

Alcohol, Cardiovascular Disease, and Cancer: Treat With Caution

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For 40 days and 40 nights, Noah, his wife, his three sons and their wives, and myriads of animal pairs remained safe in their Ark while massive flooding destroyed the rest of the world. After several more weeks, the Ark settled on dry land, and Noah and his family emerged. What was among Noah's first acts upon leaving the Ark? He "drank of the wine and became drunk," and his sons had to protect him from embarrassment (1). Thus, the book of *Genesis* reports one of the first episodes demonstrating the dangers of alcohol.

Alcoholic beverages have been with us throughout the human history. During the last century, ill-advised efforts were made to eliminate its dangers by passing a constitutional amendment prohibiting its manufacture, sale, and distribution. As is well known, this created a social disaster and was later repealed. Beyond its social dangers, many of alcohol's medical dangers are well known and have been known for a long time, including acute intoxication; chronic destructive addiction; cirrhosis of the liver; dilated cardiomyopathy; fetal alcohol syndrome; and increased risks for hypertension, stroke, cardiac arrhythmias, and fatal motor vehicle accidents.

Over the past 20–30 years, the medical position on alcohol has become somewhat more nuanced. Investigations of large-scale observational cohorts have suggested that light to moderate drinking may be associated with decreased mortality rates and with decreased risk of cardiovascular disease (2). Some studies (3), but not all (4,5), have suggested that wine may provide additional benefits over and above the effects of alcohol, perhaps because of antioxidant or other types of effects of non-alcohol grape chemicals like resveratrol (6). Some investigators have been so intrigued by the possible benefits of low-dose alcohol that they have gone so far as to consider mechanisms by which alcohol can have salutary cardiovascular effects (4). These include increased levels of high-density lipoprotein cholesterol and a decreased tendency to thrombosis. Combining these reported biological benefits with epidemiological findings, some medical organizations have stated that low levels of alcohol consumption maybe considered safe (7) or may be a legitimate "item of discussion between physician and patient" (8).

In this issue of the Journal, Allen et al. (9) present fascinating findings that should give us pause. Allen et al. have systematically surveyed more than 1 million women who between 1996 and 2001 attended breast cancer screening clinics in the United Kingdom. They found that after 7 years of follow-up, even light to moderate levels of alcohol consumption were predictive of an increased risk of several common cancers, including those of the breast, rectum, liver, esophagus, and oropharynx. Taking into account the prevalence of alcohol consumption and its observed relative risks, the authors estimated that about 13% of cancers of the breast, aerodigestive tract, liver, and rectum could be attributed to alcohol.

Because of an enormous sample size, systematic survey methodology, and an ability to capture nearly all incident diagnoses of cancer, the authors could make a number of important, heretofore unappreciated, discoveries. Previous investigations have focused on the association between alcohol and mortality (5), including mortality due to cancer, but have not been able to so carefully assess the association of alcohol intake with the subsequent diagnosis of cancer. Allen et al. could estimate the association of different levels of alcohol intake with many different kinds of cancer. Perhaps more importantly, they could evaluate key interactions for specific cancer types; for example, they demonstrated that alcohol use was strongly predictive of cancer of the upper aerodigestive tract but only in current smokers. From a standpoint of cancer risk, the message of this report could not be clearer. There is no level of alcohol consumption that can be considered safe.

How are we to interpret the findings of Allen et al. given previous investigations suggesting that alcohol may be safe or even beneficial when taken in relatively low doses (2,4)? Despite their study's many strengths, there are some important limitations that must be considered. The study was limited to women who were seen in breast cancer screening clinics; there is evidence that these women may be different in some respects from those of the general population (10). Nearly all the baseline clinical data were based on answers to a questionnaire, not direct measurement; this might be considered an acceptable sacrifice given the study's enormous sample size. This is also a limitation inherent to essentially all epidemiological investigations of alcohol use; it is doubtful that a systematic bias exists whereby women who are destined to develop cancer will misclassify their alcohol intake. Finally, the authors provide no information on all-cause mortality or incident cardiovascular disease events, despite the ability of their data to provide this information. We must hope that the authors plan to report on these outcomes in future publications.

Despite these limitations, the message from this report takes on a greater sense of urgency when considering the limitations of the many investigations suggesting beneficial cardiovascular effects of alcohol. Some have suggested that there is no real cardioprotective

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effect of alcohol (11–13). Epidemiological investigations are severely limited by failure to account for a number of important confounders, including socioeconomic status, social networks, mental health, reverse causality, and healthy cohort effects (11–13). The supposedly beneficial effects of alcohol seen in epidemiological studies may parallel the experience with hormone replacement therapy, where a number of observational reports suggested benefit, but definitive clinical trials showed harm (11). A major difference, however, is that a randomized trial of low-dose alcohol cannot happen.

Even if there are modest beneficial cardiovascular effects of alcohol, the current report of Allen et al. should remind us that we must consider these within a broader public health context. The current report, as well as a number of previous investigations, focused on middle-aged women. Among women, the major cause of death by far during the middle years is cancer (14). Although it is true that cardiovascular disease is the leading cause of death among women overall, this primarily applies to women older than 75 years. It might be reasonable to suspect that many women in the lay public who are asking physicians about any possible safe effects of alcohol are middle aged; for this large group, the only reasonable recommendation we can make is that there is no clear evidence that alcohol has medical benefits.

Still, when we think about the story of alcohol, we are left with complexities. Yes, the first recorded episode of alcohol use in *Genesis* was not a pretty one, but later in *Genesis*, we are told of two prisoners who appeared before Joseph for interpretation of their dreams. One prisoner, a baker, was executed, but the other, the keeper of the king's wines, was saved (15). Despite its attractions, alcohol has been the proximate cause of a great deal of human misery, now with additional documentation by the elegant report of Allen et al. Perhaps the complex story of alcohol can be best summed up by what the great professor Albus Dumbledore said about truth in one of his conversations with his student Harry Potter: "It is a beautiful and terrible thing, and should therefore be treated with great caution" (16).

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