Alcohol and Cancer: Existing Knowledge and Evidence Gaps across the Cancer Continuum

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ABSTRACT

Alcoholic beverages are carcinogenic to humans. Globally, an estimated 4.1% of new cancer cases in 2020 were attributable to alcoholic beverages. However, the full cancer burden due to alcohol is uncertain because for many cancer (sub)types, associations remain inconclusive. Additionally, associations of consumption with therapeutic response, disease progression, and long-term cancer outcomes are not fully understood, public awareness of the alcohol–cancer link is low, and the interrelationships of alcohol control regulations and cancer risk are unclear. In December 2020, the U.S. NCI convened a workshop and public webinar that brought together a panel of scientific experts to review what is known about and identify knowledge gaps regarding alcohol and cancer. Examples of gaps identified include: (i) associations of alcohol consumption patterns across the life course with cancer risk; (ii) alcohol's systemic carcinogenic effects; (iii) alcohol's influence on treatment efficacy, patient-reported outcomes, and long-term prognosis; (iv) communication strategies to increase awareness of the alcohol–cancer link; and (v) the impact of alcohol control policies to reduce consumption on cancer incidence and mortality. Interdisciplinary research and implementation efforts are needed to increase relevant knowledge, and to develop effective interventions focused on improving awareness, and reducing harmful consumption to decrease the alcohol-related cancer burden.

Introduction

Ethanol–the principal form of alcohol in alcoholic beverages–is a widely-used, psychoactive, and dependence-producing substance. Alcohol research and control efforts supported by multiple governmental and nongovernmental organizations (NGO) internationally have found that the public health impact of harmful alcohol consumption is substantial. In 2016, it resulted in an estimated 5.1% of the global burden of disease and injury, and 5.3% of deaths (1). A large meta-analysis of 23 health outcomes showed that the number of daily alcohol beverages that minimized harm overall was 0 (95% uncertainty interval 0.00–0.08′; ref. 2).

For cancer specifically, an estimated 4.1% of all new cases globally in 2020 (3), and from 2013 through 2016, 4.8% of all cases annually in the United States, were attributable to alcohol consumption (4). Current evidence suggests that "[t]here is no threshold of alcohol consumption below which cancer risk does not increase, at least for some cancers" (5), and cancer prevention guidelines indicate that it is best not to drink alcohol (5, 6). Despite the large body of scientific evidence on the topic, the full cancer burden due to alcohol remains uncertain because for many cancer (sub)types associations with risk and survivorship are inconsistent or there are few studies. Moreover, most U.S. adults are unaware of the alcohol–cancer link (7), and the interrelationships of alcohol control regulations and cancer risk are unclear.

To reduce the burden of disease caused by alcohol, the 2010 World Health Organization's (WHO) 63rd World Health Assembly endorsed the "Global Strategy to Reduce the Harmful Use of Alcohol" (8). Two objectives of this strategy include: ". . .rais[ing] global awareness of the magnitude and nature of the health, social and economic problems caused by harmful use of alcohol", and ". . .strengthen[ing] the knowledge base on the magnitude and determinants of alcohol-related harm and on effective interventions to reduce and prevent such harm." Consistent with these objectives, in December 2020, the U.S. NIH NCI convened a workshop and a public webinar (https://cancercontrol.cancer.gov/brp/hbrb/alcohol-and-cancer#meetings). These events brought together basic, epidemiologic, behavioral, clinical, communication, and regulatory scientists to review existing evidence, and more importantly, identify knowledge gaps in: (i) the epidemiology and biology of alcohol and cancer risk; (ii) the effects of alcohol consumption before, during, and after treatment on cancer outcomes; (iii) communication efforts to increase awareness of the alcohol–cancer link; and (iv) policy-level interventions for reducing the adverse health effects, including cancer, of alcohol consumption. The evidence reviewed and gaps identified are summarized below.

Epidemiology and Biology of Alcohol and Cancer Risk

In 1987, WHO's International Agency for Research on Cancer (IARC) first classified alcoholic beverages as carcinogenic to humans (group 1) based on finding "sufficient" scientific evidence of causality for five cancer types (9). Updated evaluations by IARC (10, 11), and the World Cancer Research Fund/American Institute for Cancer Research Continuous Update Project (WCRF/AICR CUP; ref. 5) conclude that ethanol in alcoholic beverages and/or acetaldehyde associated with the consumption of alcoholic beverages cause upper aerodigestive tract [UADT; i.e., oral cavity, pharynx, larynx, and squamous cell carcinoma

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(SCC) of the esophagus], liver (hepatocellular carcinoma), female breast, and colorectal cancers (5, 11), and probably increases stomach cancer risk (5). The estimated threshold of ethanol consumption at which risk increases is ≥45 grams/day for liver and stomach cancers, and ≥30 grams/day for colorectal cancer, whereas there is a monotonic increased risk of UADT, and breast cancers (5). For non–Hodgkin lymphoma and renal cell carcinoma there is "evidence suggesting lack of carcinogenicity" (11), and consumption of ≤30 grams/day probably decreases kidney cancer risk (5).

Numerous biological mechanisms may be involved in alcohol-related carcinogenesis. Alcohol drinking disorders can lead to liver fibrosis and cirrhosis (12)–an established cause of liver cancer. Ethanol in alcoholic beverages may enhance carcinogen diffusion into epithelial cells (13), and affect DNA repair, MAPK, sex hormone regulation, immune function and inflammation, the absorption and metabolism of essential nutrients (e.g., vitamin A, folate), and the oral and gut microbiome (10).

The oxidative metabolism of ethanol to acetaldehyde by alcohol dehydrogenase (ADH), and at high blood–alcohol concentrations by ethanol-inducible cytochrome P4502E1 (CYP2E1) and catalase, also appears to play a role in carcinogenesis (10). The induction of CYP2E1 can activate procarcinogens, leading to the formation of reactive oxygen species which react with cellular lipids to form mutagenic DNA adducts, and DNA damage (10). Acetaldehyde can interfere with DNA synthesis and repair, form DNA adducts, and cause cytotoxicity and mutagenicity (10).

Functional variants in genes encoding human ADH and aldehyde dehydrogenase (ALDH, which metabolizes acetaldehyde to acetic acid) may be involved in alcohol-induced carcinogenesis as well. The *ADH1B*2* allele forms an enzyme with considerably greater activity than the *ADH1B*1* allele (14). The *ALDH2*2* allele encodes a catalytically inactive enzyme subunit; *ALDH2*2* homozygosity results in undetectable ALDH2 activity, and alcohol intolerance due to acetaldehyde toxicity, whereas *ALDH2*2* heterozygosity yields enzyme activity roughly 1% of that of *ALDH2*1* homozygosity (14). Both *ADH1B*1* homozygosity and *ALDH2*2* heterozygosity are associated with increased risk of UADT cancers (11).

Despite substantial epidemiologic and mechanistic evidence on alcohol and cancer, several knowledge gaps remain that if filled could improve estimates of the burden of alcohol-attributable cancers, and inform tailord interventions to reduce consumption.

Assessment of alcohol consumption

Although there is reasonable consistency between estimated self-reported average daily alcohol intake assessed by food frequency questionnaires (FFQ) and daily diaries or 24-hour recalls (15), there are concerns regarding underreporting of consumption and interindividual variability in reporting a standard drink size (16). Additionally, FFQs do not typically capture lifetime patterns of consumption. Thus, the development and validation of self-report instruments that better capture amounts and patterns of consumption are needed to improve understanding of dose-response relationships. Furthermore, identifying and implementing objective measures (e.g., blood biomarkers, sensors) of consumption in the epidemiologic and clinical settings is of considerable interest to improve the assessment of consumption, and to identify those at greatest risk of alcohol-related harms (17, 18).

Alcohol consumption and risk of specific cancer (sub)types

Associations of alcohol consumption, including patterns of consumption throughout the life course, with the risk of many (sub)types of cancer such as lung, pancreas, ovary, endometrium, thyroid, skin melanoma, remains inconclusive. Leveraging prospective study resources available through large consortia (19) could accelerate our understanding of these associations. Similarly, little is known about lifetime patterns of consumption (e.g., age at initiation, cessation, amount consumed at different ages, binge drinking) and cancer risk. For example, drinking cessation has been associated with a reduced risk of laryngeal and pharyngeal cancers, with greater potential benefits observed with more years of abstinence (20), yet associations of cessation with risk of most other cancer types has not been studied.

Confounding and modifying effects of other factors

Considerable research has found a synergistic effect of tobacco use and alcohol consumption with risk of UADT cancers (10). However, further research is needed to understand these effects with risk of other types of cancer, and to clarify the confounding and modifying effects of other established and potential cancer risk factors. These include occupational or geospatial risk factors, infectious agents (e.g., human papilloma virus), diet and physical activity—both independently and as contributors to excess body fatness— and specific nutritients (e.g., folate, retinol). Additionally, questions remain regarding the susceptibility of alcohol-associated cancers among carriers of variants in genes that affect the metabolism of alcohol (beyond UADT cancers), or in genes (e.g., *methylenetetrahydrofolate reductase* gene) that affect metabolism of alcohol-related dietary factors, and among carriers of high-penetrance familial gene mutations.

Influence of alcohol on cancer disparities

There are important differences among population subgroups (e.g., ethnic/racial, age, group, geographic) in both the prevalence and patterns of alcohol consumption (21). Whether these differences, and/or variations in exposures that may have synergistic effects with alcohol (e.g., tobacco use, diet, environment), contribute to cancer disparities across subgroups is a major knowledge gap. Community-based participatory research in this area may be fruitful.

Biologic mechanisms

Greater insights into tissue-specific and systemic effects of alcohol consumption–alone or in combination with other carcinogens–on the immune system, metabolome, epigenome, and human microbiome are needed. These insights could inform evaluations of causality, particularly for (sub)types of cancer where the evidence remains inconclusive.

Effects of Alcohol Consumption Before, During, and After Treatment On Cancer Outcomes

Approximately 1.9 million Americans are expected to be diagnosed with cancer in 2021 (22), and the number of survivors will exceed 22 million by 2030 (23). Data from the 2000 through 2017 National Health Interview Surveys show that 56% of cancer survivors reported being current drinkers and nearly 35% reported consuming more than 1 drink/day among women and more than 2 drinks/day among men (24).

Few studies have examined the prognostic effects of alcohol consumption among patients with cancer in active treatment. A meta-analysis of surgical patients (not cancer-specific) showed that preoperative consumption was associated with increased risk of postoperative morbidity, infection, wound and pulmonary complications, prolonged hospitalization, and admission to intensive care, and high

consumption was associated with mortality (25). Smoking and alcohol use during and after radiation for oropharyngeal cancer have been associated with higher risk of jaw osteoradionecrosis (26). Although there are known adverse interactions between alcohol and supportive care medications such as antiemetics, painkillers, antianxiety, sleep, or other drugs (27), interactions between alcohol and chemotherapeutic agents are not fully understood. Alcohol abuse associated with comorbid psychiatric conditions may affect cancer treatment adherence and quality of life (28). Furthermore, alcohol consumption, particularly chronic consumption, may affect the immune system and increase risk of infection (29).

Most studies of alcohol consumption in relation to long-term cancer outcomes focused on risk of recurrence or death among patients diagnosed with breast, colorectum, and UADT cancers. A meta-analysis of 10 studies of patients with UADT cancer found a nearly three-fold higher risk of UADT second primary cancers for the highest versus lowest levels of consumption (30). One study found that among patients with early-stage oral cavity, pharynx or larynx cancer, both prediagnosis consumption and continuous consumption after diagnosis were associated with a higher risk of all-cause mortality (31). For colorectal cancer, a meta-analysis of prospective studies (32) showed a nonlinear association (risk was <1 for <30 grams/day of ethanol) between prediagnosis alcohol consumption and risk of death from all-causes. Similarly consumption of >0–≤12.5, and >12.5–<37.5 grams/day of ethanol (but not higher amounts) compared with no consumption were associated with a lower risk of colorectal cancer–specific mortality (32). In that study, postdiagnosis consumption was not associated with either all-cause or colorectal cancer–specific mortality, and residual confounding and misclassification due to recent quitting could not be ruled out (32). Among breast cancer survivors, a WCRF/AICR meta-analysis of 18 studies showed no associations of pre- or postdiagnosis alcohol consumption with risk of all-cause or breast cancer–specific mortality (33). In a pooled analysis of three prospective studies of women with stage I–III breast cancer, postdiagnosis consumption of ≥6 grams ethanol/day (vs. no consumption) was associated with a higher risk of recurrence among postmenopausal, but not premenopausal women (34).

Significant knowledge gaps on the impact of alcohol use (and cessation) among patients with cancer and survivors remain. A better understanding of alcohol consumption's effects on therapeutic response, disease progression, and long-term cancer outcomes may support medical decision making and improve survivorship.

Alcohol consumption and cancer outcomes

Whether alcohol is associated with rates of recurrence, new primary cancers, comorbidities, disease-specific and overall mortality, and health-related quality of life (e.g., physical function and emotional well-being) is poorly understood. Future studies must carefully consider dose-response associations, and correlations of alcohol consumption before, during, and after diagnosis, confounding and effect modification by factors associated with consumption (e.g., smoking, clinical factors), and competing risks.

Alcohol's effects on tumor progression/molecular characteristics

Knowledge is limited regarding alcohol's effects on tumor growth, metastasis, and related genetic and epigenetic mechanisms. Whether these effects vary by cancer type and stage, patient demographic characteristics (e.g., age, sex, race/ethnicity), and patterns of consumption is unclear.

Effects of alcohol consumption on treatment efficacy

There is need to better understand the effects of alcohol consumption on treatment (i.e., surgery, radiotherapy, immunotherapy, and chemotherapy) efficacy, and on drug metabolism and toxicity among specific populations of patients with cancer defined by cancer type, and other factors. Greater insight into these effects could inform targeted approaches for treating patients with cancer who drink alcohol.

Identifying and intervening on at-risk patients

Strategies are needed to identify patients with cancer at risk of alcohol-associated harms, and to query patients regarding their consumption before, during, and after cancer treatment. Assessing the efficacy of the electronic medical record (with inclusion of tools such as the Alcohol Use Disorders Identification Test, and blood alcohol calculator), along with developing and implementing biomarkers of alcohol use and abuse, may be particularly useful for screening patients. Furthermore, well-defined pathways to reach at-risk patients and to encourage healthcare providers to counsel these patients on the adverse health effects of alcohol consumption, and evidence-based messages to support patient–provider discussions could have an important impact on health outcomes.

Communication Efforts to Increase Awareness of the Alcohol–Cancer Link

A high proportion of American adults, both drinkers and nondrinkers (35), are unaware of the association between alcohol consumption and cancer risk. Between 2005 and 2019, the prevalence of awareness ranged from 33% to 46% (7). Factors that predict awareness of the association are not completely understood (36). However, the fact that most Americans are unaware of the association suggests effective evidence-based strategies are needed to increase awareness, encourage informed decision making, modify health behavior, and develop policies to reduce consumption.

Most U.S. campaigns to increase public awareness about the health effects of alcohol consumption have focused on underage drinking, binge drinking, or drinking and driving (37–39). Studies conducted in other countries suggest potential efficacy of communication strategies to increase cancer-relevant awareness. For example, a Canadian container label intervention demonstrated a 10% greater increase in knowledge of alcohol as a carcinogen in the intervention versus the comparison group 2 months postintervention (40). Another study found that using multiple and diverse information sources can reduce alcohol use intentions as compared with reliance on a single source (41).

Interpersonal influences, including interactions with family and friends, also shape knowledge and behaviors (42, 43). Because overt behaviors appear to be more susceptible to normative influence than clandestine behaviors (44), alcohol consumption behaviors in groups might be especially subject to social sanction. Increased awareness of the alcohol–cancer link might encourage some people to warn family and friends about consumption, although the efficacy of such communication on behavior is unclear.

Interactions with clinicians could affect alcohol consumption behavior, as they are relatively trusted sources of health information (45). However, in a cross-sectional survey of cancer survivors, only 14% of regular drinkers recalled receiving counseling from a clinician to quit drinking, although those who did were five-fold more likely to report reducing or stopping drinking compared with those who did not receive counseling (46). These findings suggest that clinicians may

underappreciate cancer risks due to alcohol, and need additional guidance to reinforce clear and consistent messaging to effectively discuss this issue with their patients. Addressing knowledge gaps related to alcohol–cancer communication has potential to increase awareness and affect alcohol consumption behavior.

Accessible and effective information on alcohol and cancer

The public, clinicians, policymakers, and journalists need accessible, consistent, and easily understood information regarding alcohol and cancer. However, there is a lack of evidence about the efficacy of messages such as warning labels and alcohol consumption guidelines or recommendations. Such information could inform targeted strategies to influence personal consumption. Although clear, concise, and consistent messaging is likely to encourage increased awareness (47), knowledge of statistical health risks alone is not exceptionally predictive of preventive behavior (48). Information on message dimensions that most motivate consumption behavior is needed to inform effective communication strategies.

The role of emotion and motivation in message processing

Understanding the role of emotion and motivation in message processing (49) regarding the alcohol–cancer link and alcohol use also could provide insight into message reactance and behavior in the context of messages about alcohol and cancer. Cognitive dissonance and reactance among individuals may pose challenges due to the prevalence and cultural acceptance of alcohol consumption.

Population- and individual-level communication needs

Ethical communication interventions must also address community-, and population-level factors, and focus on the needs of people across all socioeconomic and cultural groups, including those who are most marginalized. These interventions could promote greater health equity. In addition, there is a need to better understand how group identity, culture, tribalism, and even reactions to past policies (such as the U.S. Prohibition) influence message processing about the alcohol–cancer link, as well as alcohol consumption behavior.

Consensus on messaging and language

Challenges associated with the public information environment, including the (social) media, must be considered when developing communication strategies. Consensus among national and international public health organizations regarding messaging about alcohol consumption guidelines (e.g., exact quantity and frequency) could reduce confusion, misunderstanding, and mistrust created by inconsistent messaging but will require an understanding of how organizations accomplish intra- and interorganizational consensus. Alcohol industry communication efforts have included obfuscation, distortion, and omission of evidence regarding cancer risks due to alcohol consumption (50). Similarly, misleading marketing, including "pinkwashing" alcoholic beverages, by the alcohol industry complicates the information environment (51). However, just as some antitobacco campaigns have spotlighted misleading communication by industry to discourage tobacco use (52), alcohol control efforts might benefit from highlighting industry misinformation as a way of alerting individuals to the harms.

Policy-level Interventions to Reduce the Adverse Health Effects, Including Cancer, of Alcohol Consumption

Alcoholic beverage production, distribution, and consumption have been regulated throughout the world for centuries (53). In the United States, current regulation of alcohol dates from 1933 when the 21st Amendment repealed national prohibition and granted states (which may empower local jurisdictions) authority over the import, distribution, sale, and possession of alcoholic beverages, as well as penalties for violating alcohol statutes. However, the federal government retained power to regulate alcohol through control of foreign and interstate commerce, federal taxes, federal property, and financial incentives.

Alcohol regulations are designed to ensure an orderly marketplace, and to minimize or reduce the health, social, and economic harms due to consumption. The U.S. Community Preventive Services Task Force's (CPSTF) *Guide to Community Preventive Services* (54), and WHO's 2010 Global Strategy to Reduce the Harmful Use of Alcohol (8) describe a range of evidence-based alcohol control policies. WHO identified three policies–increasing alcohol taxes, banning/restricting alcohol advertising, and reducing/restricting alcohol availability (e.g., regulating the hours and days of sale and density of alcohol outlets, and establishing/enforcing legal age limits for purchasing and consuming alcohol)–as "best buys" (i.e., interventions that cost less than $100/disability-adjusted life-year averted; ref. 55). Other strategies include enforcing commercial host liability laws, restricting or banning promotions of alcoholic beverages in connection with sponsorships and activities that target youth, enacting and enforcing drinking-driving laws and blood–alcohol concentration limits, and providing consumer information about and labeling alcoholic beverages to indicate alcohol-related harm. In addition, the U.S. CPSTF also recommends against the privatization of retail alcohol sales (54).

Research indicates that effective policies can reduce alcohol consumption and alcohol-related harms (56, 57). However, knowledge regarding the association between alcohol control regulations and cancer risk is in its infancy. A recent study scored U.S. state-specific alcohol policy environments based on a validated policy scale, and found that a 10% higher average score corresponding to more restrictive policies was associated with an 8.5% lower death rate of alcohol-attributable cancers (58). The aforementioned Canadian alcohol-container cancer warning label intervention that found increases in knowledge that alcohol is a carcinogen (40), also found greater support for pricing policies (59). While these results are intriguing, numerous policy-level knowledge gaps relevant to the development and adoption of effective policies remain.

Alcohol control policies and cancer risk

Few studies have examined the impact of individual policies, policy subgroups, and aggregate policy environments (particularly policies related to price, physical availability, and marketing of alcohol), as well as changes in these policies, on total cancer or on specific types of alcohol-associated cancer incidence and mortality rates. Similarly, it is unclear whether, or the extent to which, policies targeting other cancer risk factors (e.g., tobacco, overweight) or multiple behaviors (e.g., alcohol, tobacco, and diet) might impact alcohol-associated cancer rates. Focusing on WHO "best-buy" policies to reduce alcohol consumption could advance knowledge on their return-on-investment.

Mediating and synergistic effects of other factors

The mediating and synergistic effects of alcohol consumption patterns (e.g., binge drinking, initiating consumption before legal age), other lifestyle (e.g., smoking, overweight), environmental or societal/geospatial (e.g., outlet density, drinking water pollutants) factors on either consumption-cancer or policy-cancer relationships are unclear. This information could inform community-specific prevention strategies.

Facilitators and barriers to an integrated policy approach

Alcohol control policies that integrate information about the alcohol–cancer link could increase the acceptability and impact of population-level regulations (40). Further research is needed to demonstrate the impact of integrating this information, and to understand the facilitators and barriers of an integrated policy approach. The facilitators may include: (i) knowledge mobilization and best practices for translating research and communicating alcohol policy–cancer relationships to policy makers, nongovernmental organizations (NGO), and providers; (ii) activation of stakeholders from multiple sectors including primary care providers, oncologists and other medical professionals, and NGOs; and (iii) information from the public regarding their knowledge, beliefs, and opinions regarding the policies that include cancer-relevant issues. The barriers may include: (i) inconsistencies in public health and medical education curricula related to alcohol and cancer, and the consequences of such inconsistencies; and (ii) misinformation campaigns and alcohol-related cause-branding.

Alcohol-related digital and social media policies and practices

Finally, a greater understanding the impact of digital and social media policies relevant to alcohol industry tactics and counter advertising on knowledge and behavior among all demographic groups (e.g., youth, older adults, cancer survivors, and caregivers) may advance alcohol reduction efforts. Of interest is the potential for scientists to serve as "influencers" for policy-level communications.

Conclusion

The December 2020 NCI Workshop highlighted existing evidence on the alcohol–cancer link, and revealed opportunities to strengthen relevant scientific knowledge. Additionally, the workshop panel recognized that the health, including cancer, impact of increases in alcohol consumption resulting from the coronavirus pandemic (60) will need to be carefully assessed, particularly if these behaviors are sustained long-term. Finally, the panel concluded that multi-level interdisciplinary efforts from population, basic, clinical, communication, and regulatory experts representing government, academia and other NGOs will be necessary to substantially reduce the number of individuals diagnosed with and dying from alcohol-related cancers.

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