Research and Prevention Priorities for Alcohol Carcinogenesis

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Research conducted during the last four decades has established that consumption of alcoholic beverages causes cancer. Etiologic research questions that remain relate to questions that remain concerning concentrations of alcohol, the mechanism(s) of action, including possible interactions with other agents such as tobacco smoke. Prevention priorities for alcohol-related cancer depend on whether alcohol causes only the upper aerodigestive cancers or whether it also causes breast and possibly colon cancers. If alcohol causes aerodigestive cancers only, existing prevention programs to prevent alcohol abuse by heavy drinkers are sufficient. The possible small cancer risk faced by moderate drinkers may be more than offset by a decrease in the risk of cardiovascular death. On the other hand, if alcohol consumption increases the occurrence of breast cancer, a prevention program aimed at women who are at high risk for breast cancer is worth considering, but the risks must be weighed against the cardiovascular benefits for moderate drinkers. — Environ Health Perspect 103(Suppl 8):161–163 (1995)

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Priorities for Future Etiologic Research

Research conducted during the last four decades has established beyond any question that consumption of alcoholic beverages causes cancer (1). What remains unsettled are more specific questions concerning details of the causal relationship. These questions relate to increases in risk at specific sites, the effects of various types of alcoholic beverages, the effects of various concentrations of alcohol, and the mechanisms or mechanisms of action, including possible interactions with other agents such as tobacco smoke.

Relation between Alcoholic Beverages and Specific Sites

As the first research priority, let us consider the relation between alcoholic beverages and specific sites. The consumption of alcoholic beverages inarguably increases the risk for cancer of the oral cavity, pharynx, larynx, and esophagus. Heavy consumption of alcoholic beverages is a major risk factor for these sites, multiplying the risk severalfold on average. The relation between alcoholic beverage consumption and other sites such as the breast, colon, and rectum is still uncertain, however.

The frequency of breast cancer among U.S. women is such that even a moderate relative increase in the rate would be a major public health concern. During the past several years evidence has mounted that breast cancer is, indeed, associated with the consumption of alcoholic beverages. Two important reservations have made some scientists reluctant to attribute a causal role to alcohol. First, the association is comparatively weak; second, concern has been raised that the weak association is the result of yet unidentified confounding factors. While these reservations must be taken seriously, they in turn can be criticized. First, the low strength of the association may be to some extent a consequence of the high incidence of breast cancer—it is not unusual for relative risks to be higher for rare diseases than for common diseases. Second, the argument that unknown confounding factors account for an association is irrefutable in principle and not specific enough to be helpful to researchers.

Still, the evidence for an effect of alcohol on breast cancer is not in the same category as that for head and neck cancers, for which there is no study showing an inverse association and few showing anything but a strong association. Were the evidence for a causal relation clear cut, an effect of alcohol on breast cancer risk would be important enough by itself to shape the overall public health policy about prevention of alcohol-related cancers. Consequently, a high priority for etiologic research should be to settle the question of the carcinogenicity of alcoholic beverages for female breast cancer.

Colorectal cancer is also common, and the evidence regarding a relation between alcoholic beverages and colorectal cancer is also inconclusive. As for breast cancer, etiologic research regarding alcohol and colorectal cancer is challenged by the possibility that other components of the diet confound the observed relation. This cancer site affects both sexes and a relation with alcohol would have important public health consequences. For this reason, the conflicting evidence about alcohol and colorectal cancer should be clarified as another research priority.

Mechanism(s) of Action

Next, we turn to mechanisms of action. The clear and strong relation between alcoholic beverage consumption and cancers of the upper aerodigestive tract prompts the straightforward hypothesis that the biological action of alcohol on squamous cell epithelium is a direct topical effect on the epithelium. It appears that the epithelial tissues that come into direct contact with the ingested alcohol are the most susceptible to its effect. A topical action for alcohol is also consistent with the site distribution within the oropharynx and larynx, and with studies showing an effect on oropharyngeal cancer risk from mouthwash,
which contains alcohol but is not ingested. A topical mechanism of action could also explain possible interactive effects of alcohol consumption and smoking. Tobacco smoke also appears to have a topical mechanism of action for the upper airway sites of cancer, and thus the interaction between tobacco smoke and alcohol consumption that has been observed in some studies is consistent with a topical effect for both agents. Despite the plausibility of the topical hypothesis, however, alternative mechanisms of action are possible, even for aerodigestive sites (2). Indeed, an effect of alcohol on breast cancer, for example, would have to involve a systemic explanation. Although hypotheses about mechanisms for an alcohol effect on breast cancer abound, they are mostly unobstructed by useful data. One promising lead might be the apparently stronger relation between alcohol and breast cancer occurrence among premenopausal women.

In the past, the question of whether alcoholic beverages are carcinogenic in the absence of tobacco smoke has been debated. Current evidence indicates, however, that other sources of carcinogens from combustion products, outside of direct smoking, are prevalent enough in air and food to allow the same mechanisms that operate in smokers to cause cancer in nonsmokers, albeit at a lower level of risk. The biologic detail of these mechanisms has yet to be elucidated.

**Carcinogenicity of Specific Beverages**

If the mechanism of action for most alcohol-caused cancers is topical, it is a reasonable hypothesis that the concentration of alcohol in the ingested beverage would be an important risk factor independent of the total amount of alcohol consumed. The concentration of alcohol, indeed, appears to be an important determinant of the risk reported from the use of alcohol-containing mouthwashes. If that effect is real, we should expect a comparable effect for different types of alcoholic beverages, with undiluted spirits conveying a stronger risk than mixed drinks, wine, or beer.

Some studies indicate a greater-than-additive effect of tobacco smoke and alcoholic beverages for risk of oropharyngeal cancer. Few studies have evaluated the carcinogenicity of dark liquors such as Scotch whisky or bourbon in which the beverage comes prepackaged with its own smoke. If carcinogenicity is dependent on nonalcohol components of alcoholic beverages, there will be important implications both for understanding mechanisms of action and for being able to educate people about risks.

**Dose Effects**

As a final research priority, I consider dose effects. The large American Cancer Society cohort study report of Boffetta and Garfinkel (3) showed a J-shaped relationship between alcohol and cancer risk, with those drinking one drink a day a lower risk than abstainers (Figure 1). The main criticism of such findings has been that included among nondrinkers are formerly heavy drinkers who have forsworn alcohol consumption because of its effect on their health, thus artificially raising their rate above that of moderate drinkers. In the study by Boffeta and Garfinkel, however, subjects were followed for up to 12 years, and the results, at least for cardiovascular disease, remained the same if the analysis omitted the first 6 years of follow-up. These data refute the criticism that the J-shape is caused by the inclusion of diseased subjects among nondrinkers.

No mechanism yet proposed for alcohol-caused cancer would readily account for a J-shaped curve between alcohol and cancer. Nevertheless, the Boffeta and Garfinkel results clearly show such a relationship. A threshold effect for alcohol would be easier to understand. Most studies of head and neck cancers show steadily increasing rates with any increase in the amount of alcohol consumed, but confounding by tobacco smoke is a serious concern in these studies; the correlation between the two exposures is strong and the effect of tobacco smoke on head and neck cancers is at least as strong as that of alcohol. It is of the greatest practical importance to settle the issue of how much increase or decrease in overall cancer risk results from moderate drinking—up to one or two drinks per day. This level of alcohol consumption is convincingly protective of cardiovascular disease, and, therefore, it is important to be able to assess the extent to which moderate drinkers are trading one risk for another.

**Prevention Priorities**

In considering priorities for prevention I emphasize some caveats that must be taken into account before a defensible prevention strategy can be formulated. Alcoholic beverage consumption unquestionably is a cause of cancer of the oral cavity, pharynx, larynx, and esophagus. The evidence is much less certain for two much more common sites—breast and colorectal cancers. Prevention priorities for alcohol-related cancer depend on whether alcohol causes only the upper aerodigestive cancers or whether it also causes breast and possibly colon cancers.

If we assume that alcohol is a cause of aerodigestive cancers only, it can be reasonably argued that no prevention program directed at alcohol-caused cancer is needed. The reason is that alcohol abuse brings with it other serious health and social consequences that outweigh as a public health problem the increase in risk for aerodigestive cancers. Concern for these problems already motivates educational and other intervention campaigns to prevent or mitigate alcohol abuse. Those who drink moderately may also face a small increase in risk for aerodigestive cancers, but if there is such an increase, it is relatively small and will be more than offset for most people by a decrease in the risk of cardiovascular death.

On the other hand, if alcohol consumption increases the occurrence of breast cancer, a prevention program targeted at women at high risk for breast cancer is worth considering. The prevention strategy would need to weigh the benefit of preventing breast cancers against the possibility that reduced consumption of alcohol might cause some additional morbidity and mortality from cardiovascular disease. Thus, women at high risk for cardiovascular disease who are moderate drinkers might be better off continuing their consumption than curtailing it. Women at comparatively low risk for cardiovascular disease and high risk for breast cancer might be better off curtailing their consumption.

In summary, the advisability of preventing alcohol-related cancers is difficult to judge because it depends on whether breast cancers (and colon cancers) are also
caused by alcohol consumption. For men, it is doubtful that there would be a net decrease in mortality if moderate drinkers reduced their intake of alcohol. For women, expert advice will vary according to each expert's views of the scientific evidence. This situation will surely change as more data become available. Until then, a public health program that educates women about the risks and benefits of decreasing their alcohol intake based on current knowledge is always defensible.

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