American Journal of Epidemiology

Vol. 150, No. 11
Printed in U.S.A.

Invited Commentary: More Evidence of Increased Risks of Cancer among Alcohol Drinkers

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The report by Schlecht et al. (1) in this issue of the *Journal* from a case-control study in Brazil provides further confirmation of the adverse effects of alcohol and tobacco consumption on oral, pharyngeal, and laryngeal cancer. The data add to consistent epidemiologic evidence from around the world that clearly document that drinking alcoholic beverages, especially in large amounts, conveys an increase in risk of upper aerodigestive tract (UADT) cancer (2–4). The view that alcoholic beverages can be considered as a known human carcinogen is not universally shared, however, as witnessed by a split vote on this issue late in 1998 by the National Toxicology Program's Board of Scientific Counselors Report on Carcinogens (5).

The relatively large size of the study (over 2,000 participants) in Brazil enabled Schlecht et al. to assess the risks of drinking among nonsmokers. The impact of drinking alcoholic beverages in nonsmokers, and of smoking in nondrinkers, has been difficult to evaluate in most studies because of the strong correlation of the two habits. Most smokers also drink, and until recently most drinkers (especially heavy drinkers) have also smoked cigarettes or other forms of tobacco, hindering the disentanglement of effects of alcohol and tobacco. The correlation between smoking and drinking was found in Brazil, but sufficient numbers of cases and controls who were heavy users of one but not the other substance existed. Rising trends in odds ratios for UADT cancer could then be seen with increasing intake of each of alcoholic beverages and cigarettes in non/light users of the other. Hence, this study bolsters the worldwide science base which shows an adverse effect of alcohol independent of tobacco (6).

The authors also examined the potential for interactive effects from joint exposure to both alcohol and tobacco. They compared odds ratios from logistic regression models with only terms for the main effects of drinking and smoking with similar models with the main effects plus alcohol-tobacco cross-product terms. The former models assume that the relative risks from joint exposure can be obtained by multiplication of the relative risks for each factor, while the latter allow (and measure) non-constancy of the relative risks of one substance across differing levels of the other (7). For oral and laryngeal cancer, the two models yielded very similar odds ratio estimates for each of the alcohol-smoking cross-classifications. For pharyngeal cancer, the pattern was less clear, and the authors stated that there was a supramultiplicative effect between alcohol and tobacco when smoking was at moderate levels, but a submultiplicative effect between alcohol and tobacco when smoking was at heavy levels. This interpretation seems a bit tortured, however, especially since the numbers of subjects with heavy intake of one substance but light intake of the other was small (there were at most four cases in four of the nine alcohol-tobacco cross-classification cells). An as plausible or more plausible interpretation would be that the observed fluctuations in risk estimates for pharyngeal cancer are related to the inherent instability of odds ratios estimated from sparse data, rather than to a complex biologic phenomenon requiring contrasting effects on this cancer between moderate and heavy smokers.

The simplest summarization of the Brazilian data is that risks of each of oral, pharyngeal, and laryngeal cancer increase with increasing intake of alcoholic beverages in approximately the same fashion across all levels of tobacco intake, with about a three- to fourfold increase in risk among heavy compared with non/light drinkers in this population. The data thus indicate that both alcohol and tobacco can increase risk of these cancers in the absence of the other, with risks from combined exposure tending to be simple multiples of risks from each product separately.

The reluctance by some scientists to conclude that the drinking of alcoholic beverages per se increases cancer risk seems to arise primarily because alcohol has generally not induced tumors in studies of experimental animals, although in some animal models ethanol enhanced the effects of known carcinogens

Received for publication May 19, 1999, and accepted for publication May 26, 1999.

Abbreviations: ADH, alcohol dehydrogenase; UADT, upper aerodigestive tract.

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(2). The findings from Brazil should help allay any lingering doubts that alcohol consumption is a cancer risk factor, and a relatively strong one when consumption levels are high, at least for UADT cancers. The strength of the association in Brazil and elsewhere is noteworthy. Indeed, in the largest study to date, risk of oral and pharyngeal cancer was more than 35 times higher among US consumers of >4 drinks and ≥2 packs of cigarettes per day than among abstainers of both tobacco and alcohol (8).

To be considered a human carcinogen, a substance need be shown to increase risk of only one type of cancer in people. Alcoholic beverages exceed this requirement, substantially increasing risks for oral, pharyngeal, esophageal, and laryngeal cancers (2–4). Their role in most other types of cancer appears to be minimal, although drinking has been implicated in small to moderate elevations in risks of liver and breast cancers, and some reports have noted higher risks of colorectal and lung cancers among drinkers, but these latter findings are inconsistent and etiologic associations are not established (2–4). The situation for breast cancer, the most common cancer among women in the United States, is becoming clearer. Evidence has accumulated over the past decade from observational case-control and cohort studies demonstrating a low-level but consistent elevation in risk among even moderate (1–2 drinks per day) alcohol consumers compared with abstainers (3, 4, 9).

The totality of epidemiologic evidence indicates that the drinking of alcoholic beverages leads to an increase in risk in cancer, with the relative increase associated with heavy drinking being sizeable for UADT cancers. The mechanism(s) by which alcoholic beverages induce cancer are not clear. The lack of a parallel effect in bioassays in experimental animals has largely precluded laboratory clues to potential mechanisms for alcohol-induced cancer, but several causal pathways described below seem plausible.

One of the most likely explanations is that alcohol and/or its metabolites are human carcinogens, despite the lack of clear positive findings regarding carcinogenicity of ethanol in rats and other experimental animals. Although the study in Brazil did not report results by type of alcoholic beverage, other authors have noted elevated UADT cancer risks for all types of alcoholic beverages, from beer to wine to distilled spirits, all of which have ethanol as the common ingredient (2–4). The level of risk sometimes varies by type of beverage, but some excess is repeatedly seen. While ethanol exposure is common, an exposure that may be as relevant is that to acetaldehyde, the major intermediate metabolite of ethanol. Levels of human exposure to acetaldehyde are not well documented, and exposures may be short lived, but acetaldehyde is recognized as a known carcinogen in experimental animals (10).

Ethanol is oxidized to acetaldehyde mainly by alcohol dehydrogenase (ADH), and to a lesser extent by liver enzymes, namely CYP IIE1 (11). There are several ADH subtypes, one of which, ADH_3, is polymorphic in whites and influences the rapidity with which ethanol is metabolized to acetaldehyde. A recent study in Puerto Rico (11) revealed that persons with fast-metabolizing ADH_3 genes may be at proportionally greater risk of alcohol-related oral and pharyngeal cancer, especially from heavy drinking, than persons with slower-metabolizing ADH_3 genotypes. Only the minority of the tumors were related to fast metabolic status, but the findings are consistent with an etiologic role for acetaldehyde.

Besides ethanol, alcoholic beverages may contain congeners and other substances which are carcinogenic. Various agents, including asbestos filtration products, tannins, N-nitroso compounds, urethan, arsenic pesticide residues, and other substances which may be carcinogenic, have been found in some alcoholic beverages (2–4).

Alcohol drinking may influence cancer risk through its solvent action, perhaps in this way enhancing the effects of tobacco or other carcinogens. The highest alcohol-related risks tend to occur for tissues that come in direct contact with alcohol, namely the mouth, throat, esophagus, and extrinsic larynx (2–4). The study by Schlecht et al. indicates a stronger effect of alcohol for the extrinsic than intrinsic larynx, providing further data in support of this notion. However, a non-topical, systemic effect is also likely, since alcohol intake, particularly heavy consumption, may through its effect on the liver and hepatic enzyme systems reduce the detoxification of carcinogenic substances and/or catalyze the metabolic activation of certain compounds into carcinogens (2–4). Ethanol, for example, influences liver enzymes involved in the metabolism of tobacco-specific nitrosamines, some of which are potent carcinogens in experimental animals and may play a role in the enhanced effects of tobacco among drinkers (12).

Alcohol drinking may increase exposure to cellular oxidants increasing the risk of DNA damage and influencing the formation or inactivation of carcinogens in specific tissues, including those in the mouth and throat. Conversion of ethanol to acetaldehyde occurs not only in the liver but also in local tissues, especially in the digestive tract, although differences in acetaldehyde levels in various organs among drinkers have not been well quantified (11).

The link between alcohol drinking and breast cancer raises the possibility that alcohol may influence the level, function, and metabolism of hormones. Increased levels of total as well as bioavailable estrogens have been found in a small trial among premenopausal women who ingested moderate amounts of alcohol (13). A possible role for alcohol as a folate antagonist was recently suggested by a large cohort study of US nurses (14), in which the increased incidence of breast cancer among alcohol drinkers was nearly eliminated among women with high dietary folate status.

Additionally, alcohol consumption, particularly high intakes, can result in lowered intake and bioavailability of a variety of essential nutrients. Dietary factors have been implicated in oral, pharyngeal, and laryngeal cancer, with nearly doubled risks among those with the lowest intakes of fruits and vegetables and various accompanying nutrients (15). Occasionally, the lowered intake among heavy drinkers may lead to alterations in epithelial cell chemistry and induce methyl deficiencies which in experimental animals can cause liver tumors (16).

While the data presented by Schlecht et al. do not directly address the mechanistic considerations listed above, the findings clearly indicate that alcohol intake, especially at high levels, is a strong risk factor for UADT cancer with or without concomitant tobacco exposure. Such information needs be kept in mind and balanced against reports of the potential beneficial effects of moderate alcohol intake with respect to cardiovascular disease and total mortality (overall mortality in most populations appears related to alcohol consumption in a U-shaped fashion, with reduced risks among moderate and elevated risks among heavy drinkers (17)). While the mechanisms of action of alcohol-related risks and benefits await clarification, the net public health message still remains that high daily alcohol intake can adversely affect health and that moderation in consumption continues to be prudent.

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