sweden's government retail alcohol monopoly for a study on the public health consequences of government controls.

Keywords Alcohol, cancer, cardiovascular disease, chronic disease, former drinkers, misclassification error.

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ALCOHOL AND CANCER—INDIVIDUAL RISK FACTORS

The risk of developing certain types of cancer associated with chronic alcohol consumption is modified by individual factors which vary inter-individually and consist, among other things, of genetics, gender, life-style factors (smoking, nutrition), simultaneous exposure to certain xenobiotics and pre-existing diseases.

Connor's paper [1] reviews the available epidemiological data on alcohol and cancer and reports an increased risk for the upper aero digestive tract (UADT), the liver, the colon, the rectum and the breast. Although there is no doubt about this association, individual-level moderators of the risk for a carcinogenic effect from alcohol also have to be considered, besides the daily amount of alcohol consumed chronically.

Among these factors, genetic predisposition is probably the most important one. As acetaldehyde is a carcinogen its accumulation is a risk factor for cancer, especially in the UADT [2]. Its accumulation is due either to a reduced degradation of acetaldehyde or to an increased production [2]. The enzymes involved in this process are acetaldehyde dehydrogenase (ALDH) and alcohol dehydrogenase (ADH), and the genes which code for these enzymes are polymorphic. Fifty per cent of Asians reveal a mutation in the ALDH2 gene, leading to insufficient enzyme activity which results in the accumulation of acetaldehyde. These individuals exhibit an increased risk for UADT cancer, especially of the oesophagus [3], but also for colon cancer [3]. Landmark studies from Japan have identified ALDH2*1/2 heterozygotes who consume alcohol as a high-risk group for developing UADT cancer, in particular oesophageal cancer [3]. The relative risk (RR) for oesophageal cancer in this high-risk group compared with ALDH2*1 homozygotes was reported to be 10–15 times higher, and the RR for multiple oesophageal carcinomas in one study was found to be as much as 54 times higher [3].

In addition, ADH1C is polymorphic [2]. ADH1C*1 increases ethanol metabolism by approximately 2.5 times compared with ADH1C*2. Although studies on the effect of ADH1C polymorphism on UADT cancer in Caucasians have shown contradictory results [2], studies in which alcohol was consumed at high enough levels to produce sufficient acetaldehyde have shown an increased risk for cancer at various sites, including the UADT [4–6], the colon, the rectum [7] and the breast [8]. Thus, for the colon and the rectum the threshold level for an increased cancer risk in individuals with ADH1C*1 homozygosity was found to be more than 30 g of ethanol per day [7].

As well as the tissues associated with oxidation of ethanol to acetaldehyde, bacteria are also capable of oxidizing ethanol to acetaldehyde [9]. This is true for bacteria present in the oral cavity [10], in the stomach [11] and in the large intestine [12]. Some of these bacteria, including *Helicobacter pylori*, may contribute to alcohol-associated cancer risk due to their capability to produce acetaldehyde from ethanol [11].

Another most striking factor with a synergistic effect on the alcohol-mediated cancer risk is smoking. For example, one bottle of wine per day increases the RR of oesophageal cancer by a factor of 18, while smoking 20 cigarettes per day increases the RR by a factor of five compared to non-drinkers and non-smokers; however, both factors together act synergistically, resulting in an increased RR of 44 [13].

It is also noteworthy that the combination of alcohol and vitamin A increases cancer risk, as ethanol induces cytochrome P-4502E1 (CYP2E1), which results in an enhanced degradation of retinol and retinoic acid regulating cell regeneration and cell differentiation [14]. Supplementation of vitamin A is dangerous, because the products of its degradation via CYP2E1 are highly apoptotic (i.e. they lead to cell death) [15]. Finally, pre-existing disease which, by itself, may lead to cancer, is especially associated with an additional cancer risk in the presence of chronic alcohol consumption. This is true for gastroesophageal reflux leading to cancer of the cardia, as ethanol stimulates acid secretion and gastroesophageal reflux. Another most important condition is cirrhosis of the liver. It is important to emphasize that alcohol is not only a risk factor for hepatic cirrhosis and hepatocellular cancer (HCC), but also modifies cirrhosis and HCC risk in patients with other causes of liver disease, such as hepatitis B and C, hereditary haemochromatosis and non-alcoholic fatty liver disease (NAFLD) [16]. Finally, female gender is also a risk factor for the development of alcoholic liver disease. Women are more susceptible to the toxic effect of ethanol compared to men, and this is especially true for the liver [17]. In summary, chronic alcohol consumption is an important risk factor for cancer of the UADT (mouth, pharynx, larynx, oesophagus), for the liver, the colon, the rectum and the breast. As more alcohol is consumed the risk becomes greater. However, individual factors modify

