

Alcohol and Cancer: Drink at Your Own Risk

Laura A. Stokowski, RN, MS | November 23, 2015

A Palatable Carcinogen

Fine wines, craft beers, cocktails, and champagne made by French monks are considered by many as complements to good company and fine cuisine. The last thing anyone wants to hear is that alcohol causes cancer.

However, the sobering truth is that alcohol consumption increases the risk for cancer, and this link has been known for some time. In 1988, the International Agency for Research on Cancer (IARC) declared that alcohol was a carcinogen.^[1] The World Cancer Report released in 2014 highlighted the role of alcohol in cancer, finding that alcohol accounts for 3.5% of cancers (about 1 in 30 cancer deaths) globally.^[2] Recent data indicate that the proportion of cancers attributable to alcohol worldwide has increased. In 2012, alcohol consumption caused 5.5% of all cases of cancer and 5.8% of all cancer deaths.^[3] This increase is believed to be attributable primarily to an increase in the prevalence of drinkers and in the amount of alcohol consumed, particularly by women.

The fact that alcohol is a carcinogen has been clearly confirmed.

Jürgen Rehm, PhD, Director of the Social and Epidemiological Research Department at the Centre for Addiction and Mental Health in Toronto, Ontario, Canada, describes how our knowledge about the role of alcohol in cancer has advanced during the past year. "Very simply, the cancers that have been determined previously to be caused by alcohol have been confirmed. There is no discussion about whether alcohol causes these cancers. The fact that alcohol is a carcinogen has been clearly confirmed."

The cancers that Dr Rehm refers to include those of the oral cavity, pharynx, larynx, esophagus, breast, colon, rectum, gallbladder, and liver.^[4] It is also considered probable that alcohol increases the risk for pancreas cancer, although the evidence is inconclusive.^[4]

Recent evidence suggests that melanoma, as well as cancers of the stomach, lung, and prostate, may be associated with alcohol consumption, although only with high levels of consumption and to a moderate excess risk.^[3] There are also differences of opinion on whether liver cancer should be considered an alcohol-related cancer and whether the risk for colorectal cancer is increased in both sexes or only in men.^[5]

Alcohol-Cancer Link: New Evidence

Several large cohort studies of the association between alcohol and cancer, published in the past year, shed more light on this link.

The increased risk for cancer appears to be significant at lower levels of alcohol consumption in women than in men.

In August of 2015, data were published from two large, prospective, ongoing cohort studies—the Nurses' Health Study and the Health Professionals Follow-up Study.^[6] During long-term follow-up (up to 30 years) of 88,084 women and 47,881 men, 19,269 and 7571 incident cancers were diagnosed, respectively (excluding nonadvanced prostate cancers). Alcohol consumption was significantly associated with increased risk for cancer, in both women ($P_{\text{trend}} < .001$) and men ($P_{\text{trend}} = .006$), with linear dose-response relations. The increased risk for cancer appears to be significant at lower levels of alcohol consumption in women than in men, and total alcohol consumption, rather than regularity of drinking or heavy episodic drinking, drove the association between alcohol consumption and risk for cancer.

In this same study,^[6] Cao and colleagues analyzed the risks for the so-called "alcohol-related cancers," (colorectum, female breast, oral cavity, pharynx, larynx, liver, and esophagus) and documented 9016 cases of these cancers in women and 1611 cases in men. For cancers with an established link to alcohol consumption, the

respective relative risks were 1.13 (confidence interval [CI], 1.06-1.20; $P_{\text{trend}} < .001$) for women and 1.26 (CI, 1.06-1.50; $P_{\text{trend}} = .004$) for men. The leading alcohol-related cancer in women was breast cancer, whereas it was colorectal cancer in men.

Of note, this study also examined cancer risk associated with alcohol intake and smoking, including those who had never smoked ("never smokers"). The risk for cancer, including alcohol-related cancers, was not elevated in men who had never smoked. In women, however, even in never smokers, the risk for alcohol-related cancers was increased because of the association of alcohol with breast cancer.

Dr Arthur Klatsky, from the Division of Research and Department of Cardiology at Northern California Kaiser Permanente, and colleagues^[7] conducted a cohort study of incident cancer risk relative to light-to-moderate and heavy drinking in a large, multiethnic population (n=124,193) of adults with no history of cancer who were members of a comprehensive prepaid health plan in the San Francisco Bay Area. The mean follow-up was 17.8 years, yielding an estimated 2,216,631 person-years of follow-up. They found that compared with lifelong abstinence, heavy drinking (≥ 3 drinks per day) was associated with increased risk for five cancer types: upper airway/digestive tract, lung, female breast, colorectal, and melanoma, with light-to-moderate drinking related to all but lung cancer.

No significantly increased risk was seen for 12 other cancer sites: stomach, pancreas, liver, brain, thyroid, kidney, bladder, prostate, ovary, uterine body, cervix, and hematologic system. These associations were largely independent of smoking, but among light-to-moderate drinkers, there was evidence of confounding by inferred underreporting. These investigators concluded that heavy alcohol drinking is related to increased risk for some cancer types but not others and that because of probable confounding, the role of light-to-moderate drinking remains unclear.

Bagnardi and colleagues^[8] conducted a meta-analysis of 572 studies (486,538 cancer cases) to investigate the effect of alcohol on 23 cancer types. Relative risks (RRs) for heavy drinkers compared with nondrinkers and occasional drinkers were 5.13 for oral and pharyngeal cancer, 4.95 for esophageal squamous cell carcinoma, 1.44 for colorectal cancer, 2.65 for laryngeal cancer, and 1.61 for breast cancer, showing a clear dose-risk relationship. Heavy drinkers also had a significantly higher risk for cancer of the stomach (RR, 1.21), liver (2.07), gallbladder (2.64), pancreas (1.19), and lung (1.15). There was indication of a positive association between alcohol consumption and risk for melanoma and prostate cancer. Alcohol consumption and risk for Hodgkin and non-Hodgkin lymphomas were inversely associated.

Alcohol consumption was significantly related to breast cancer risk; each 10-g/day increase in alcohol intake raised the hazard ratio by 4.2%.

Another recent study looked at breast cancer specifically.^[9] A dose-response relationship exists between alcohol and breast cancer in pre- and postmenopausal women. In an analysis of the European Prospective Investigation Into Cancer and Nutrition (EPIC), 334,850 women, aged 35-70 years at baseline, were recruited in 10 European countries and followed an average of 11 years. Alcohol intake at baseline and average lifetime alcohol intake were calculated from country-specific dietary and lifestyle questionnaires. During a total of 3,670,439 person-years, 11,576 incident breast cancer cases were diagnosed.

Alcohol consumption was significantly related to breast cancer risk; each 10-g/day increase in alcohol intake raised the hazard ratio by 4.2% (95% CI, 2.7%-5.8%). Compared with an alcohol intake of 0-5 g/day (up to one half drink), an alcohol intake of 6-15 g/day (0.5-1.5 drinks) was associated with a 5.9% increase in breast cancer risk (95% CI, 1%-11%). Risk was elevated for both hormone receptor-positive and hormone receptor-negative breast tumors and was stronger among women who started drinking before their first full-term pregnancy. The full complement of evidence to date is sufficient to conclude that alcohol is causally related to the development of breast cancer, both premenopausally and postmenopausally, and that the risk increases dose-dependently with no lower threshold.^[5]

How Does Alcohol Cause Cancer?

Ethanol and its first metabolite, acetaldehyde, are classified as "group 1 carcinogens" by the IARC, having attained the highest level of evidence for a carcinogenic effect in both humans and animals.^[5] But cancer is a heterogeneous disease, and the mechanisms by which different cancers are induced by alcohol vary. Ethanol

induces hepatocarcinogenesis by first causing cirrhosis of the liver, where conversion to acetaldehyde primarily occurs.^[10]

Ethanol also promotes the production of highly reactive oxygen species, generated predominantly by cytochrome P450 2E1, which have multiple mutagenic effects on DNA and can alter histone methylation and acetylation.^[11] Conversion to acetaldehyde in saliva, the first point of contact with ethanol, results in salivary acetaldehyde levels that are 10-100 times higher than in the blood; a factor in the development of upper aerodigestive tract cancers.^[10] And a reduction in retinoic acid levels sets the stage for cell proliferation, differentiation, and possibly malignant transformation. Ethanol also has hormonal effects, such as increasing estradiol levels, which may be a factor in the development of breast cancer,^[10] along with nonhormonal mechanisms.

Genetics certainly play a role in alcohol-related cancer risk. The amount of acetaldehyde present in various tissues following ethanol ingestion may not only depend on the amount of ethanol consumed but also on the genotype coding for ethanol-metabolizing enzymes. In carriers of alleles that influence the activity of alcohol dehydrogenase or aldehyde dehydrogenase, acetaldehyde levels following alcohol consumption can be elevated and prolonged, increasing the cancer risk.^[12]

How Much Alcohol Raises Cancer Risk?

A persistent question is: What constitutes safe consumption? Is there a definite, known level of alcohol consumption that is not associated with increased cancer risk? Unfortunately, given our current state of knowledge, this "safe zone"—if it exists—cannot be defined. Heavy alcohol consumption has been consistently linked with cancer, but less is known about the impact of light or moderate drinking on cancer risk.

Many studies have defined light, moderate, and heavy alcohol intake differently.

One difficulty in establishing guidelines about "safe alcohol intake" and cancer risk is that many studies have defined light, moderate, and heavy alcohol intake differently. Moreover, the alcohol content of a typical drink can vary from country to country. In the United States, a standard drink is defined as approximately 14 g of alcohol, regardless of beverage type.

Despite differences in standard drink size, all studies have made some attempt to classify drinkers according to typical daily consumption of alcohol. Definitions of "light-to-moderate" and "heavy" drinking are arbitrary as used in epidemiologic research. Typically, the ingestion of three (two for women) or more standard-sized drinks per day is termed "heavy" and fewer than three (two for women) standard-sized drinks daily is "light-to-moderate" drinking. And it has been consistently found that heavy drinking elevates the risk for certain cancers substantially.

The gray area, then, is with a light or light-to-moderate intake of alcohol. Do small quantities of alcohol (eg, a daily glass of wine, or even less) increase risk for cancer? Dr Rehm has no doubt that for breast cancer, the answer is "yes." A dose-response relationship exists between alcohol and breast cancer in both pre- and postmenopausal women.^[9] Each additional 10 g of pure alcohol ingested per day raises the risk by 2%-12%. "All of the major studies published recently show, clearly and consistently, that the more a woman drinks, the higher the risk for breast cancer. There is no lower threshold."

For other cancers, adds Dr Rehm, the relative risks associated with light-to-moderate intake are not as definitive. "Although it is clear that alcohol causes esophagus cancer, for example, there is some discussion about whether drinking a single glass of wine daily is linked to a statistically significant increase in risk for esophagus cancer."

Light-to-moderate drinking. Dr Klatsky questions the role of light or moderate drinking in the development of cancer because of the potential role of underreporting of alcohol intake in alcohol research.^[13] "Underreporting is a factor in all alcohol research because it is widely assumed that people report less drinking than they really do. Some of the individuals who report light or moderate drinking are actually heavy drinkers."

In their study, Klatsky and colleagues^[14] inferred underreporting of drinking habits by determining whether participants were likely to be underreporters on the basis of other health records indicating heavier alcohol intake (eg, an alcohol-related diagnosis or self-report of heavy drinking on a different questionnaire). Stratifying light-to-moderate drinkers by likelihood of underreporting revealed that the increased risk for cancer, in their study, was

concentrated in the stratum suspected of underreporting. Among persons reporting one to two drinks per day on the index examination but considered likely underreporters, the hazard ratio for any cancer was 1.4 (CI, 1.3-1.7, $P < .001$), whereas among those considered unlikely to be underreporters, it was 1.1 (CI, 0.9-1.2).

Dr Rehm argues that the effect of underreporting, if valid, applies only to cohort studies but not to the many case-control studies that also show relationships between alcohol and cancer. "In a cohort study, like the Nurses' Health Study, if you are a good, health-conscious nurse, you might indeed underreport your alcohol intake. But in a case-control study, when you are studying people who have just been diagnosed with breast cancer, for example, these women really scrutinize their lives, thinking back and trying to figure out why they got cancer. They are unlikely at that time to underreport their alcohol intake. We find the association between breast cancer and alcohol in both case-control and cohort studies, so it is unlikely that it is just an effect of underreporting."

The 'official line' from the IARC is that no lower threshold exists.

Much discussion has taken place among the scientific community on the issue of "safe" lower thresholds of alcohol intake, but the issue is not resolved for most cancers. However, Dr Rehm explains that the "official line" from the IARC is that no lower threshold exists. This view acknowledges, says Dr Rehm, that "some individual studies may not show increased cancer risk with small amounts of alcohol intake, but when combined into meta-analyses, the evidence does not support a lower limit of alcohol consumption." Indeed, "less is better" is becoming an increasingly common refrain.^[15]

Beverage type. Over the years, various alcoholic beverage types have been blamed for the increased incidence of certain cancers. At one time, Calvados (apple brandy) was blamed for a high rate of esophageal cancer,^[16] and beer was blamed for a high rate of rectal cancer in specific populations.^[17,18] Many of these associations were later disputed.

Recent studies have not provided strong evidence of an association between alcoholic beverage type and cancer. Cao and colleagues^[6] found the same risk with all beverage types, concluding that ethanol, but not other components of alcoholic beverages, was the culprit.

The Kaiser Permanente study found some small associations with different beverage types, but Dr Klatsky did not find them very convincing, believing that these differences were more likely related to the type of person who chooses a certain beverage than to the beverage itself. The effect of beverage choice is confounded by a healthier drinking pattern and more favorable risk traits in wine drinkers.^[7] He explains, "Most people tend to drink predominantly one type of alcoholic beverage—whether it's beer, wine, or spirits. The wine drinkers tend to be better educated and have better diets and healthier lifestyle habits. They get more medical care and are more affluent, so the outcomes are biased in favor of the wine drinkers. We found that wine drinkers were more likely to develop melanoma, but that may be because they go on more vacations and lay on the beach in the sun. We also found that beer drinkers get more breast cancer, but I suspect that women who drink a lot of beer don't have particularly favorable lifestyles in other respects. So I think that there is probably not much difference in type of beverage with respect to cancer risk."

If you are diagnosed today with cancer, it is likely that the alcohol exposure began at least 15-20 years ago.

Drinking patterns and duration. Both duration of drinking (in terms of years) and the age at which drinking started are important determinants of cancer risk. Taking one drink daily at age 25 years has no immediate health consequences. But, Dr Rehm explains, most people drink alcohol regularly throughout their adult lives. The more alcohol that is consumed, the higher the risk. "Cancer risk is a function of the overall level of tissue exposure to alcohol. If you are diagnosed today with cancer, it is likely that the alcohol exposure began at least 15-20 years ago."

With respect to patterns of drinking, most studies are not able to assess binge drinking behaviors, so the relationship between heavy, episodic alcohol consumption and cancer is not clear. However, it is believed that, with few exceptions, alcohol-related cancer is primarily caused by long-term heavy drinking rather than by only binge drinking.^[3]

The role of smoking. An interaction exists between alcohol consumption, tobacco, and cancer. In fact, evidence

suggests that the combined effect of alcohol and smoking on the incidence of head and neck cancer (oral cavity, pharynx, and larynx) is greater than multiplicative.^[19] This interaction is biologically plausible. Alcohol can act as a solvent for carcinogens in cigarette smoke and render the mucosa more permeable to these carcinogens.^[20]

Data pooled from 17 European and American case-control studies (11,221 cases and 16,168 controls) participating in the International Head and Neck Cancer Epidemiology consortium showed that the population-attributable risk for alcohol on cancer was 72% (95% CI, 61%-79%) for head and neck cancers, of which 4% was due to alcohol alone, 33% was due to tobacco alone, and 35% was due to tobacco and alcohol combined. The risk was higher for men. An effect of smoking on alcohol-related cancers has been confirmed by recent studies. Concurrent smoking and moderate-to-heavy drinking substantially raises the overall population-attributable risk for upper aerodigestive tract cancers compared with nonsmoking drinkers.^[21]

However, the fact that a significant proportion of aerodigestive tract cancers can be attributed to either alcohol or smoking does not diminish the importance of the role of alcohol.^[3]

Do Cardiovascular Benefits Outweigh Cancer Risk?

Alcohol is associated with both benefits and harms to cardiovascular health, although not all of the relevant mechanisms are fully understood.^[22] Heavy drinking can lead to alcoholic cardiomyopathy, systemic hypertension, atrial arrhythmias, and hemorrhagic stroke.^[22] At the same time, light-to-moderate alcohol intake is associated with reduced risks for coronary artery disease, myocardial infarction, ischemic stroke, and heart failure. Like the alcohol-cancer link, no randomized controlled trial data exist for alcohol and cardiovascular outcomes, so it is impossible to completely rule out confounding lifestyle or other factors.^[22]

A light-to-moderate drinker may enjoy the cardiovascular benefit, but this does not negate the cancer risk.

Given the association with cancer on the one hand, and the cardiovascular benefits on the other, people often want to know the net benefit or harm that is associated with long-term daily alcohol consumption. However, one does not cancel out the other. A light-to-moderate drinker may enjoy the cardiovascular benefit, but this does not negate the cancer risk.

Dr Klatsky maintains that "there is very little doubt that light-to-moderate drinking reduces the risk for heart attack and death from coronary disease. This benefit is pretty well-established for light-to-moderate drinking in a healthy pattern; for example, sipping wine with meals." Light-to-moderate drinkers aged 50 years and older, with no significant risk factors for either cancer or heart disease, have the lowest overall mortality, comments Dr Klatsky. "If an older adult wants to lower his or her risk for myocardial infarction, many factors are important—avoidance of smoking, maintaining ideal body weight, exercising, and controlling such risk factors as hypertension and hypercholesterolemia. Does alcohol drinking have a place in that list? It might, but it's not the most important factor."

Younger women with a family history or risk factors for breast cancer, and no major risk factors for heart disease, should not drink for the cardiovascular benefits, reports Dr Klatsky. "Light-to-moderate drinkers who are younger than age 50 will not experience any net benefit from drinking alcohol—they are more likely to experience adverse effects from alcohol."

Dr Rehm's view is that "the negative effects of alcohol consumption, overall, are more than 10-fold its beneficial effects." Indeed, no net benefit of alcohol consumption on a composite of health outcomes was found in a recent study^[23] of an international cohort drawn from low-, middle-, and high-income countries. High alcohol consumption (defined as more than 14 drinks per week for women or more than 21 drinks per week for men) was associated with increased risk for mortality, cancer, and injury and a nonsignificantly reduced risk for myocardial infarction.

Communicating Risk to Patients

Alcohol is a modifiable risk factor for cancer.^[5] Of all dietary factors associated with cancer risk, alcohol has the strongest and most consistent evidence for a carcinogenic effect.^[5] The worldwide burden of cancer incidence and mortality could be reduced simply by lowering alcohol consumption.^[5] However, the importance of alcohol as a human carcinogen is underappreciated by the public.^[5] Not only are people generally reluctant to accept the

alcohol-cancer link, they are unwilling to alter their drinking patterns.^[24-26] Whereas 94% of Americans acknowledge that smoking is a risk factor for cancer, only 43% have heard that alcohol might cause cancer.^[27] Even a serious alcohol-related disorder such as chronic liver disease isn't always enough to persuade the affected person to abstain from alcohol.^[28]

Weiss and colleagues^[24] conducted a survey of almost 1700 women (a nationally representative sample) with an 87% completion rate. Although at least half of the women knew that alcohol was one element in a long list of lifestyle behaviors and exposures that might influence cancer risk, the women were relatively uninterested in learning how to lower their alcohol consumption to reduce this risk.

Confusion about reports of the health benefits of alcohol can interfere with messages about the association between alcohol and cancer and limit awareness of this relationship. In fact, the link has, at times, been so completely ignored that pink ribbons, the international symbol for breast cancer awareness, have been used to market beer and wine.^[29]

Answering the Question: How Much Can I Drink?

No simple message about alcohol consumption can simultaneously address cancer risk, cardiovascular outcomes, and mortality for the entire population. As starting points, however, most experts can agree on a couple of broad recommendations:

1. Heavy drinking should be avoided to reduce cancer risk; and
2. Smoking plus drinking increases the risk for cancer, especially of the upper aerodigestive tract.

"Alcohol and smoking are related," explains Dr Klatsky. "It's been difficult to tease out the separate effects of smoking and drinking because very few people smoke heavily without drinking at least some alcohol."

Light-to-moderate drinking, for those who choose to drink, should be limited to no more than 10 g of pure alcohol a day for women and 20 g for men (roughly one standard drink a day for women and two standard drinks for men, as defined in most countries). This agrees with definitions of drinking established by the National Institute on Alcohol Abuse and Alcoholism.^[30]

For advice that goes beyond avoidance of heavy, regular drinking, binge drinking, and smoking, both Dr Klatsky and Dr Rehm advocate individual decision-making on whether drinking (and how much) is likely to be beneficial or harmful. Dr Klatsky believes that, "Advice should combine objectivity with common sense. Each individual needs to consider his or her own risks, potential benefits, and priorities." Setting aside the issue of willingness to modify one's lifestyle to prevent outcomes, good or bad, that might not show up for decades, key factors in this decision-making include age, sex, medical history, current health status, and family risk factors.

Once you get to two or more drinks daily, however, the balance is always negative.

Dr. Rehm provides an example. "For those who consume just one alcoholic drink daily and no more, the risk will depend on whether they have a medical or family history that is more in the cardiovascular area or in the cancer (especially the alcohol-related cancers) area. If family history is strong for cancer, then even with one drink daily, the benefit is negative for alcohol. If they have a strong family history of myocardial infarction, then the benefit of daily alcohol may outweigh the risk. Once you get to two or more drinks daily, however, the balance is always negative."

Public Health Messages Silent About Alcohol-Cancer Link

Ideally, patients would consult their healthcare providers to assess the nature of personal alcohol consumption as one element of a healthy lifestyle. However, unless alcoholism is an issue, most people don't turn to healthcare providers for drinking advice. Their information comes from the world around them—mainly headlines, tweets, sound bites, and advertisements that feature happy, healthy people drinking alcohol in every imaginable setting.

Alan Blum, MD, a professor in the University of Alabama School of Medicine and director of the university's Center

for the Study of Tobacco and Society, believes that organizations such as the American Cancer Society (ACS) have not sufficiently educated the public about the strong link between alcohol consumption and several common cancers. Dr Blum does not see the current [ACS statement on alcohol and cancer](#) as a sincere attempt to raise public awareness about this issue, nor does he mince words when explaining why he believes the organization has failed in this public health duty. "No doubt, ACS doesn't want to come off like a nanny or get the reputation of a prohibitionist. Nor do they want to offend the fundraising cocktail party set. Alcohol is so ingrained in society that any serious effort by the ACS to raise public awareness of the link with cancer would seem doomed to failure."

Dr Blum also views the relative silence on the alcohol-cancer link as deafening in the face of the dramatic increase in alcohol advertising on television and the internet. This culture of alcohol can strongly influence the drinking habits of college students.

"At most universities, entering college students must complete a brief computerized alcohol education module—often funded by the alcohol industry," commented Dr Blum. "The entire theme is 'responsible drinking' with scant reference to *not* drinking. The industry's solution to drunk driving is designated drivers."

He adds, "This may not seem to be related to cancer, but just as discouraging adolescents from taking up smoking to prevent lung and other cancers later on, discouraging the college-age population from drinking practices can lay the groundwork to prevent alcohol-related cancers down the road. What do we have to lose?"

Dr Rehm and Dr Klatsy have disclosed no relevant financial relationships.

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