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Alcohol and Cancer: A Statement of the American Society of Clinical Oncology

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ABSTRACT

Alcohol drinking is an established risk factor for several malignancies, and it is a potentially modifiable risk factor for cancer. The Cancer Prevention Committee of the American Society of Clinical Oncology (ASCO) believes that a proactive stance by the Society to minimize excessive exposure to alcohol has important implications for cancer prevention. In addition, the role of alcohol drinking on outcomes in patients with cancer is in its formative stages, and ASCO can play a key role by generating a research agenda. Also, ASCO could provide needed leadership in the cancer community on this issue. In the issuance of this statement, ASCO joins a growing number of international organizations by establishing a platform to support effective public health strategies in this area. The goals of this statement are to:

- Promote public education about the risks between alcohol abuse and certain types of cancer;
- Support policy efforts to reduce the risk of cancer through evidence-based strategies that prevent excessive use of alcohol;
- Provide education to oncology providers about the influence of excessive alcohol use and cancer risks and treatment complications, including clarification of conflicting evidence; and
- Identify areas of needed research regarding the relationship between alcohol use and cancer risk and outcomes.

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INTRODUCTION

The importance of alcohol drinking as a contributing factor to the overall cancer burden is often underappreciated. In fact, alcohol drinking is an established risk factor for several malignancies. As a potentially modifiable risk factor for cancer, addressing high-risk alcohol use is one strategy to reduce the burden of cancer. For example, in 2012, 5.5% of all new cancer occurrences and 5.8% of all cancer deaths worldwide were estimated to be attributable to alcohol.[1] In the United States, it has been estimated that 3.5% of all cancer deaths are attributable to drinking alcohol.[2] Alcohol is causally associated with oropharyngeal and larynx cancer, esophageal cancer, hepatocellular carcinoma, breast cancer, and colon cancer.[3] Even modest use of alcohol may increase cancer risk, but the greatest risks are observed with heavy, long-term use.

Despite the evidence of a strong link between alcohol drinking and certain cancers, ASCO has not previously addressed the topic of alcohol and cancer. In addition, alcohol drinking is a potentially modifiable risk factor that can be targeted with preventive interventions at both the policy and the individual levels. Here, we provide an overview of the evidence of the links between alcohol drinking and cancer risk and cancer outcomes. The areas of greatest need for future research are highlighted. On the basis of this evidence and guidelines adopted by other cancer-focused organizations, ASCO-endorsed strategies for the reduction of high-risk alcohol consumption are presented.

EPIDEMIOLOGY OF ALCOHOL USE

Beyond oncology, alcohol use and abuse together pose a significant public health problem. According to the Centers for Disease Control and Prevention, approximately 88,000 deaths were attributed to excessive alcohol use in the United States between 2006 and 2010.[4] Approximately 3.3 million deaths worldwide result from the harmful use of alcohol each year.[5] Population surveys demonstrate that 12% to 14% of adults have a current alcohol use disorder and that 29% have had such a disorder at some point in their lifetime.[6,7] In addition to alcohol use disorder,

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other measures used to assess the impact of alcohol are excessive drinking, binge drinking, and heavy drinking. Excessive drinking includes binge drinking and is defined as consumption of four or more drinks during a single occasion for women, or five or more drinks during a single occasion for men. Binge drinking is the most common form of excessive drinking compared with heavy drinking, which is defined as eight or more drinks per week or three or more drinks per day for women, and as fifteen or more drinks per week or four or more drinks per day for men.[8] Recent work has shown that the prevalence of adults who drink more than four to five drinks per occasion, defined as extreme binge drinking, has been increasing during the past decade.[9] This study estimated that 13% of the US adult population engaged in extreme binge drinking on at least one occasion in the previous year. Moderate drinking is defined at up to one drink per day for women and up to two drinks per day for men.[1,4] Most individuals who drink excessively do not meet the clinical criteria for alcoholism or alcohol dependence.[10]

Alcohol use during childhood and adolescence is a predictor of increased risk of alcohol use disorder as an adult.[11] College-age and younger people who drink are prone to develop an alcohol use disorder later in life.[7] Most adults who engage in high-risk alcohol drinking behavior started drinking before age 21 years. Among US youth age 12 to 20 years, 23% were current drinkers in the past 30 days, 10% were episodic drinkers, 2% were heavy episodic drinkers, and 6% met criteria for alcohol use disorder.[11] Among childhood cancer survivors, the prevalence of alcohol use in the past 30 days in adulthood (7.8 mean years since diagnosis of their cancer) was 25%, which was lower than that observed in the general population.[12] However, alcohol use among teenage patients with cancer is a common occurrence overall and has been observed to be as high among teens without cancer.[13-15]

DRINKING GUIDELINES AND DEFINITIONS

Internationally, more than 40 countries have issued alcohol drinking guidelines; however, these vary substantially.[16] The American Heart Association, American Cancer Society, and US Department of Health and Human Services all recommend that men drink no more than one to two drinks per day and that women drink no more than one drink per day.[17-19] In addition, it is recommended that drinking alcohol should only be done by adults of legal age. People who do not currently drink alcohol should not start for any reason.

Defining risk-drinking can be challenging, because the amount of ethanol contained in an alcoholic beverage will vary considerably depending on the type of alcohol (eg, beer, wine, or spirits) and the size of the drink consumed. In addition, the definition of a standard drink varies among countries and ranges from 8 g to 14 g.[20,21] The National Institute of Alcohol Abuse and Alcoholism (NIAAA) defines a standard drink as one that contains roughly 14 g of pure alcohol, which is the equivalent of 1.5 ounces of distilled spirits (approximately 40% alcohol by volume); 5 ounces of wine (approximately 12% alcohol by volume); or 12 ounces of regular beer (approximately 5% alcohol by volume).[22] However, evidence shows that drinkers are often unaware of how standard drinks are defined and that these standard drink sizes are commonly exceeded.[20]

ALCOHOL AND CANCER

Evidence to Link Alcohol Consumption to Specific Cancers

The relationship between drinking alcohol and cancer risk has been evaluated extensively in epidemiologic case-control and cohort studies. In a thorough systematic review of the world's evidence that adhered to prespecified criteria for drawing inferences, a World Cancer Research Fund/American Institute for Cancer Research (AICR) report judged the evidence to be convincing that drinking alcohol was a cause of cancers of the oral cavity, pharynx, larynx, esophagus, breast, and colorectum (in men).[23] Also, alcohol was judged to be a probable cause of increased risk of liver cancer and colorectal cancer (in women).[23] An updated review of the evidence for liver cancer upgraded the conclusion for an association between alcohol drinking and liver cancer to convincing.[24] The International Agency for Research on Cancer (IARC),[25] a branch of WHO, has assessed the evidence and come to virtually identical conclusions: that alcohol is a cause of cancers of the oral cavity, pharynx, larynx, esophagus, colorectum, liver (ie, hepatocellular carcinoma), and female breast. For esophageal cancer, the association with alcohol drinking is largely specific to squamous cell carcinoma.[25] The more that a person drinks, and the longer the period of time, the greater their risk of development of cancer, especially head and neck cancers.[3]

A valid question is whether these associations are specific to ethanol per se or whether they vary according to the type of alcoholic beverage (ie, beer, wine, or spirits/liquor). The answer is that the associations between alcohol drinking and cancer risk have been observed consistently regardless of the specific type of alcoholic beverage.[25]

The full range of cancers for which alcohol drinking represents a risk factor remains to be clarified. For example, the index of suspicion is high that alcohol drinking leads to excess risk of pancreatic cancer[25] and gastric cancer.[26] For some malignancies, alcohol drinking clearly is statistically associated with increased risk but, because of its strong correlation with other risk factors, it is difficult to discern if alcohol drinking is truly an independent risk factor. For example, alcohol drinking consistently has been statistically strongly associated with increased lung cancer risk.[23] However, cigarette smokers also are more likely to be alcohol drinkers, and cigarette smoking is such an overwhelming lung cancer risk factor that confounding by cigarette smoking—rather than a direct association with alcohol drinking—currently cannot be ruled out as a possible explanation.[27] As evidence continues to accumulate, the list of alcohol-associated cancers is likely to grow.

Magnitude of the Associations

Characterization of the dose-response relationship between alcohol and cancer is important for causal inference, because, if alcohol increases the risk for a specific cancer, one would expect the magnitude of the cancer risk to increase commensurate with increasing levels of alcohol consumption. Furthermore, the nature of the dose-response relationship provides useful information for communicating with patients about this issue. For alcohol-associated cancers, Table 1 summarizes results from a large-scale

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meta-analysis[28] that show the relative risks of cancer in a comparison of nondrinkers with categories of people with light, moderate, and heavy alcohol consumption. The results summarized in Table 1 illustrate several key points. First, the magnitude of the association between alcohol drinking and cancer risk varied by type of cancer. Compared with nondrinkers, the summary relative risks (sRRs) for those classified as heavy drinkers ranged from 1.44 for colorectal cancer to 5.13 for cancer of the oral cavity and pharynx. The corresponding sRRs were 1.61, 2.07, 2.65, and 4.95 for cancers of the breast, liver, larynx, and esophagus, respectively. The strongest associations were observed for upper aerodigestive tract cancers (ie, larynx, esophagus, and oral cavity/pharynx), which involve tissues that come into direct contact with ingested alcohol. Second, monotonic dose-response relationships are evident for cancers of the oral cavity and pharynx, squamous cell carcinoma of the esophagus, and breast cancer. For liver, laryngeal, and colorectal cancers, the sRRs for the moderate category were intermediate between nondrinkers and heavy drinkers, but there was no evidence of increased risk in the light-drinker category. In a dose-response meta-analysis, the risk of secondary malignancies in patients with upper aerodigestive tract cancers increased incrementally by 9% for every increase in alcohol intake of 10 g/day.[29]

Clearly, the greatest cancer risks are concentrated in the heavy and moderate drinker categories. Nevertheless, some cancer risk persists even at low levels of consumption. A meta-analysis that focused solely on cancer risks associated with drinking one drink or fewer per day observed that this level of alcohol consumption was still associated with some elevated risk for squamous cell carcinoma of the esophagus (sRR, 1.30; 95% CI, 1.09 to 1.56), oropharyngeal cancer (sRR, 1.17; 95% CI, 1.06 to 1.29), and breast cancer (sRR, 1.05; 95% CI, 1.02 to 1.08), but no discernable associations were seen for cancers of the colorectum, larynx, and liver.[30] On the basis of the lesser overall cancer risk at the lower end of the dose-response continuum, the World Cancer Research Fund/AICR made the following recommendation: "If alcoholic drinks are consumed, limit consumption to two drinks a day for men and one drink a day for women."[23] They also recommend that, "for cancer prevention, it's best not to drink alcohol." Recent updates to the AICR report estimate a 5% increase in premenopausal breast cancer per 10 grams of ethanol consumed per day (pooled relative risk [RR], 1.05; 95% CI, 1.02 to 1.08). The risk was even greater for postmenopausal breast cancer, which had an RR of 1.09 (95% CI, 1.07 to 1.12) for each 10 grams of ethanol per day.[31]

Does Cessation of Alcohol Consumption Lead to Lower Cancer Risk?

A key question relevant both to the assessment of causality and the provision of advice and effective interventions to patients is whether the risk of developing an alcohol-associated cancer is reduced after one stops drinking alcohol. The results of meta-analyses and pooled analyses that have focused directly on this question for upper aerodigestive tract cancers indicate that risk of these cancers declines in those who quit drinking alcohol compared with those who remain alcohol drinkers.[32-35] The evidence from these studies suggests that the risk of cancer may be reduced to that seen in never drinkers after long-term ($\geq$ 20 years) cessation from alcohol drinking. Unfortunately, there are limited existing data on the impact of alcohol cessation on the risk of other alcohol-related cancers. This important topic is in need of more thorough investigation, particularly because those who quit drinking alcohol may differ from current drinkers in important ways that are also associated with cancer risk. For example, similar to smoking cessation, an increased short-term risk of cancer after alcohol cessation may be due to the onset of cancer-related symptoms that contribute to the individual's decision to stop drinking. Studies that carefully assess the time period between alcohol cessation and cancer diagnosis will help disentangle these complex methodological issues. Another potential bias is introduced by the finding that the category of former drinkers can be overrepresented by former heavy drinkers or alcoholics.[36] When present, the risk of cancer after alcohol cessation may be higher than that observed for current drinkers because of the high alcohol exposure doses of those classified as former drinkers. Carefully designed prospective cohort studies will help overcome these bias-based limitations and will lead to a more refined characterization of the impact of cessation of alcohol drinking on cancer risk by longitudinally quantifying the amount of alcohol consumed and the duration of cessation.

Impact of Smoking in Combination With Alcohol Consumption

Some malignancies are causally linked to both alcohol drinking and cigarette smoking; in some cases, an established synergistic interaction between alcohol drinking and cigarette smoking exists. This means that, in cancers for which both alcohol drinking and cigarette smoking are causal factors, the cancer risks in those who are both alcohol drinkers and cigarette smokers are much larger than the risks seen for those who only drink alcohol or

Table 1. Summary of Relative Risks From a Meta-Analysis for the Association Between Amount of Alcohol Drinking and Risk of Cancer

Type of Cancer	Relative Risk (95% CI)			
	Nondrinker	Light Drinker	Moderate Drinker	Heavy Drinker
Oral cavity and pharynx	1.0 (referent)	1.13 (1.0 to 1.26)	1.83 (1.62 to 2.07)	5.13 (4.31 to 6.10)
Esophageal squamous cell carcinoma	1.0 (referent)	1.26 (1.06 to 1.50)	2.23 (1.87 to 2.65)	4.95 (3.86 to 6.34)
Larynx	1.0 (referent)	0.87 (0.68 to 1.11)	1.44 (1.25 to 1.66)	2.65 (2.19 to 3.19)
Liver	1.0 (referent)	1.00 (0.85 to 1.18)	1.08 (0.97 to 1.20)	2.07 (1.66 to 2.58)
Female breast	1.0 (referent)	1.04 (1.01 to 1.07)	1.23 (1.19 to 1.28)	1.61 (1.33 to 1.94)
Colorectum	1.0 (referent)	0.99 (0.95 to 1.04)	1.17 (1.11 to 1.24)	1.44 (1.25 to 1.65)

NOTE. Adapted from results of Bagnardi et al (2015).[28]

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only smoke cigarettes. Specific upper aerodigestive tract cancers provide the strongest examples of robust synergistic interactions between alcohol drinking and cigarette smoking. A pooled analysis of 17 case-control studies identified a potent interaction between alcohol drinking and cigarette smoking in cancers of the oral cavity, pharynx, and larynx,[37] and a review identified evidence of robust interaction in 22 of 24 published studies on oral, pharyngeal, laryngeal, and esophageal cancers.[38] Despite the clear presence of synergistic interaction, the biologic underpinnings of the interaction between alcohol drinking and cigarette smoking are not well understood.

The Mechanistic Role of Alcohol in Carcinogenesis

When the evidence of alcohol's role in carcinogenesis is considered, a key point is that, in biochemical reactions that are sequentially catalyzed by alcohol dehydrogenase and aldehyde dehydrogenase, ethanol is eliminated from the body by its oxidation first to acetaldehyde and then to acetate. Ethanol per se is not mutagenic, but acetaldehyde is carcinogenic and mutagenic, by binding to DNA and protein.[39]

The IARC reviewed the potential role of alcohol in carcinogenesis by synthesizing multiple bodies of evidence that included (1) experiments in which ethanol (or aldehyde) is administered to mice and rats in drinking water; (2) the absorption, distribution, metabolism, and excretion of ethanol and its metabolites; and (3) the genotoxicity of alcohol in various experimental systems, including biomarkers in humans.[23] One key conclusion of the review was that, in animal models, administration of ethanol or acetaldehyde in drinking water increased the incidence of various tumors in mice and rats; also administration of other known carcinogens with ethanol in drinking water enhanced tumor development more.[23] Another key conclusion was that "the role of ethanol metabolism in tumor initiation is implied by the associations observed between different forms of cancer and polymorphisms in genes involved in the oxidation of ethanol."[23] This point about polymorphisms is premised on the fact that genetic predisposition may amplify the toxic and mutagenic effects of alcohol consumption. A specific example of this line of reasoning is that most of the acetaldehyde generated during alcohol metabolism in vivo is eliminated promptly by aldehyde dehydrogenase-2 (ALDH2). However, a genetic variant of *ALDH2* exists ([(rs671]*2) that encodes a catalytically inactive protein. Alcohol drinkers with the inactive form of ALDH2 experience excessive accumulation of acetaldehyde, which amplifies its toxic and mutagenic effects, and the amplification would be expected to lead to greater susceptibility to alcohol-induced cancer. Several studies in East Asian populations, who have the highest prevalence of this high-risk genotype, have documented that alcohol drinking is more strongly associated with cancers of the upper aerodigestive tract among those with a high-risk genotype.[40] The IARC review also invoked mechanisms that included oxidative stress, sex hormones, folate metabolism, and DNA methylation as well as cirrhosis for hepatocellular carcinoma. Alcohol-induced oxidative stress, via the CYP2E1 pathway, for example, can result in chronic tissue inflammation.[23] Alcohol drinking affects circulating concentrations of androgens and estrogens, which is a pathway of particular relevance to breast cancer.[23] Consumption of alcohol is associated with lower folate concentrations—a relationship that has been extensively studied in relation to the etiology of colon cancer.[41]

Classification of Alcohol as a Carcinogen by the WHO

On the basis of the sum total of the evidence from research on mechanistic studies of the carcinogenicity of alcohol and the epidemiologic evidence to link alcohol with increased risk of multiple forms of cancer, the IARC classified alcohol as a group 1 carcinogen, because they found that it causes cancer in humans.[41] Specifically, IARC concluded that there is sufficient evidence in humans for the carcinogenicity not only of alcohol consumption but also for the carcinogenicity of acetaldehyde associated with alcoholic beverage consumption.[41]

DISPARITIES IN ALCOHOL USE AND RELATED CANCERS

Blacks, Asian Americans, and Hispanic individuals have lower rates of current alcohol use disorder than whites. However, rates among these groups appear to be increasing overall. The NIAAA has accumulated data during two decades by conducting large general-population surveys among US adults age 18 years and older. Their longitudinal surveys from 1991 to 1992 and 2001 to 2002 showed increases in alcohol abuse among men, women, and young black and Hispanic minorities. Rates of dependence also increased among men, young black women, and Asian men, which underscores the need to continue monitoring of prevalence and trends. It is now known that Hispanics and blacks have a higher risk than whites for developing alcohol-related liver disease.[42] The longitudinal design of the NIAAA surveys enable the collection of data on cultural variables, such as acculturation. In addition to increasing overall rates, blacks and Hispanics are less likely to use alcohol treatment when it is available.[43]

All segments of US social strata are affected by alcohol abuse, but the prevalence of alcohol abuse is particularly high within American Indian and Alaska Native (AIAN) populations. AIAN people drink more alcohol and are more highly affected by alcohol-related illness than other populations.[44] Among people age 12 years and older, the prevalence of binge drinking was 28% for AIAN people compared with 23% for whites, 22% for blacks, and 14% for Asian Americans. Findings from the 2000 to 2006 Behavioral Risk Factor Surveillance System showed that the rate of binge drinking was a major difference between non-Hispanic white and AIAN people, especially men.[45] Similarly, rates of heavy drinking were highest (9%) among AIAN people and lowest (2%) among Asian Americans.[44] The Indian Health Service, which provides a large amount of the health care to the AIAN community, addresses alcohol from a disease-model perspective.[46] The Indian Health Service identifies alcoholism as a chronic disease with genetic, psychosocial, and environmental factors.[47] Individuals with cirrhosis and chronic liver disease are at much higher risk of liver cancer, and the main preventable causes of these conditions are chronic infection with hepatitis B and C, chronic alcohol abuse, and nonalcoholic fatty liver disease. Though viral hepatitis prevention and treatment may be making a significant health difference already, addressing chronic alcohol abuse would be an important cancer prevention strategy.

Differential rates of alcohol use according to socioeconomic status hypothetically could contribute to cancer disparities. In reality, the relationship between alcohol drinking and socioeconomic status is complex, because it depends on how alcohol drinking is measured. When measures of alcohol use are used,

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those of a higher socioeconomic status are more likely to drink and to drink more heavily.[48] However, for reasons that are poorly understood, measures of adverse consequences of alcohol tend to concentrate more among those of a lower socioeconomic status.[48] A disproportionate share of the overall burden of cancer occurs in those of a lower socioeconomic status, so alcohol drinking may be a contributing factor to cancer disparities observed across the spectrum of socioeconomic status; however, this remains a relatively unexplored topic.[49]

Patterns of alcohol use and treatment also vary by sex and sexual orientation; higher rates are seen in sexual and gender minority populations (ie, lesbian, gay, bisexual, transgender, and intersex).[50] This population also is known to bear a greater burden of cancer incidence.[50] For example, although men have a higher prevalence of heavy drinking, women are less likely to use alcohol treatment services,[43] even among those with alcohol dependence.[51] Lesbian or bisexual female veterans had higher rates of alcohol misuse than heterosexual female veterans did, which may result at least in part from higher rates of trauma exposure and mental health difficulties experienced by the lesbian/bisexual women.[52] Lesbian, gay, and bisexual young adults (ages 17 to 19 years) consume more alcohol both in high school and in college.[53] A study of the National Longitudinal Study of Adolescent Health also confirmed significantly increased alcohol use and abuse among lesbian, gay, and bisexual youth.[54] A recent ASCO position statement recommended increased cancer prevention education efforts, including reduction in high-risk alcohol use as a target effort.[50]

ALCOHOL AND CANCER: OUTCOMES AND EFFECT ON TREATMENT

Compared with the wealth of evidence about the associations between alcohol drinking and the risk of developing cancer, research on the impact of alcohol drinking on outcomes in patients with cancer is still in its nascent stages. For cancers that have known associations with alcohol drinking, it would be expected that alcohol drinking at the time of diagnosis also would be associated with risk of cancer recurrence and/or secondary primary tumors (SPTs). This association has been observed for patients with upper aerodigestive tract cancer when nondrinkers are compared with occasional drinkers. The risk of cancer-specific mortality is increased significantly in moderate drinkers (RR, 1.79; 95% CI, 1.26 to 2.53) and heavy drinkers (RR, 3.63; 95% CI, 2.63 to 5.0).[55] Among survivors of upper aerodigestive tract cancer, continued alcohol use after diagnosis is associated with a three-fold increased risk of upper aerodigestive tract second primary tumors,[56] and cessation may reduce the increased risk for SPTs in pre-diagnosis drinkers compared with pre-diagnosis nondrinkers.[29] In breast cancer survivors, several studies suggest that alcohol drinking is not associated with decreased overall survival,[57] whereas other studies indicate that breast cancer–specific mortality may be increased in at least some subgroups of the patient population.[58-60] The increase in breast cancer–specific mortality or risk of recurrence has been observed with moderate to heavy levels of alcohol drinking.[60,61] Li et al showed that, among women with estrogen receptor–positive breast cancer, consumers of seven or more drinks per week versus none had a 90% increased risk of asynchronous contralateral breast cancer,[62] which was higher than the 30% increased risk observed in a multicentered case-control study.[63] Other SPTs in patients with breast cancer that have been associated with greater alcohol consumption ($>$ 7 drinks per week versus none) include an increased risk of subsequent colorectal cancer (hazard ratio [HR], 1.92; 95% CI, 1.07 to 3.43) and a decreased risk of ovarian cancer (HR, 0.45; 95% CI, 0.21 to 0.98).[64] Results of studies to evaluate the relationship between alcohol consumption and colorectal cancer have been mixed; one study observed that heavy drinking was associated with poorer survival,[65] whereas the majority of studies have demonstrated either no association between alcohol drinking overall and colorectal cancer outcomes[66] or a suggestion of better overall survival with higher levels of wine consumption.[67] A recent meta-analysis of cohort studies among 209,597 cancer survivors showed a statistically significant 8% increase in overall mortality and a 17% increased risk for recurrence in the highest versus lowest alcohol consumers.[68] More evidence is needed to clarify the impact of both alcohol drinking and cessation on cancer outcomes.

The majority of studies to evaluate the direct effects of alcohol use on cancer treatment have focused on patients with upper aerodigestive tract cancer, because 34% to 57% continue to drink after diagnosis.[69] Smoking and alcohol use during and after radiation therapy have been associated with an increased risk of osteoradionecrosis of the jaw in patients with oral and oropharyngeal cancers.[70-73]

Alcohol abuse also complicates treatment outcomes among patients with cancer by contributing to longer hospitalizations, increased surgical procedures, prolonged recovery, higher health care costs,[74-76] and higher mortality.[77] Heavy alcohol use and abuse are important modifiable risk factors for postoperative morbidity.[78] Heavy alcohol use[79] and alcohol abuse,[80] compared with no alcohol use, are associated with higher risks of anastomotic complications after colorectal surgery. Alcohol abuse, compared with no abuse, also has been shown to contribute to low quality-of-life outcomes in patients with head and neck cancer after treatment.[81,82] Patients with cancer who abuse alcohol have increased comorbidities that can complicate treatment choices and that are affected by alcohol-related subclinical factors, including nutritional deficiencies, immunosuppression, and cardiovascular insufficiencies that increase treatment morbidity.[83-85]

Light alcohol use among cancer survivors has been perceived as potentially beneficial for treatment-related adverse effects, although there is little evidence to support this concept. A cross-sectional study of patients with head and neck cancer showed that patients who reported drinking at least one serving of alcohol in the past month reported better functional scores and lower levels of symptoms, such as fatigue, pain, dysphagia or dry mouth after treatment than those who reported that they had not used alcohol.[86] Given the inability to distinguish the sequence of events in a cross-sectional study design, it is unclear whether light alcohol use promotes treatment recovery and well-being or is the result of improved health-related quality of life among survivors. The consumption of light alcohol for increasing appetite has been regarded as potentially beneficial for patients with cancer,[87] because alcohol can stimulate appetite and snacking in cancer-free individuals.[88] However, a recent study of patients with advanced cancer who had self-reported loss of appetite and who were randomly assigned to white wine with $\leq$ 15% alcohol content

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twice a day for 3 to 4 weeks versus a nutritional supplement showed no improvement in appetite or weight.[89]

BARRIERS TO ADDRESSING ALCOHOL AND CANCER IN THE ONCOLOGY SETTING

In addition to the perception that light alcohol use may have a beneficial effect on appetite and tolerance of cancer treatment, conflicting data about the heart health of alcohol, especially red wine, is one additional barrier to addressing alcohol and cancer risk in the oncology setting. However, subsequent work has revealed multiple confounders to this conclusion about heart health, including frequent classification of former and occasional alcohol drinkers as nondrinkers.[90] For example, people who now abstain from alcohol often have underlying health concerns, which explains their reasons to cut down on alcohol and thereby makes the current alcohol drinkers appear healthier than former and occasional drinkers—a so-called abstainer bias.[90] In addition, larger studies and meta-analyses have failed to show an all-cause mortality benefit for low-volume alcohol use compared with abstinence or intermittent use, which suggests the lack of a true benefit to daily alcohol use.[91,92] Differences in alcohol dehydrogenase variants are associated with nondrinking, and nondrinkers have had lower rates of coronary heart disease and stroke than even light drinkers.[93] As such, the benefit of alcohol consumption on cardiovascular health likely has been overstated.[94,95] As reviewed in the Magnitude of the Association section, the risk of cancer is increased even with low levels of alcohol consumption,[30] so the net effect of alcohol is harmful. Thus, alcohol consumption should not be recommended to prevent cardiovascular disease or all-cause mortality.

Low physician knowledge of alcohol use and cancer risk is another barrier to addressing alcohol use with patients. This lack of knowledge has been demonstrated among general practitioners, who were aware of an association of alcohol with cardiovascular health and obesity and who also felt that preventive health was an important aspect of their work; however, the majority of providers did not ask their patients about alcohol consumption, and most were unaware of alcohol as a carcinogen.[96,97] A knowledge deficit was also seen among medical students relative to the role of alcohol as a risk factor in head and neck cancers.[98] Knowledge of the association between cancer and alcohol also has been shown to be low among dentists and allied health professionals, who may be evaluating patients for these cancers. For example, dentists and dental hygienists have lower awareness of the association between alcohol use and head and neck cancers than family physician do (40% for dentists *v* 94% for family physicians), and this lack of knowledge would hamper their ability to counsel patients about alcohol-related cancers.[99]

In addition to a lack of knowledge of alcohol use as a cancer risk factor, physicians use different approaches to counseling patients about alcohol use. Just as overweight or obese physicians are less likely to counsel their patients about obesity,[100] alcohol use among physicians may make them less likely to counsel patients about the risks of alcohol use. In one study of Danish physicians, 18.8% of physicians met criteria for risky alcohol consumption.[101] Estimates indicate that up to 14% of American physicians will have an alcohol use disorder in their lifetime, which is a rate similar to the general population.[102] Burnout, which is very common among oncology providers, also is strongly associated with high-risk alcohol use.[103-107]

RESEARCH NEEDS

Although alcohol is a well-established risk factor for the development of certain cancers, very little is known about how current alcohol use affects cancer treatment delivery. Thus, the most compelling and urgent research need for the oncology community with regard to alcohol is better definition of the effect of concurrent alcohol use on cancer treatments, including chemotherapy, radiation, and surgery, as well as on cancer outcomes. Anecdotal stories from providers about the effect of alcohol on cancer treatment are intriguing, but rigorous scientific studies are needed to accurately quantify the effect. Underexplored research areas include the effects of alcohol exposure on postoperative morbidity; on the efficacy of chemotherapy and radiation; and on novel targeted therapies, such as immunotherapy and radiation.

Increased knowledge about the mechanistic effects of alcohol on cancer-related pathways and treatments may improve understanding of its role in disease progression and therapeutic responsiveness and toxicity. For example, a preclinical study demonstrated overlap between alcohol responsive genes and genes that are involved in responsiveness to endocrine therapy in breast cancer cells.[108] The insufficient knowledge about the detrimental or potentially beneficial effects of alcohol use overall, as well as effects of its dose and frequency, among patients with cancer creates missed opportunities to intervene to improve overall quality of life and to educate patients about the cancer-specific prognostic role of alcohol.

Systems-based research, including research into successful means for the oncology community to identify patients who are currently using alcohol or who may be at high risk for alcohol relapse, will be critical. How to effectively apply evidence-based clinical interventions to assist patients in reduction of abstention from alcohol use also should be explored.

PUBLIC HEALTH STRATEGIES TO REDUCE HIGH-RISK ALCOHOL CONSUMPTION

Policies to reduce excessive alcohol consumption should be evidence based (such as those identified by WHO[109] or the Community Preventive Services Task Force[110]), culturally sensitive, and equitable in their implementation. Recognizing that excessive alcohol use can delay or negatively impact cancer treatment and that reducing high-risk alcohol consumption is cancer prevention, ASCO joins the growing number of cancer care and public health organizations to support strategies designed to prevent high-risk alcohol consumption such as the following and those in Table 2.[111-129]

- Clinical strategies of alcohol screening and brief intervention provided in clinical settings: Health care providers can screen adults, including pregnant women, for excessive alcohol use to identify people whose levels or patterns of alcohol use place them at increased risk of alcohol-related harms. Health care

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Table 2. Policy Recommendations of International Cancer Care and Public Health Organizations

Organization	Recommendation
Association of European Cancer Leagues (25 associations)[111,112]	• Supports minimum pricing legislation • Monitoring implementation of the European Union Alcohol Strategy and the impact of the strategy on marketing to young people and reducing alcohol-related harm • Calls for stronger recognition of alcohol causality of cancer and other chronic diseases and European Code Against Cancer
Cancer Research UK[113]	• Supports a comprehensive alcohol strategy to reduce drinking in the United Kingdom to levels where the risks are minimal • Recognizes need for measures to reduce the affordability of alcohol and to restrict young people's exposure to alcohol advertising are needed if alcohol consumption will be reduced to historic levels and reduce the risk of cancer in the United Kingdom
Irish Cancer Society[114]	• In May 2013, called on government to ban alcohol advertising
Cancer Council Australia[115-117]	• Recommends the increased price of alcohol through taxation and an investigation into the need for the introduction of minimum pricing of alcohol[115] • Endorses the need for compulsory warning labels on all alcoholic products[116] • Supports a strategy to limit the exposure of marketing and promotion of alcohol overall and specifically to children[117]
Cancer Council Victoria (Australia)[118,119]	• Member of the Alcohol Policy Coalition • Recognizes the harmful link between advertising and harmful drinking in young people, and actively works to implement alcohol advertising restrictions to reduce exposure among people age 18 years and younger
Cancer Association of South Africa[120]	• Advocates against consumption of any alcohol • Does not support any form of pink washing to market any product that contributes to cancer disease and death (including the alcohol industry)
World Cancer Research Fund International[121]	• Recommends policies that will reduce the availability and affordability of alcohol

European Society for Medical Oncology[123]	• Party to the European Chronic Disease Alliance position statement on the need for European Union action to help Europeans reduce alcohol consumption, and supports the following policy goals[122]:
	  ° ensure the implementation of the WHO Global Strategy to Reduce the Harmful Use of Alcohol
	  ° ensure achievement of WHO Global noncommunicable disease target for a 10% relative reduction in the harmful use of alcohol
	  ° ensure a new comprehensive European Union alcohol strategy
	  ° ensure that countries also have national alcohol strategies
	• Supports both supply- and demand-oriented strategies to reduce alcohol consumption including[123]:
	  ° increasing prices of alcoholic beverages;
	  ° limit the number of alcohol outlets (outlet density);
	  ° limit the hours of sales and establish regulations for minimum age of purchase;
	  ° implement school-based education to influence drinking behavior; and
	  ° restrict advertising, particularly to young people

American Medical Association[124,125]	• Advocates for legislation aimed at minimizing alcohol promotions, advertising, and other marketing strategies by the alcohol industry aimed at adolescents[124] • Supports a ban on the marketing of products, such as alcopops, gelatin-based alcohol products, food-based alcohol products, alcohol mists, and beverages that contain alcohol and caffeine and other additives to produce alcohol energy drinks that have special appeal to youths under the age of 21 years and supports state and federal regulations that would reclassify alcopops as a distilled spirit so that they can be taxed at a higher rate and cannot be advertised or sold in certain locations[125]
American Academy of Family Physicians[126]	• Supports efforts to reduce the amount of alcohol advertising, particularly content appealing to youth, and the development of educational programs and counter-advertising designed to illustrate more realistic images on the effects of alcohol
American Public Health Association[127]	• Supports the development and adoption of an international framework convention on alcohol control[127] • Supports the implementation of the recommendations of the National Research Council and Institute of Medicine's report entitled "Reducing Underage Drinking: A Collective Responsibility," including the monitoring of youth exposure to alcohol advertising and the raising of excise taxes[128]
European Public Health Alliance[129]	• Supports limitations on advertising of alcohol and product placement to minimize youth exposure to the marketing of these products

providers can then recommend or offer treatment services to those at risk. Brief counseling interventions for adults who drink excessively have been found to positively affect several patterns of excessive drinking, including heavy episodic (binge) drinking and high average weekly intake of alcohol.[130]

- Regulate alcohol outlet density: An alcohol outlet is defined as any site where alcohol may be legally sold to an individual to either consume on premises (eg, bars or restaurants) or off premises (eg, liquor stores or other retail settings).[131] Using regulatory authority to reduce the number of alcohol outlets in a given area (ie, density) has proven to be an effective strategy for reducing excessive alcohol consumption.[131-134] This is frequently executed through outlet licensing or zoning processes.
- Increase alcohol taxes and prices: Taxes are placed on all alcohol beverages by both individual states and the federal government, and a portion of the federal excise tax may or may not be used to support treatment programs. Alcohol taxes vary from state to state and also differ in the amount applied based on the type of alcohol (eg, beer, wine, or spirits/hard liquor). Increasing taxes, and therefore the overall price of alcohol, has been shown to inversely effect levels of excessive consumption and related health harms.[135-137] Other regulations that may directly or indirectly affect the price of alcoholic beverages, including regulations on wholesale distribution and bans on price-related promotions, may have some impact on excessive consumption, though more research is needed.[138]

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- Maintain limits on days and hours of sale: Limiting the days or hours during which alcoholic beverages can be sold can be applied to both outlets where the alcohol is consumed on premises and retail outlets where the alcohol is consumed off premises. These policies, made at the state and local levels, are intended to prevent excessive consumption by reducing access to the alcohol.[139] Evidence from several studies has demonstrated the positive impact that reducing the number of days or hours that alcoholic beverages are sold generally result in a decrease in related harms.[140,141]
- Enhance enforcement of laws prohibiting sales to minors: The minimum legal drinking age is 21 years in all US states. Enhanced enforcement of the minimum legal drinking age can reduce sales to minors (younger than 21 years) in retail settings (such as, bars, restaurants, liquor stores), thereby helping to reduce youth access to alcohol.[130]
- Restrict youth exposure to advertising of alcoholic beverages: Early onset of drinking has been associated with an increased likelihood of developing dependence on alcohol later in life,[142] and studies have demonstrated that youth exposed to more advertisements also show increases in drinking levels.[143,144] The alcohol industry has only voluntary advertising codes created by the major trade groups, and are not subjected to federal restrictions. Currently, industry codes require that at least 70% of the audience of the advertisements (including print, radio, television, and internet/digital) consists of adults of legal drinking age.[145-147] However, the alcohol industry is frequently noncompliant with its own self-regulation guidelines.[148]
- Resist further privatization of retail alcohol sales in communities with current government control. Following the end of Prohibition in 1933, all states had wholesale of alcoholic beverages under state control. "License" states allowed retail sales by commercial interests, while some "control" states allowed alcohol to be sold, but only through government-run retail stores that restrict off-premises sales outlets (ie, outlets where alcohol is sold for consumption elsewhere). In the United States, all states and counties that permit the sale of alcohol allow privatized retail sales of beer, and most allow privatized retail sale of all alcoholic beverages. Privatization most often affects wine and spirits (eg, vodka and whiskey) in the control states.[149]
- Include alcohol control strategies in comprehensive cancer control plans: State, tribal, and territorial comprehensive alcohol control strategies are not commonly included in comprehensive cancer control plans. Supporting the implementation of evidence-based strategies to prevent the excessive use of alcohol is one tool the cancer control community can use to reduce the risk of cancer.[150]

In addition to these strategies, ASCO supports efforts to eliminate pinkwashing in the marketing of alcoholic beverages. Pinkwashing is a form of cause marketing in which a company uses the color pink and/or pink ribbons to show a commitment to finding a cure for breast cancer. Given the consistent evidence that shows the link between alcohol consumption and an increased risk of breast cancer,[25,151] alcoholic beverage companies should be discouraged from using the symbols of the battle against breast cancer to market their products.

THE ROLE OF THE ONCOLOGIST

Worldwide, alcohol-related cancers are estimated to be 5.5% of all cancers treated annually, which represents a large number of patients. Oncologists frequently are the ones who manage the treatment of these patients, and they have a direct interest in promotion of the health of patients. Such promotion likely will include helping patients reduce high-risk alcohol use. Oncologists also stand in a position to drive the alcohol-related research agenda as it affects patients with cancer. The most pressing questions include how active alcohol use affects cancer treatments, how alcohol use affects risk of recurrence and overall prognosis, and how alcohol interacts with oral chemotherapy and supportive care medications. As front-line providers for these patients, another need to support is identification of the most effective strategies to help patients reduce their alcohol use. Ways to address racial, ethnic, sex, and sexual orientation disparities that will place these populations at increased rates for cancer also are needed. Oncology providers can serve as community advisors and leaders and can help raise the awareness of alcohol as a cancer risk behavior. Finally, because alcohol use is quite common, an initiative to address alcohol use (particularly high-risk alcohol use) is a potential preventive strategy to decrease the burden of cancer. Policy efforts are likely to be the most effective way to address this need.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Alcohol and Cancer: A Statement of the American Society of Clinical Oncology

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