

NCI Monograph 24

Tobacco and Alcohol: Understanding Co-Use to Reduce Cancer Incidence and Mortality

Chapter 4

Cancer Epidemiology of Tobacco and Alcohol Co-Use

Chapter Contents

Introduction.....	257
Cancer Epidemiology of Tobacco, Alcohol, and Their Co-Use.....	259
Epidemiology of Tobacco Use and Cancer Risk.....	260
Tobacco and Cancer by Demographic Subgroup.....	261
Tobacco and Cancer by Tobacco Product.....	262
Epidemiology of Alcohol Use and Cancer Risk.....	262
Trends in Alcohol Use by Demographic Subgroup.....	264
Alcohol and Cancer by Alcohol Product.....	265
Reduction in Alcohol Consumption and Cancer Risk.....	266
Mechanisms of Carcinogenesis for Tobacco and Alcohol.....	267
Epidemiology of Synergistic Cancer Risk for Joint Tobacco and Alcohol Exposures.....	268
Aerodigestive Tract Cancers.....	269
Synergistic Effects Between Tobacco and Alcohol Use for Other Cancer Sites.....	274
Lung Cancer.....	274
Hepatocellular Carcinoma.....	275
Female Breast Cancer.....	276
Thyroid Cancer.....	277
Cohort Studies of Cancer at Multiple Sites.....	279
Measurement and Analysis.....	279
Measurement of Frequency of Use, Intensity of Use, and Simultaneous Use.....	281
Measurement of Lifetime Exposure and Use Patterns.....	282
Measurement of Product Characteristics.....	283
Methods and Measurement of Tobacco and Alcohol Consumption Across the Life Course.....	284
Biomarkers of Exposure to Tobacco.....	284
Biomarkers of Exposure to Alcohol.....	285
Mendelian Randomized Studies of Alcohol and Tobacco.....	286
Measurement Needs Related to Health Disparities.....	286
Alcohol Harms and Socioeconomic Status.....	287
Chapter Summary.....	287
Research Needs.....	289
Conclusions.....	291
References.....	299

Figures and Tables

Figure 4.1	Risk of Cancer at Different Sites for Alcohol, Tobacco, and Combined Use.....	270
Table 4.1	Rates of Cancer Incidence and Mortality per 100,000.....	260
Table 4.2	Findings From the 2010 International Agency for Research on Cancer Monograph, <i>Evaluation of Carcinogenic Risks to Humans: Alcohol Consumption and Ethyl Carbamate (Volume 96)</i>	265
Table 4.3	Summary of Literature on Independent and Synergistic Cancer Risk Related to Tobacco Smoking and Alcohol.....	269

Table 4.4	Evidence From Selected Studies of Differences in Synergistic Effect by Demographics.....	272
Table 4.5	Selected Tobacco and Alcohol Use Measures Useful for Epidemiological Studies.....	280

Appendices

Appendix 4A	Literature Search Strategy.....	292
Appendix 4B	Select Studies Examining Synergy Between Tobacco and Alcohol Use and Cancer	293

This page left blank intentionally.

Chapter 4

Cancer Epidemiology of Tobacco and Alcohol Co-Use

Introduction

Tobacco and alcohol independently cause cancer at numerous sites, and their combined use results in additive or multiplicative increases in risk for some types of cancer.¹⁻⁴ This chapter summarizes the epidemiologic research examining associations between the use of tobacco and alcohol products with cancer risk, as well as interactions between tobacco and alcohol that influence cancer risk, including established synergistic increases in risk for cancers of the aerodigestive tract. For tobacco use, this chapter focuses on cigarette smoking because most of the extant literature pertaining to the cancer-related risks of combined tobacco and alcohol use has focused on this product. This does not diminish the importance of understanding the cancer-related risks posed by other tobacco products in the context of alcohol use, and research is needed to investigate this area. In this chapter, “alcohol” is used both to refer to alcohol-containing beverages and to ethanol, the psychoactive ingredient and primary carcinogen contained in alcoholic beverages.

One important motivation for studying tobacco and alcohol co-use is the presence of synergy between tobacco and alcohol exposures in risk of aerodigestive tract cancers (and potentially for other sites).⁵⁻⁷ Synergy occurs when the interaction between two factors (e.g., tobacco and alcohol use) results in a total effect (e.g., cancer risk) that is greater than the sum of the individual effects.^{8,9} Synergy can be assessed with statistical tests for interaction in regression models⁹ and is sometimes examined by calculating a synergy index.^{5-7,10-12} Further details concerning different types of synergy, synergy indices, and statistical approaches to synergy are available elsewhere.¹⁰

The strong epidemiological evidence for the presence of synergy makes it especially important to address tobacco and alcohol co-use for cancer prevention and control. As discussed in detail in chapter 5, plausible mechanisms underlying synergy between tobacco and alcohol include increased exposure to acetaldehyde derived both from tobacco smoke and ethanol metabolism, alcohol-induced increases in membrane permeability that increase exposure to carcinogens from tobacco and alcohol and increased reactive oxygen species and chronic inflammation. Furthermore, successful efforts to reduce tobacco and/or alcohol use would be especially beneficial in the context of co-use. For example, a 2024 systematic review conducted by Burton and colleagues⁷ aimed to quantify the independent and joint associations of exposure to alcohol consumption, cigarette smoking, and excess weight across health outcomes and identify whether these associations are synergistic. They reported a synergy index for smoking and alcohol use on head and neck cancer death/disease that was 3.78 times greater than the additive effect of each exposure (95% confidence interval [CI] = 2.61–5.48). Their findings suggest that true population-level risk may be underestimated and that, compared to individuals with one risk factor, those with multiple risk factors would experience a greater absolute risk reduction for an intervention that targets a single exposure. Tobacco cessation alone is known to reduce cancer risk at multiple sites, and reviews published as of 2026 indicate that reduction/cessation of

alcohol use also reduces risk of head and neck cancers (see the section “Reduction in Alcohol Consumption and Cancer Risk” in this chapter; smoking cessation in the context of alcohol use is discussed in detail in chapter 7).

Major reports and reviews have examined and summarized existing research on the associations between alcohol use, tobacco use, and cancer risk, including the 2014 Surgeon General’s report, *The Health Consequences of Smoking—50 Years of Progress*,³ the International Agency for Research on Cancer (IARC) *Monographs on the Evaluation of Carcinogenic Risks to Humans*,^{1,2,13-15} and *Handbooks of Cancer Prevention*,¹⁶ and the American Institute for Cancer Research (AICR) and World Cancer Research Fund (WCRF) Continuous Update Project.⁴ This chapter summarizes research with attention to (1) the scientific evidence on the synergistic risk of cancer associated with the use of both tobacco and alcohol products and (2) different population subgroups and types of alcohol or tobacco products used. The literature review search terms and methods used throughout this chapter are described in Appendix 4A.

This chapter seeks to identify gaps in the understanding of the cancer epidemiology of tobacco and alcohol use in relation to changes in prevalence of use and product types. As previously noted, most of the epidemiological research summarized in this chapter examines cigarettes, as there are far fewer epidemiological studies of tobacco and alcohol cancer risk for other tobacco products. Additionally, over the past 20 years, there have been considerable changes in both the tobacco and alcohol marketplaces, with many new products being added to the market.¹⁷⁻¹⁹ In addition to cigarettes, cigars, and smokeless tobacco products, the tobacco product market now includes products such as e-cigarettes, which are available in thousands of flavors; nicotine pouches; and heated tobacco products (e.g., IQOS).^{19,20} Although products such as beer, wine, and distilled spirits continue to predominate, the alcohol market has also expanded in the past 20 years with the addition of low-calorie options (many of which feature sweeteners like stevia and erythritol), craft products, and alcohol-containing seltzers and beer-fruit infusions.²¹ Like newer tobacco products, many of these newer alcohol products come in appealing flavors and are relatively inexpensive compared to wine and spirits, making them especially attractive to young people.^{22,23} Tobacco and alcohol products also vary in the amount of nicotine and alcohol they contain, respectively. For example, FDA-authorized e-cigarette products contain nicotine concentrations ranging from 2% to 5% and come in tobacco and menthol flavors,^{24,25} but there are many e-cigarette products in the marketplace that come in large capacity cartridges with 5% or higher nicotine concentration.^{17,26} As of 2026, the nicotine concentration in FDA-authorized nicotine pouches range from 3 mg to 9 mg, but companies have sought authorization for products with nicotine concentrations of up to 12 mg.^{25,27} With regard to alcohol content, beer, hard seltzers, and canned cocktails typically contain 4%–6% alcohol by volume (ABV),^{28,29} but products are available at both higher levels (e.g., canned cocktails with >20% ABV)³⁰ and lower levels (e.g., beer with 2%–3% alcohol).²⁸ There are also high-alcohol-content products that particularly appeal to youth, such as Four Loko.^{31,32} Alcohol per volume of spirits is typically 40%.³³ Furthermore, similar to how tobacco products have been marketed for decades, the marketing of alcohol products has expanded to more explicitly target specific demographic subgroups, such as women and sexual minorities.^{17-19,34,35} Some alcohol marketing has also involved health-related claims concerning calories, gluten, sugar, and health outcomes

(including diabetes). In 2022, the U.S. Alcohol and Tobacco Tax and Trade Bureau (TTB) released a reminder that “TTB advertising regulations [for alcohol products] prohibit any health-related statement that is untrue in any particular or tends to create a misleading impression as to the effects of consumption on health.”³⁶

The internet, social media, mobile apps, and other related technologies have changed consumer behavior and increased the capacity for targeted marketing for consumer products, including tobacco and alcohol products.³⁷⁻³⁹ Changes in the product market are accompanied by changes in the populations using these products, including the disproportionate use of tobacco products (particularly cigarettes) among people in medically underserved communities, the increase and substantial prevalence of e-cigarette use among youth and young adults, and changes in the alcohol market with significant decreases in alcohol use among adolescents and young adults in the past 20 years (see chapter 2).⁴⁰ Understanding the circumstances and motivations that are driving product use changes, such as targeted marketing by the tobacco industry to promote cigarette smoking among specific subpopulations⁴¹ and increased health consciousness among young adults,⁴² are essential to understanding the patterns of use of these products and their association with cancer risk. Addressing the needs of underserved populations is an important priority across the medical and research communities, although more research is needed to understand and address disparities in health behaviors and in cancer incidence and mortality.

This chapter does not present new meta-analyses or a formal systematic review. Rather, the main aims are (1) to summarize existing literature concerning the associations between tobacco and alcohol and cancer and (2) to assess whether synergy between alcohol and tobacco is present for a given cancer site. Knowledge of underlying biological mechanisms is critical to interpreting the results from epidemiology studies. As such, this chapter uses the mechanisms presented in chapter 5 to help interpret the empirical evidence from cancer epidemiology studies and assess whether tobacco and alcohol are associated with each cancer site and whether they together pose synergistic risk.

Cancer Epidemiology of Tobacco, Alcohol, and Their Co-Use

The causal relationship between the use of tobacco and alcohol individually and the risk of cancer is well established and includes increased risk for many of the most common cancers including lung, colon, female breast, head and neck, and bladder cancer. Although their combined effects have not been as well studied, convincing evidence demonstrates synergistic increases in the risk of aerodigestive tract cancers with tobacco and alcohol co-use. This section reviews the extensive epidemiological evidence regarding the relationship between tobacco and alcohol use, separately and together, and the risk of cancer. To further contextualize the magnitude of impact that tobacco and alcohol have on population-level health in relation to cancer, the incidence rates for cancer sites causally related to tobacco and/or alcohol use are presented in Table 4.1.

Table 4.1 Rates of Cancer Incidence and Mortality per 100,000

Disease site	Cancer incidence (age-adjusted) Rate per 100,000 (95% CI), 2018–2022			Cancer mortality (age-adjusted) Rate per 100,000 (95% CI), 2019–2023		
	Overall	Female	Male	Overall	Female	Male
Esophagus	4.2 (4.1, 4.2)	1.7 (1.7, 1.8)	7.1 (7.0, 7.2)	3.7 (3.7, 3.7)	1.4 (1.4, 1.4)	6.5 (6.4, 6.5)
Larynx	2.5 (2.5, 2.6)	1.0 (0.9, 1.0)	4.4 (4.3, 4.5)	0.9 (0.9, 0.9)	0.3 (0.3, 0.3)	1.6 (1.5, 1.6)
Oral cavity and pharynx	11.6 (11.6, 11.7)	6.6 (6.5, 6.7)	17.4 (17.2, 17.5)	2.7 (2.6, 2.7)	1.4 (1.4, 1.5)	4.1 (4.0, 4.1)
Colon and rectum	37.1 (37.0, 37.2)	32.6 (32.4, 32.8)	42.3 (42.1, 42.5)	12.9 (12.8, 12.9)	10.8 (10.7, 10.9)	15.3 (15.2, 15.4)
Liver and intrahepatic bile duct	9.4 (9.4, 9.5)	5.5 (5.5, 5.6)	13.9 (13.8, 14.0)	6.6 (6.6, 6.7)	4.3 (4.2, 4.3)	9.4 (9.3, 9.5)
Stomach	7.3 (7.2, 7.3)	5.7 (5.6, 5.8)	9.2 (9.1, 9.3)	2.7 (2.7, 2.7)	2.0 (2.0, 2.1)	3.5 (3.5, 3.6)
Urinary bladder	18.0 (17.9, 18.1)	7.7 (7.6, 7.8)	31.2 (31.0, 31.4)	4.1 (4.1, 4.2)	2.0 (2.0, 2.1)	7.1 (7.1, 7.2)
Acute myeloid leukemia	4.3 (4.2, 4.3)	3.6 (3.6, 3.7)	5.1 (5.1, 5.2)	2.7 (2.7, 2.7)	2.1 (2.1, 2.1)	3.4 (3.4, 3.5)
Cervix uteri	-	7.7 (7.6, 7.8)	-	-	2.2 (2.1, 2.2)	-
Kidney and renal pelvis	17.5 (17.5, 17.6)	12.0 (11.9, 12.1)	23.8 (23.7, 24.0)	3.4 (3.4, 3.5)	2.1 (2.1, 2.1)	5.1 (5.0, 5.1)
Lung and bronchus	47.8 (47.7, 48.0)	43.9 (43.7, 44.1)	53.1 (52.9, 53.4)	31.5 (31.4, 31.6)	27.1 (27.0, 27.2)	37.2 (37.0, 37.3)
Pancreas	13.8 (13.7, 13.8)	12.3 (12.2, 12.4)	15.5 (15.4, 15.6)	11.3 (11.2, 11.3)	9.9 (9.8, 9.9)	12.9 (12.8, 13.0)
Breast	-	130.8 (130.4, 131.1)	1.2 (1.2, 1.3)	-	19.2 (19.1, 19.3)	0.3 (0.3, 0.3)

Note. CI = confidence interval. Rates are per 100,000 and age-adjusted to the 2000 U.S. Standard Population. Cancer sites are listed in the same order as in Table 4.3. A dash (-) indicates that data are not available.

Source: SEER*Explorer.⁴³

Epidemiology of Tobacco Use and Cancer Risk

The evidence summarizing the health risks from smoking and the benefits of cessation on cancer outcomes are documented in the 2014 Surgeon General's report, *The Health Consequences of Smoking—50 Years of Progress*³; the 2020 Surgeon General's report, *Smoking Cessation: A Report of the Surgeon General*⁴⁴; National Cancer Institute (NCI) *Monograph 23: Treating Smoking Cessation in Cancer Patients*⁴⁵; and the National Toxicology Program's *15th Report on Carcinogens*.⁴⁶ Conclusive evidence demonstrates that cigarette smoking causes cancers at multiple sites, including cancers of the oral cavity, pharynx, larynx, esophagus, lung (including trachea and bronchus), stomach, liver, pancreas, kidney and ureter, bladder, cervix, colorectum, and blood (acute myeloid leukemia).³ Cigarette smoking is estimated to have caused about 170,000 cancer deaths, or approximately 28.5% of all cancer deaths, in the United States in

2019; it is estimated that in 2019 about 19.3% of incident cancers, or about 350,000 cases, were attributable to cigarette smoking.⁴⁷ Globally, an estimated 2.5 million cancer-related deaths were attributable to cigarette smoking in 2019.⁴⁸ Additionally, cigarette smoking also causes many other conditions including cardiovascular disease, respiratory disease, adverse reproductive outcomes, and diabetes.^{3,47} Furthermore, exposure to secondhand smoke causes many diseases, as well as increasing the risk of lung cancer among people who do not smoke and asthma among youth.³ Tobacco smoke contains thousands of harmful chemicals, including a complex mixture of carcinogens, that contribute to the development of many serious health conditions.^{3,47,49,50}

Tobacco cessation improves health status and quality of life and decreases risks for morbidity and mortality at any age.⁴⁴ The 2020 Surgeon General's report⁴⁴ concluded that smoking cessation reduces the risk of premature death and can add as much as a decade to life expectancy. The report also concluded that quitting smoking reduces the risk of many adverse health effects, including adverse reproductive health outcomes, cardiovascular diseases, chronic obstructive pulmonary disease, and cancer. Regarding cancer, the evidence is sufficient to infer that smoking cessation reduces the risk of cancers of the oral cavity, pharynx, larynx, esophagus, lung (including trachea and bronchus), stomach, liver, pancreas, kidney and ureter, bladder, cervix, colorectum, and blood (acute myeloid leukemia).⁴⁴ The 2020 Surgeon General's report also found that evidence is sufficient to infer that the relative risk (RR) of lung cancer decreases steadily after smoking cessation when compared to people who continue to smoke. For example, at 10 to 15 years after smoking cessation, the lung cancer risk of individuals who quit is about half that of individuals of the same age who continue to smoke.⁴⁴

Tobacco and Cancer by Demographic Subgroup

Tobacco use prevalence has slowly trended downward among the general population in the United States over many decades (see chapter 2). In 2024, a record low of 9.9% of U.S. adults reported current use of cigarettes compared with 20.9% in 2005.^{51,52} However, many population subgroups continue to have a higher prevalence of tobacco use and associated diseases relative to the population overall, including people living in rural communities, military veterans, sexual minorities, people with lower educational attainment or income level, people without health insurance, people who have mental or behavioral health conditions, people with alcohol and other substance use disorders, and certain racial and/or ethnic groups, most notably American Indian and Alaska Native populations.⁵³ For example, the cigarette smoking prevalence among African American and Hispanic populations in 2022 differed by sex compared to White populations, with higher prevalence of smoking among African American men compared to non-Hispanic White men, but lower prevalence among African American women and Hispanic men and women than White women.⁵⁴

As described in NCI Tobacco Control Monograph 22, *A Socioecological Approach to Addressing Tobacco-Related Health Disparities*, many factors contribute to the prevalence of tobacco use, including the interaction of factors at the individual, interpersonal, community/neighborhood, societal, and policy level.⁵⁵ Tobacco and alcohol industry practices, including marketing and product formulation also influence prevalence and product type used by different demographic groups.⁵⁵⁻⁵⁷ These factors continue to influence tobacco use prevalence in these population groups, helping to maintain higher levels of tobacco use and negative health outcomes, and lower rates of decline in prevalence, compared with the general population.

Similarly, key indicators of smoking cessation, including quit attempts, receiving advice to quit from a health professional, and use of evidence-based cessation therapies, also vary across populations, with lower prevalence across certain subgroups defined by educational attainment, poverty status, age, health insurance status, race, ethnicity, and geography.^{44,53,58}

Tobacco and Cancer by Tobacco Product

Although attention has focused primarily on cigarette smoking, other tobacco products, including cigars, cigarillos, pipes, and hookah, contain nicotine and toxic compounds and expose the user and the bystander to carcinogens and other harmful constituents. Cigars and pipes are established causes of cancer^{2,3,15} and substantial evidence supports that cigarillo and hookah use are also causes of cancer.^{2,59-61} Hookah smoking was traditionally viewed as a relatively safe form of tobacco use,⁶² but studies demonstrate that hookah use results in exposure to significant levels of carbon monoxide⁶³ and many harmful toxicants, including carcinogens.^{2,3,59,61,64,65} A growing body of epidemiological evidence links hookah use to lung, oral, and esophageal cancers.^{66,67} Smokeless tobacco products also cause cancer, including cancers of the oral cavity, esophagus, and pancreas.^{3,14,68,69} Research on the cancer risk of alcohol in combination with tobacco products other than cigarettes is very limited.

Surveys from 2013 to 2016 indicated that a substantial proportion of individuals, particularly young people, engaged in polytobacco use (i.e., the use of multiple tobacco products).^{70,71} Results from the 2024 National Youth Tobacco Survey found that 8.1% of middle and high school students in the United States reported current use of any tobacco product; 3.0% reported use of multiple tobacco products, and e-cigarettes were the most frequently reported product currently used (5.9%).⁷² The Population Assessment of Tobacco and Health Study in the United States found that among participants who smoked cigarettes, polytobacco use was more common among youth (12–17 years) and young adults (18–24 years), than among adults 25 years and older.⁷⁰ Mattingly and colleagues (2021)⁷³ examined adult (18 years and older) tobacco use patterns using data from the 2014–2015 and 2018–2019 Tobacco Use Supplement to the Current Population Survey and the 2015–2019 National Health Interview Survey, 2 nationally representative U.S. surveys. They found that both dual use of electronic nicotine delivery systems (ENDS) and cigarettes, as well as cigarettes with polytobacco use (ENDS, cigars/cigarillos/little filtered cigars, and pipe or hookah) decreased over time; in contrast polytobacco use without cigarettes increased over time. These complex trends also varied by age, sex, and race and/or ethnicity. These data are important for understanding tobacco use trends across the population; however, as of 2026, little evidence exists concerning the effects of co-use of e-cigarettes, or polytobacco use and alcohol, on cancer risk.

Epidemiology of Alcohol Use and Cancer Risk

The two major authoritative sources for summary and adjudication of evidence concerning the causal and dose–response relationships between alcohol and cancer are IARC and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR). IARC develops monographs assessing the mechanistic and epidemiological evidence for whether an exposure is

related to cancer.⁷⁴ IARC monographs do not assess dose–response relationships, though this topic is discussed as part of their assessment of causality. By contrast the WCRF/AICR Continuous Update Project focuses on the epidemiological evidence and includes meta-analyses assessing dose–response relationships.⁴

Globally, about 741,000, or 4.1%, of all new cases of cancer in 2020 were attributable to alcohol consumption.⁷⁵ In 2019 in the United States, 96,730 (5.4%) of incident cancers were estimated to be caused by alcohol consumption with 42,400 of these in men and 54,330 in women.⁴⁷ For cancer mortality, an estimated 20,216 deaths were attributable to alcohol during 2020–2021, with 14,562 in men and 5,654 in women.⁷⁶ Alcohol is the third leading modifiable risk factor for cancer in the United States, after cigarette smoking and excess bodyweight, highlighting the importance of efforts to reduce alcohol consumption for cancer prevention.⁴⁷

The large body of evidence concerning alcohol and cancer demonstrates that consumption of alcoholic beverages causes increased risk for oral and pharyngeal cancer, laryngeal cancer, esophageal cancer (specifically, squamous cell carcinoma),⁷⁷ female breast cancer in women, colorectal cancer, and liver cancer.¹ WCRF/AICR also judges the evidence linking stomach cancer and alcohol to be strong.⁴ Importantly, the shape of the dose–response curves for alcohol and the risk of specific cancers appears to differ by site. For example, very strong evidence of increased risk is observed even at low levels of drinking for female breast cancer, one of the most common cancers in the United States.⁷⁸ Evidence is also growing that head and neck cancer risk increases with consumption of <1 drink per day⁷⁹ and a 2023 meta-analysis reports elevated risk for colorectal cancer with reported consumption of <1 U.S. standard drink per day.⁸⁰

Two meta-analyses of alcohol consumption and liver cancer reported increased risk at one or more drinks per day.^{81,82} In contrast, the WCRF/AICR concluded that risk for liver and stomach cancer does not increase until three drinks per day.⁴ This suggests that low levels of alcohol consumption may increase the risk for some, but not all, cancers related to alcohol consumption.¹ A 2021 meta-analysis reported a linear dose–response relationship for stomach cancer and alcohol consumption with risk increasing linearly beginning at consumption of 5 grams per day of alcohol.⁸³ Finally, a large 2023 meta-analysis found that less than one U.S. standard drink per day was associated with increased risk of esophageal, colorectal, and female breast cancers, as well as increased risk of other cancers at higher levels of alcohol consumption.⁶

Some studies have found an association between alcohol and an increased risk for other cancer sites, including ovary, prostate, uterus, and bladder, but the evidence for these associations is deemed inconclusive.² More evidence is needed to understand the mechanisms potentially underlying associations between alcohol and increased risk of skin cancers (both melanoma and nonmelanoma skin cancers) as well as cancers of the prostate and pancreas. In 2010, the evidence linking alcohol and pancreatic cancer was rated as “limited.”² In 2025, a study that used a large, pooled analysis of individual-level data from 30 cohorts with >10,000 incident cases of pancreatic cancer found significant increases in risk associated with consumption of 30–59 grams of ethanol per day and even greater risk at higher levels of consumption.⁸⁴ Evidence for associations between alcohol consumption and melanoma also appears to be strengthening,⁸⁵ but the relationship with prostate cancer remains unclear, with meta-analyses published in 2020⁸⁶ and 2023⁸⁰ reporting somewhat different results based on alcohol type consumed and cancer type.

More research is also needed on mechanisms underlying associations between alcohol consumption and increased risk for liver and female breast cancer, although major aspects of these mechanisms have been identified.⁸⁷ Alcohol consumption is associated with decreased risk of kidney cancer (Strong Evidence/Probable grading by WCRF/AICR)⁴ and non-Hodgkin lymphoma.^{4,88} Inverse associations with kidney cancer could be related to alcohols' diuretic effects, insulin sensitivity, or perhaps poorly measured or unmeasured confounding; further epidemiological studies could help clarify the potential importance of these mechanisms.⁸⁹⁻⁹¹ More research is also needed to examine potential mechanisms for an inverse association between alcohol use and non-Hodgkin lymphoma.⁹² Nevertheless, the reduced number of cases of kidney cancer and non-Hodgkin lymphoma attributable to alcohol consumption are much lower than the increased number of cancers observed at other sites.

Compared with people who do not drink, regular consumption of about 50 grams of ethanol per day is associated with an approximately 3-fold increase in risk for oropharyngeal cancers, a 2-fold risk for cancers of the larynx and esophagus, and a risk ratio (RR) of 1.5 for female breast cancer and 1.4 for colorectal cancer.¹ For reference, 50 grams of alcohol per day corresponds to about 3.5 U.S. standard drinks per day.^{1,33} Ten grams of ethanol per day is associated with a RR of 1.15 (95% CI, 1.09–1.22) for oral cavity cancer, 1.13 (95% CI, 1.05–1.21) for pharynx cancer, 1.09 (95% CI, 1.05–1.13) for larynx cancer, 1.07 (95% CI, 1.05–1.08) for colon cancer, 1.04 (95% CI, 1.01–1.08) for premenopausal female breast cancer, and 1.08 (95% CI, 1.05–1.10) for postmenopausal female breast cancer,⁷⁵ providing further evidence that low level alcohol use is carcinogenic. Table 4.2 summarizes results of the 2010 IARC monograph, *Monographs on the Evaluation of Carcinogenic Risks to Humans: Alcohol Consumption and Ethyl Carbamate (Volume 96)*. Rumgay and colleagues (2021)⁸⁷ provide a thorough review of the epidemiology and biological mechanisms associated with alcohol use and cancer. Their review highlights the evolving nature of the evidence linking alcohol and some of the cancer sites, including sparse or inconsistent evidence. For example, the WCRF/AICR Continuous Update Project concluded that there was limited—but suggestive—evidence that alcoholic drinks increase risk of lung, pancreatic, and skin cancers.⁴

Trends in Alcohol Use by Demographic Subgroup

Research on alcohol consumption consistently shows variations in drinking by race and/or ethnicity, sex, age, socioeconomic status (SES), and other demographic characteristics. Associations between demographic characteristics and alcohol use differ from tobacco in several important ways. Most notably, people of higher SES report drinking more alcohol than those of lower SES, but those of lower SES who drink tend to report more heavy drinking and greater negative alcohol-related consequences.⁹³⁻⁹⁵ Patterns of beverage consumption are changing in association with reductions in alcohol consumption, the COVID-19 pandemic, and changes in types of products available along with marketing practices and price.^{21,96-100} Detailed descriptions of tobacco and alcohol use and co-use for the population overall and for specific demographic groups are presented in chapters 2 and 3.

Secular trends in alcohol consumption in the population overall and by demographic group will influence the future incidence of cancers related to alcohol and to the co-use of tobacco and alcohol. Efforts at modeling the effects of these changing patterns of use with approaches such as those used by the Cancer Intervention and Surveillance Modeling Network (CISNET) project for

tobacco and cancer screening would be valuable for understanding future cancer trends and developing appropriate cancer control strategies.¹⁰¹ These modeling tools have not yet been applied specifically to alcohol and cancer or tobacco and alcohol co-use.

Alcohol and Cancer by Alcohol Product

Sufficient evidence demonstrates (1) the consumption of alcoholic beverages is causally related to several types of cancer and (2) ethanol in alcoholic beverages and its metabolic product, acetaldehyde, are carcinogenic.¹ Unlike tobacco products that can have different strengths of association with cancer and other diseases (e.g., cigarettes compared with smokeless tobacco), cancer risk does not vary by the type of alcoholic beverage consumed (e.g., wine, beer, or spirits), with the prime determinant of cancer risk being the amount and frequency of ethanol consumed.¹ Although some studies report differences in risk for different types of alcoholic beverages, these are most often attributed to chance or more commonly to confounding. For example, people who report largely or entirely wine consumption are likely to have different and healthier dietary intakes as well as reporting higher levels of physical activity than those who report largely beer or spirits consumption.¹⁰²⁻¹⁰⁴

Table 4.2 Findings From the 2010 International Agency for Research on Cancer Monograph, *Evaluation of Carcinogenic Risks to Humans: Alcohol Consumption and Ethyl Carbamate (Volume 96)*

Findings regarding alcohol consumption and cancer	
There is sufficient causal evidence of an association between alcohol consumption and risk for cancer of the—	• Oral cavity/pharynx • Larynx • Esophagus • Liver • Colon and rectum • Female breast
There is insufficient causal evidence of an association between alcohol consumption and risk for cancer of the—	• Stomach • Lung
There is evidence of no increase in risk between—	• Consumption of alcoholic beverages and renal-cell cancer – In several studies, increasing intake of alcoholic beverages was associated with a significantly lower risk for kidney cancer.
There is evidence of an inverse association or no association between—	• Consumption of alcoholic beverages and the risk for non-Hodgkin lymphoma – Most studies of non-Hodgkin lymphoma showed a lower risk for drinkers compared with nondrinkers.

Table 4.2 (continued)

There is sparse and/or inconsistent evidence for an association between consumption of alcoholic beverages and risk for cancer of the—	• Pancreas • Cervix • Endometrium • Ovary • Vulva and vagina • Male breast • Urinary bladder • Prostate • Testis • Brain • Thyroid • Skin melanoma • Hodgkin disease, leukemias • Multiple myeloma
--	--

Source: Adapted from IARC 2010.¹

Reduction in Alcohol Consumption and Cancer Risk

In 2023, IARC convened a working group of 15 scientists from 8 countries to qualitatively evaluate the strength of published epidemiologic evidence on the potential for alcohol reduction or cessation to reduce alcohol-related cancer risk. They also evaluated mechanistic evidence on the potential effects of alcohol reduction or cessation to reduce alcohol-related carcinogenesis.¹⁶ A summary of this IARC report by the authors¹⁰⁵ supports findings from previous IARC and WCRF/AICR reports suggesting that sufficient evidence shows that alcohol reduction or cessation reduces alcohol-related risk for cancers of the oral cavity and esophagus, while only limited evidence exists regarding the impact of alcohol reduction or cessation on reduction of risks for cancers of the larynx, colorectum, and female breast, and inadequate evidence exists regarding risks for cancers of the pharynx and liver. Differences in the conclusions about the effects of alcohol consumption reflect limitations in the available epidemiologic data by cancer site. Research on mechanisms linking alcohol and cancer support the idea that cessation or reductions in consumption should reduce risk of alcohol-related carcinogenesis across sites. However, for some sites, such as colon and rectum, there are few epidemiological studies, some of them small, and results are mixed.¹⁰⁵

A 2024 study estimated that 20,216 cancer deaths in the United States in 2020–2021 were attributable to alcohol consumption, and 16,800 of these could have been prevented if no adults exceeded the 2020–2025 U.S. Dietary Guidelines recommended intake of no more than 1 (for women) or 2 (for men) drinks per day.⁷⁶ Worldwide, of 741,000 cancer cases attributable to alcohol, approximately 86% are associated with self-reported consumption of 20+ grams per day (~1.5 standard drinks).⁷⁵ Together, these studies support addressing alcohol as a target for cancer prevention and show that the greatest reductions in cancer mortality could be achieved by preventing consumption of larger amounts of alcohol.

Mechanisms of Carcinogenesis for Tobacco and Alcohol

Detailed review of the extensive literature on mechanisms of carcinogenesis of tobacco and alcohol can be found in chapter 5. Briefly, there are many mechanisms by which tobacco products cause cancer. These underlying mechanisms vary by the type of tobacco product used, with the strongest risks found for combusted tobacco products such as cigarettes, pipes, and cigars.^{50,106} Tobacco smoke contains more than 7,000 compounds and at least 80 carcinogens.¹⁰⁷ These compounds cause cancer via diverse mechanisms including direct exposure to carcinogens; DNA damage; oxidative stress; inflammation; and changes in cell proliferation, immune response, and cellular metabolism.⁵⁰

For alcohol, a primary mechanism for carcinogenesis, particularly for cancers of the aerodigestive tract, is the formation of acetaldehyde, a carcinogenic byproduct of alcohol metabolism.^{1,87,108} Other mechanisms thought to contribute to carcinogenesis from alcohol include changes in DNA methylation, induction of the cytochrome P450 2E1, and increased inflammation and oxidative stress.^{87,109} Additionally, alcohol consumption affects estrogen regulation, which is thought to play a role in the relationship between alcohol consumption and female breast cancer.⁸⁷

As described in chapter 5, several potential mechanisms have been proposed for how tobacco and alcohol act synergistically to cause cancer, including that tobacco and alcohol expose users to some of the same carcinogens. Acetaldehyde, the most important of these overlapping exposures, is produced by the metabolism of ethanol in alcoholic beverages in the oral cavity and elsewhere in the digestive system by alcohol dehydrogenase (ADH) enzymes that are found endogenously and in the oral microbiome.^{110,111} Acetaldehyde is also one of the major volatile organic compounds found in tobacco smoke, primarily produced by the combustion of polysaccharides.¹¹² Tobacco smoke also contains a wide variety of carcinogenic polycyclic aromatic hydrocarbons (PAHs), and some alcoholic beverages also contain PAHs,¹¹³ potentially increasing exposure among people who both smoke tobacco and drink alcohol. Additionally, ethanol might promote cancer development by acting as a solvent for other carcinogenic agents, such as chemicals in tobacco and tobacco smoke.⁸⁷ Lastly, alcohol consumption can increase membrane permeability in the aerodigestive system, especially the oral cavity, pharynx, larynx, and esophagus increasing uptake of carcinogens from both the alcohol itself and from tobacco smoke.¹¹⁴

Studies of individuals with aldehyde dehydrogenase 2 (ALDH2) deficiency, also known as alcohol flushing syndrome, have provided important evidence concerning mechanisms of carcinogenesis related to alcohol (see chapter 5). The ALDH2 gene codes for a key enzyme involved in the detoxification of acetaldehyde.¹¹⁵ ALDH2 deficiency affects approximately 8% of the world's population and is very common in East Asian people, with an allele frequency of 35% to 45%.^{116,117} Alcohol consumption by individuals with ALDH2 deficiency results in facial flushing, tachycardia, nausea, and headache, due to a rapid increase in circulating acetaldehyde concentrations.^{115,116} ALDH2 deficiency is associated with increased risk of aerodigestive tract cancers, including cancers of the oral cavity, pharynx, larynx, and esophagus.¹¹⁶⁻¹¹⁸ Among those who chronically drink alcohol, ALDH2 deficiency is one of the highest risk factors for cancer, with risk increasing with the extent of drinking.^{116,119} For example, a meta-analysis and Mendelian randomization approach of six case-control studies

by Boccia and colleagues (2009)¹²⁰ found that, compared with the ALDH2*1/*1 polymorphism (rs671), the ALDH2*1/*2 was associated with an increased risk of head and neck cancers among people who reported moderate and heavy drinking, but not among people who reported never drinking. The authors also noted that substantial increases in blood acetaldehyde levels were observed in people heterozygous for ALDH2 with administration of ethanol.¹²⁰ Further, a 2022 review indicated that risk for esophageal cancer was significantly higher among those with ALDH2 deficiency who consumed alcohol, with the risk increasing 50-fold among those who are ALDH2 deficient, drink alcohol, and also smoke cigarettes.¹¹⁶

The dramatic increase in risk observed for people with the ALDH2 deficiency who consume alcohol provides strong evidence for the causal role of acetaldehyde in head and neck cancers.^{117,121} Furthermore, these physiological processes provide a clear mechanism for the synergistic effects of tobacco and alcohol on head and neck cancers.¹²² Thus, established biological factors could account for both additive and multiplicative effects of tobacco and alcohol on cancer risk. Combined use of tobacco and alcohol in the context of ALDH2 deficiency could also influence behavioral factors related to risk, such as the probability of binge drinking or the specific temporal pattern of co-use.^{117,121,123,124} More research is needed to enhance prevention of cancers of the aerodigestive system addressing behavior, exposure, and the biological factors relate to use and co-use of tobacco and alcohol.

Historically, the unpleasant effects of alcohol consumption have been a deterrent against heavy drinking among people with ALDH2 deficiency, resulting in protective effects against heavy alcohol use and resulting disease.¹¹⁹ However, influenced by social, cultural, and economic factors, alcohol use has become more common among men in some populations that include large number of ALDH2 deficient individuals.¹¹⁹ Absent intervention, increased rates of cancers and other alcohol-associated disease among people with ALDH2 deficiency who drink can be expected in the future. Relatively little research has been carried out in the United States addressing alcohol use among people with ALDH2 deficiency¹²⁵ or the combined effects of ALDH2 variants and tobacco use.¹²⁶ Efforts to improve surveillance of alcohol use in subgroups who are at increased risk, such as East Asian communities, could increase awareness and bring important public health benefits.¹²⁷

Epidemiology of Synergistic Cancer Risk for Joint Tobacco and Alcohol Exposures

Comprehensive reviews by IARC and WCRF/AICR of the alcohol literature examine the question of whether cancer risk is synergistically affected by combined tobacco smoking and alcohol exposures.^{1,2,4} These reports systematically explore combined effects and provide a comprehensive assessment of the literature. The WCRF/AICR report, based on epidemiological evidence, identified “amplified” risk for tobacco and alcohol exposures for cancers of the oral cavity, pharynx, larynx, and esophagus.⁴ The 2010 and 2012 IARC reports, based on epidemiological, animal, and mechanistic evidence, reached similar conclusions and showed that the joint effects were multiplicative rather than additive for cancer of the esophagus, larynx, and oral cavity.^{1,2} Other cancer sites, such as lung, produced less clear evidence of synergy. A summary of the cancer risk from tobacco smoking, alcohol use, and synergistic cancer risk is shown in Table 4.3.

Table 4.3 Summary of Literature on Independent and Synergistic Cancer Risk Related to Tobacco Smoking and Alcohol

Disease site	Caused by tobacco	Caused by alcohol	Evidence of synergy
Aerodigestive tract	Yes ^{a,b}	Yes ^{c,d}	Yes ^{b,c,d}
Esophagus (squamous)	Yes ^{a,b}	Yes ^{c,d}	Yes ^{b,c,d}
Larynx	Yes ^{a,b}	Yes ^{c,d}	Yes ^{b,c,d}
Oral cavity and pharynx	Yes ^{a,b}	Yes ^{c,d}	Yes ^{b,c,d}
Colon and rectum	Yes ^{a,b}	Yes ^{c,d}	-
Liver	Yes ^{a,b}	Yes ^{c,d}	-
Stomach	Yes ^{a,b}	Yes ^d	-
Bladder	Yes ^{a,b}	-	-
Blood	Yes ^{a,b}	-	-
Acute myeloid leukemia	Yes ^{a,b}	-	-
Hodgkin lymphoma	-	-	-
Myeloma	-	-	-
Non-Hodgkin lymphoma	-	*	-
Cervix	Yes ^{a,b}	-	-
Kidney and renal pelvis	Yes ^{a,b}	*	-
Lungs, bronchus, trachea	Yes ^{a,b}	-	-
Pancreas	Yes ^{a,b}	-	-
Breast (female)	-	Yes ^{c,d}	-
Endometrium	-	-	-
Ovary	-	-	-
Prostate	-	-	-
Skin	-	-	-
Thyroid	-	*	-

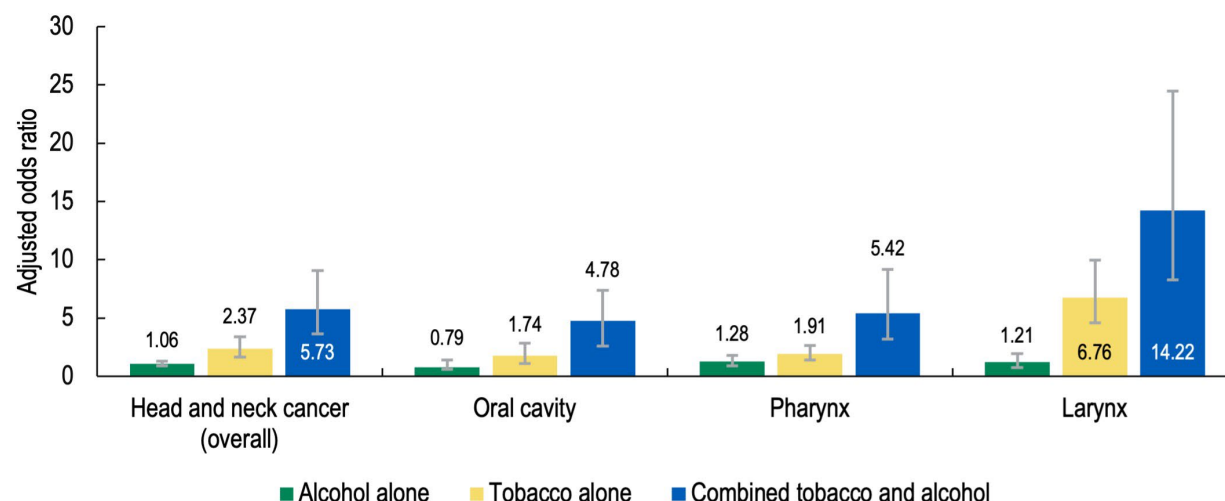
Note. Cancers are presented in order of evidence of synergy (caused by tobacco and alcohol), caused by tobacco but not alcohol, caused by alcohol but not tobacco, or caused by neither; they are then listed alphabetically within those clusters. A dash (-) indicates that as of 2026, there is no conclusive evidence regarding a causal relationship with tobacco or alcohol use or synergy related to tobacco and alcohol use.

^aUSDHHS 2014,³ ^bIARC 2012,² ^cIARC 2010,¹ ^dWorld Cancer Research Fund/American Institute for Cancer Research 2018.⁴

*Inverse associations with alcohol consumption are observed for kidney cancer, non-Hodgkin lymphoma, and thyroid cancer (see sections “Epidemiology of Alcohol Use and Cancer Risk” and “Thyroid Cancer” in this chapter).

Aerodigestive Tract Cancers

Based on the IARC and WCRF/AICR reports, a synergistic relationship between tobacco use and alcohol use and cancer risk on a multiplicative scale has been observed for squamous cell cancers of the oral cavity, larynx, pharynx, and esophagus.^{1,4} A 2009 pooled analysis of 18 case-control studies, with 11,221 cases and 16,168 controls, reported greater than multiplicative joint effects of tobacco smoking and alcohol for head and neck cancers overall and separately for cancers of the oral cavity and pharynx.⁵ Results were positive but not statistically significant for the larynx. These interactions are illustrated in Figure 4.1.

Figure 4.1 Risk of Cancer at Different Sites for Alcohol, Tobacco, and Combined Use

Note. Adjusted odds ratios are the results of random effects logistic regression models comparing ever use of tobacco and/or alcohol compared to never use of tobacco and/or alcohol, adjusted for age, sex, education, race/ethnicity, and study center.

Source: Hashibe et al. 2009.⁵

An important early study examining levels of tobacco smoking and drinking in a population with a wide range of consumption levels showed much more dramatic increases in risk of esophageal cancer for those who smoked and drank heavily, providing evidence of synergistic effects on cancer risk.¹²⁸ Castellsagué and colleagues (1999)¹²⁸ analyzed risk of esophageal cancer in 5 hospital-based, case-control studies of 830 cases and 1,779 controls in Argentina, Brazil, Paraguay, and Uruguay. The study was coordinated by IARC, and the 5 studies took place from 1986 to 1992. Compared with men who reported never smoking or drinking, men who reported using 1–7 cigarettes per day and 1–24 ml of ethanol per day had an adjusted odds ratio (aOR) of 4.15, whereas men who reported use of ≥ 25 cigarettes per day and ≥ 150 ml of ethanol had an aOR of 50.85 (95% CI, 22.80–113.39). The interaction between tobacco and alcohol use for esophageal cancer risk was not statistically significant, likely reflecting the modest sample sizes for the highest levels of exposure.

Most past research on interactions between tobacco and alcohol use and cancer risk has focused on combusted tobacco products, especially cigarettes. A systematic review and meta-analysis of 2 cohort studies and 31 case-control studies examined the risk of oral squamous cell carcinoma in people who used smoked tobacco, smokeless tobacco, and alcohol.¹²⁹ An elevated risk of oral squamous cell carcinoma was found for both co-use of smoked tobacco and alcohol (odds ratio [OR] = 4.74, 95% CI = 3.51–6.40) as well as co-use of smokeless tobacco and alcohol (OR = 7.78, 95% CI = 2.86–21.14). The highest relative risk of oral squamous cell carcinoma was observed for combined use of alcohol, smoked tobacco, and smokeless tobacco of (OR = 16.17, 95% CI = 7.97–32.79). Elevated risks for oral squamous cell carcinoma were also observed for use of each of the three products separately. Formal tests for interaction between products were not presented. Given the growing global market for smokeless tobacco products, further studies of interactions between smokeless tobacco and alcohol use are urgently needed.

Overall, these synergistic increases in risk observed in many studies of head and neck cancers strongly support efforts to address tobacco and alcohol co-use for cancer prevention.

A few studies have examined potential for differential cancer risk among those who consume tobacco and alcohol products by demographic factors. Three studies examined key differences for specific oral cancers by several factors, including sex, race, age, geographic region, and human papillomavirus (HPV) status (Table 4.4). In a narrative review of studies conducted in the Americas, Europe, and Asia, Pelucchi and colleagues (2006)¹³⁰ concluded that the evidence supported the presence of synergistic increases in risk of oral, laryngeal, and esophageal squamous cell cancer associated with co-use of tobacco and alcohol. For liver cancer they concluded that tobacco and alcohol use appeared to be independent risk factors.

Hashibe and colleagues (2009),⁵ in a pooled analysis of case-control studies, evaluated differences between esophageal and head and neck cancers, respectively, by tobacco and alcohol use. They reported multiplicative joint effects for cancer risk among male and female participants who used both tobacco and alcohol (multiplicative interaction parameters for men: 2.36 [95% CI, 1.66–3.36] and women: 2.05 [95% CI, 1.35–3.11]) and in different age groups (multiplicative interaction parameters for <45 years = 2.93 [95% CI, 1.42–6.02], 45–60 years = 1.93 [95% CI, 1.40–2.66], >60 years = 2.19 [95% CI, 1.46–3.29]). Brown and colleagues (1994)¹³¹ conducted a case-control study of 373 patients with squamous cell esophageal cancer (124 White men; 249 Black men) and 1,364 control subjects (750 White men; 614 Black men) to explore racial disparities in rates of squamous cell esophageal cancer. At every level of tobacco-alcohol co-use, the aOR for esophageal squamous cell carcinoma was higher among Black men than among White men. At the highest levels of exposure to tobacco and alcohol, the aORs for esophageal squamous cell carcinoma (adjusted for age, geographic area, and income) were 149.2 (95% CI, 39.2–367.4) among Black men, compared to 35.4 (95% CI, 10.0–125.5) among White men. The authors suggested that these differences in risk may be attributed to qualitative differences in alcohol consumption, differences in other environmental exposures, or genetic differences in susceptibility to these factors.

Examination of the development of head and neck squamous cell carcinoma and interactions between established risk factors, including tobacco smoking, alcohol drinking, and human papillomavirus (HPV) in a modest sized case-control study ($N = 145$ cases), suggested that the effects of tobacco, alcohol, and their interaction could be weaker in patients positive for high-risk HPV genotypes than in patients negative for high-risk HPV genotypes.¹³² When stratified by high-risk HPV status, the effect estimates for tobacco smoking, alcohol drinking, and their additive and multiplicative interactions were consistently smaller and non-significant in the high-risk HPV-positive subsample, whereas patients positive for HPV but negative for high-risk HPV had significant, positive effect estimates for tobacco and alcohol effects and for the additive interaction. This may be related to the observation that HPV is a strong initiator of carcinogenesis in oropharyngeal squamous cell carcinoma via a specific molecular mechanism independent of alcohol or tobacco. However, alcohol consumption can increase the probability of risky sexual behavior, thus increasing the likelihood of HPV infection.¹³³⁻¹³⁷

Table 4.4 Evidence From Selected Studies of Differences in Synergistic Effect by Demographics

Cancer type	Study	Study design	Sample	Results	Key demographic differences
Squamous cell esophageal cancer	Brown et al. 1994 ¹³¹	Population-based, case-control study	U.S. adult male participants from 3 geographic areas; 124 White and 249 Black male cases; 750 White and 614 Black male controls	• aOR for esophageal squamous cell carcinoma was higher among Black men (aOR = 149.2, 95% CI = 39.2–567.4) and White men (aOR = 35.4, 95% CI = 10.0–125.5) who reported heavier tobacco and alcohol use compared with men of those racial groups who reported no or light amounts of tobacco and alcohol use.	Race
Head and neck	Hashibe et al. 2009 ⁵	Pooled analysis, case-control studies	International Head and Neck Cancer Epidemiology (INHANCE) consortium; Since 2004; 18 studies; 12,282 cases and 17,189 controls	• A greater than multiplicative joint effect between ever-tobacco and -alcohol use was observed for head and neck cancer risk. • Multiplicative joint effects for cancer risk estimated for men and for women (multiplicative interaction parameters of 2.36 [95% CI, 1.66–3.36] and 2.05 [95% CI, 1.35–3.11] respectively) and differences by age (multiplicative interaction parameters for <45 years = 2.93 [95% CI, 1.42–6.02], 45–60 years = 1.93 [95% CI, 1.40–2.66], >60 years = 2.19 [95% CI, 1.46–3.29])	Sex (male/female); age (<45/45–59/60+); geographic region

Table 4.4 (continued)

Cancer type	Study	Study design	Sample	Results	Key demographic differences
Head and neck squamous cell carcinoma (HNSCC)	Auguste et al. 2020 ¹³²	Population-based case-control study	145 cases and 405 controls	• Current smoking (aOR = 11.6, 95% CI = 6.7–20.1), drinking >5 glasses of alcohol per day (aOR = 2.4, 95% CI = 1.2–4.7), and oral infection with high-risk HPV (aOR = 2.4, 95% CI = 1.1–5.0) were significantly associated with HNSCC. • The combined exposure to tobacco and alcohol produced a significant additive synergistic effect on the incidence of HNSCC (RERI = 9.8 [95% CI, 3.2–16.6]), but the multiplicative synergistic effect was not significant (multiplicative interaction parameter = 2.0 [95% CI, 0.8–5.4]). • The effects of tobacco, alcohol, and the combined exposure of tobacco and alcohol on HNSCC were consistently lower in high-risk HPV-positive than in high-risk HPV-negative individuals, though the three-way interaction of tobacco, alcohol, and high-risk HPV status was not explicitly tested.	HPV-positive versus HPV-negative HNSCC

Note. aOR = adjusted odds ratio; CI = confidence interval; HPV = human papillomavirus; RERI = relative excess risk due to interaction.

Synergistic Effects Between Tobacco and Alcohol Use for Other Cancer Sites

Convincing evidence supports the presence of synergistic interactions between tobacco and alcohol use and cancers of the aerodigestive system. Epidemiological evidence for these interactions is also supported by strong mechanistic evidence (see chapter 5). This section reviews evidence of a synergistic tobacco/alcohol exposure relationship with cancer sites not already identified by IARC or WCRF/AICR. Separate subsections address studies of cancers of the lung, liver and colon, female breast, thyroid and other sites. This section focuses on studies with more rigorous designs; however, a formal quality or risk of bias assessment was not conducted. Further details of the literature search are described in Appendix 4A, and selected studies are summarized in Appendix 4B. Overall, literature published since the 2010 and 2012 IARC reports and the 2018 WCRF/AICR report suggest additional potential examples of synergy between tobacco and alcohol consumption and cancer risk.

This section further describes evidence of differential synergistic relationships across population subgroups (e.g., sex, race, and ethnicity) for any cancer site, although few studies by population subgroup were identified. As noted previously, this chapter seeks to identify studies that assessed synergistic relationships by exposure to specific types of tobacco products (i.e., cigars, e-cigarettes, smokeless tobacco) or specific alcoholic beverages (i.e., wine, liquor, beer). However, few studies by tobacco product type or alcoholic beverage type were identified. The studies reviewed primarily address cigarettes and other combusted tobacco products. Research has also focused on the combined effects of smokeless tobacco products and alcohol use on head and neck cancer risk, because smokeless tobacco is associated with increased risk of these cancers.

Lung Cancer

Brenner and colleagues (2019)¹³⁸ published a pooled analysis examining the potential effect of alcohol consumption on lung cancer risk, using data from the International Lung Cancer Consortium and Synergy Consortium Studies. Their study included 21 case-control studies and 1 cohort study from North America (11), Europe (8), and Asia (3) with data on participants' alcohol intake. The interaction analysis between tobacco smoking and drinking, including 19,149 cases and 362,340 controls, suggested lung cancer risk was associated with higher levels of tobacco consumption (i.e., pack years), with an interaction observed for those in the highest tobacco and alcohol consumption groups. The effect estimate deviated from that expected on the additive scale among those who consumed ≥ 20 grams/day of alcohol and ≥ 10 pack years of tobacco (OR = 11.23, 95% CI = 10.29–12.26). The test for a multiplicative interaction between alcohol consumption and smoking intensity was also significant ($p < .001$). This study found an overall positive interaction between high pack years of smoking and elevated levels of drinking. However, the authors of the study noted:

This may reflect some type of biological interaction of the combination of the two exposures, or it may also reflect a different exposure profile across drinking categories, where those at higher levels of both tobacco and alcohol consumption may be exposed to other factors, such as second-hand smoke from time spent in bars.

Furthermore, analyses from the Alberta's Tomorrow prospective cohort of 26,607 adults did not find evidence for an alcohol effect on lung cancer or interactions with tobacco use.¹³⁹ Further mechanistic research could help determine whether these epidemiological results are replicable and if they reflect a biological interaction related to carcinogenesis rather than unmeasured aspects of exposure.

Overall, there is inadequate evidence to support an association between alcohol consumption and lung cancer risk.¹ Ongoing epidemiological research has had mixed results,¹⁴⁰ with some studies suggesting an increased risk of lung cancer associated with drinking alcohol¹⁴¹ and others reporting protective effects.¹⁴²

Hepatocellular Carcinoma

Marrero and colleagues (2005)¹⁴³ examined the associations between cigarette smoking and alcohol use on hepatocellular carcinoma (HCC) in a case-control study of 70 patients with HCC, 70 patients with cirrhosis, and 70 patients without liver disease. Patients with cirrhosis and those without liver disease were included because cirrhosis is among the most important risk factors for development of HCC.¹⁴⁴ This study found that both tobacco and alcohol use were independent, dose-dependent risk factors for HCC.¹⁴³ When patients with hepatocellular carcinoma were compared to patients with cirrhosis, HCC risk increased nearly 6-fold for more than 1,500 grams of alcohol consumed per year (aOR = 5.7, 95% CI = 2.4–13.7), and nearly 5-fold for more than 20 pack years of smoking (aOR = 4.9, 95% CI = 2.2–10.6). Adjusted odds ratios for smoking and alcohol were far higher when patients with HCC were compared with patients without liver disease. The study also looked for an interaction effect between exposure to smoking and alcohol on HCC risk. When patients with HCC were compared to patients with cirrhosis, the risk for HCC was higher when patients were exposed to both cigarette smoking and alcohol (aOR = 7.2, 95% CI = 2.2–14.1), with a synergistic index >1, compared with exposure to cigarette smoking alone (aOR = 2.5, 95% CI = 1.7–15.0). or alcohol alone (aOR = 1.4, 95% CI = 1.1–4.0). The study concluded that alcohol and smoking are independent risk factors for HCC, and they also interact synergistically.¹⁴³

A further study in 2000 reported an interaction between tobacco and alcohol consumption for liver cancer in a case-control study in Greece of 333 patients with cancer and 360 controls.¹⁴⁵ More recently, a 2024 case-control study in Korea of 15,352 patients with liver cancer and 92,112 matched controls reported a synergistic interaction between light-to-moderate alcohol consumption and heavy smoking with a significant synergy index (2.75, 95% CI = 1.85–3.66).¹⁴⁶ Despite its importance, few studies have addressed the combined effects of tobacco and alcohol use on liver cancer. These analyses are complicated by the fact that patients with a diagnosis of cirrhosis of the liver, a common precursor to liver cancer, are strongly advised to abstain from alcohol consumption,^{147,148} highlighting the need for more detailed assessments of alcohol consumption over the life course, especially where circumstances are likely to lead to changes in consumption.

A 2025 study assessed the individual and interactive effects of cigarette smoking and alcohol consumption on HCC risk, using a nested case-control analysis of 108 HCC cases and 108 matched controls.¹⁴⁹ The analysis found a positive relationship between serum smoking biomarkers and HCC risk, serum alcohol biomarkers and HCC risk, smoking and HCC risk, and

alcohol use and HCC risk.¹⁴⁹ However, there was no evidence of synergistic effects between smoking and alcohol use on HCC risk, as interactions between self-reported smoking and alcohol use (synergy index = 1.27, 95% CI = 0.98–1.66), and interactions between smoking and alcohol biomarkers were not significant in predicting HCC (synergy index for 2-hydroxy-3-methylbutyric acid and cotinine = 1.59, 95% CI = 0.58–4.33; synergy index for 2-hydroxy-3-methylbutyric acid and nicotine = 1.36, 95% CI = 0.60–3.10).¹⁴⁹

Female Breast Cancer

Alcohol use causes female breast cancer. IARC has concluded that the “occurrence of malignant tumors of the female breast is causally related to the consumption of alcoholic beverages,”¹ and the WCRF/AICR review concluded that alcohol consumption is a “probable cause” for premenopausal and a “convincing cause” for postmenopausal breast cancer.⁴ Furthermore, alcohol alters some hormone levels that are associated with breast cancer risk, providing a plausible biological mechanism for the association (see chapter 5).^{87,150,151} Risk of breast cancer related to alcohol use may be increased for estrogen receptor positive women. Some research on the association between alcohol consumption and breast cancer also suggests that the time between menarche to first pregnancy may represent a period when breast tissue is particularly susceptible to carcinogens.¹⁵⁰

The potential for an association between active smoking, passive smoking (i.e., exposure to secondhand smoke), and female breast cancer has been addressed in several previous Surgeon General’s reports.^{3,152,153} The 2014 Surgeon General’s report reviewed epidemiologic studies and studies of biological mechanisms to understand associations between exposure to tobacco smoke and female breast cancer. This report concluded that the evidence was suggestive but not sufficient to infer a causal relationship between tobacco smoke and female breast cancer or between active smoking and female breast cancer and between exposure to secondhand tobacco smoke and female breast cancer.³ Similar conclusions were reached by a 2012 IARC review.²

However, some recent studies suggest a potential association. For example, a 2023 meta-analysis of 169 case-control or cohort studies of the relationship between cigarette smoking and female breast cancer reported a pooled RR of 1.07 (95% CI, 1.05–1.10) for women who currently smoked, compared with women who never smoked.¹⁵⁴ These authors also found that breast cancer risk increased with both the intensity of cigarette smoking (i.e., number of cigarettes smoked per day) and with increased duration of smoking.¹⁵⁴ The authors concluded, “this meta-analysis convincingly supports the contention that cigarette smoking is a risk factor for breast cancer.”¹⁵⁴ However, concerns remain in the field regarding possible poorly measured and unmeasured confounding, the timing of exposure, and the possibility of etiologic differences across the major subtypes of breast cancer.¹⁵⁵ Even after decades of study, further large and robust studies are needed to resolve the relationship between tobacco use and female breast cancer.

Moderate and heavy alcohol consumption during the developmental window between menarche to first pregnancy could potentially increase the lifelong risk of breast cancer.^{156,157} Such windows of susceptibility may also be present for smoking, as research examining the mechanism for smoking increasing female breast cancer risk suggests a potential increase in risk among women who initiated smoking before first childbirth.¹⁵⁸ However, this association was

only noted when the analyses did not adjust for age at first pregnancy and was attenuated by adjustment for pack years of smoking. The 2014 Surgeon General's report concluded that there was not clear evidence for a greater risk of female breast cancer associated with initiating smoking during adolescence or young adulthood than with initiating smoking at an older age.³

Several studies have reported significant multiplicative interactions for cigarette smoking and drinking alcohol in relation to female breast cancer risk,^{139,155,159,160} but in other studies, apparent interactions were not significant or not tested directly.^{158,161} Gaudet and colleagues (2017)¹⁵⁵ conducted a pooled analysis of 14 cohort studies that included 36,060 invasive female breast cancer cases and reported statistically significant positive interactions between alcohol consumption and several measures of smoking, including smoking status, cigarettes per day and years of smoking among those who currently smoked, and years of smoking and years since quitting in those who formerly smoked. The large sample size in this study is a notable strength. Zeinomar and colleagues (2019)¹⁶¹ found a significant 3-way multiplicative interaction between familial risk profile, alcohol consumption, and cigarette smoking ($p = .005$), primarily driven by women with very high familial risk profile, who saw a 30% increase in overall breast cancer risk compared to women who never smoked. Similarly, Li and colleagues (2020)¹⁶⁰ reported a significant synergistic increase in breast cancer risk for carriers of the *BRCA2* mutation in a retrospective analysis among women who consume alcohol and who also smoke cigarettes (i.e., at least 1 glass per month for 1 year plus at least 1 pack of cigarettes per month for 1 year; aHR = 1.43, 95% CI = 1.13–1.81; $p = .003$). Additionally, Viner and colleagues (2019)¹³⁹ found a “U-shaped curve” for the association with breast cancer, observing a lower cancer incidence among those who reported moderate alcohol consumption and minimal cigarette smoking, changing to a multiplicative interaction with increased consumption of cigarettes and alcohol, compared to people who did not smoke or drink.

Other studies have not found a synergistic relationship between alcohol consumption, smoking, and female breast cancer risk.^{162–164} As with other cancer sites, this may be due in part to differences in definitions of tobacco and alcohol use and measurement, as well as differences in specific outcome measures. Additional studies are needed to clarify the role of tobacco and alcohol in female breast cancer risk, with attention to the potential role of genetics and family history. Increases in alcohol-induced deaths among women in the United States emphasizes the importance of this area of research.¹⁶⁵

Thyroid Cancer

The relationship between cigarette smoking, alcohol consumption, and thyroid cancer risk is unclear. A pooled analysis in the United States¹⁶⁶ and a large study in Korea¹⁶⁷ examined the individual and combined risk of these substances on thyroid cancer risk. The pooled analysis of 5 U.S.-based cohort studies by Kitahara and colleagues (2012)¹⁶⁶ included more than 740,000 participants and 1,000 incident cases of thyroid cancer and was conducted to examine the association between cigarette smoking, alcohol consumption, and the risk of thyroid cancer. This study found that current smoking was associated with a significantly reduced risk of thyroid cancer (adjusted hazard ratio [aHR] = 0.68, 95% CI = 0.55–0.85) compared with never smoking.

Furthermore, the risk of thyroid cancer decreased with greater smoking intensity and duration. Among people who formerly smoked, the risk was lowest among those who quit more recently (<5 years), but not as low as for people who currently smoked. The risk for people who quit smoking 5 or more years ago was similar to people who never smoked.¹⁶⁶

Kitahara and colleagues also found that alcohol consumption was associated with a significant reduction in thyroid cancer risk, which was highest among those who consumed ≥ 7 drinks/week (aHR = 0.72, 95% CI = 0.58–0.90).¹⁶⁶ Additionally, compared to never smoking and nondrinking, current smoking and consumption of ≥ 1 drinks per week was associated with 36% reduced risk of thyroid cancer (joint aHR = 0.64, 95% CI = 0.47–0.86). The joint aHR for current smoking among participants who did not drink alcohol was weaker (aHR = 0.46, 95% CI = 0.29–0.73), while the joint aHR among participants who reported never smoking and reported ≥ 1 drink per week was similar (aHR = 0.70, 95% CI = 0.56–0.87). Overall, the reduced risk for current smoking was most pronounced among people who never drank, while the reduced risk for alcohol drinking was most pronounced for people who never smoked. The authors characterize the joint association of smoking and alcohol with thyroid cancer as submultiplicative (p for interaction = .004).¹⁶⁶

Yeo and colleagues (2022)¹⁶⁷ conducted a retrospective cohort study using data from the Korean National Health Insurance database ($N = 9,699,104$ participants). After a mean follow-up period of more than 8 years, there were ~90,000 cases of thyroid cancer (0.9%) among participants. These authors identified an inverse association between cigarette smoking and the risk of thyroid cancer, as well as an inverse association between alcohol consumption and thyroid cancer. The risk of thyroid cancer was significantly lower among participants who currently smoked (aHR = 0.74, 95% CI = 0.72–0.76), compared with participants who never smoked, using a model controlling for multiple covariates, including alcohol consumption. Adjusted hazard ratios for thyroid cancer among those who never smoked were 0.91 (95% CI, 0.89–0.92) among those with mild drinking, 0.80 (95% CI, 0.76–0.84) among those with moderate drinking, and 0.80 (95% CI, 0.74–0.86) among those with heavy drinking. The lowest risk of thyroid cancer was observed in participants reporting the highest levels of both drinking and smoking; among people reporting current smoking and drinking >30 g of alcohol per day the adjusted hazard ratio was 0.62 (95% CI, 0.59–0.66). Analyses of the risk of thyroid cancer for combined use were statistically significant (p for interaction < .001).

The submultiplicative effects of cigarette and alcohol co-use observed by Kitahara and colleagues as well as Yeo and colleagues report could be related to lower thyroid hormone and thyroid stimulating hormone levels, as well as lower prevalence of thyroid autoantibodies. This further suggests that there may be related, or common, biological pathways involved in observed reductions in thyroid cancer risk related to tobacco and alcohol use separately. However, a 2023 study using data from the NIH-AARP Diet and Health Study reported that associations between thyroid cancer and cigarette smoking and alcohol drinking were restricted to thyroid cancers at low risk for recurrence or mortality (“low-risk” thyroid cancers); no associations were observed for high-risk thyroid cancers.¹⁶⁸ Thus, these inverse associations may be due in whole or part to

detection bias (i.e., individuals who currently smoke or drink more heavily are less likely to undergo thyroid cancer surveillance or screening).¹⁶⁸ Furthermore, Kitahara and colleagues report a lower risk of thyroid cancer for people who report cigarette smoking but no alcohol use than for people who currently smoke and report one or more drinks per day.¹⁶⁶ This is consistent with the possibility of common biological pathways for tobacco and alcohol but their effects on such pathways may differ.

Cohort Studies of Cancer at Multiple Sites

A prospective cohort analysis by Pirie and colleagues (2013)¹⁶⁹ examined combined effects of alcohol and cigarette smoking on mortality in the Million Women Study cohort of 1.3 million women in the United Kingdom recruited between 1996 and 2001 and followed until January 1, 2011. The study authors conducted sensitivity analyses among women who did not drink or who consumed fewer than 3 units of alcohol (30 ml of ethanol or 1.67 U.S. standard drinks) per week. Compared to risk ratios for smoking-related mortality among the entire sample, sensitivity analyses found modest reductions in adjusted risk ratios from 4.38 in the entire sample to 3.76 (95% CI, 2.65–5.31) in the sensitivity analysis for cancer of the mouth, pharynx, larynx, nasal cavity, or sinuses; from 3.10 in the entire sample to 2.74 (95% CI, 2.27–3.30) in the sensitivity analysis for esophagus cancer; from 1.52 in the entire sample to 1.43 (95% CI, 1.11–1.85) in the sensitivity analysis for liver cancer; and from 1.13 in the entire sample to 1.06 (95% CI, 0.95–1.18) in the sensitivity analysis for breast cancer.¹⁶⁹

These results do not examine interactions between tobacco and alcohol use and cancer risk directly, highlighting the need for formal tests of interaction. Viner and colleagues (2019)¹³⁹ examined individual and combined effects of cigarette smoking and alcohol use on cancer risk among participants ($N = 26,607$) in Alberta's Tomorrow Project. Results suggested additive effects of tobacco and alcohol on risk of all cancers, colon, and prostate cancer.

All together, these studies highlight the need for further pooled analyses of epidemiological studies addressing the combined effects of tobacco and alcohol on cancer risk at multiple sites along with further mechanistic research. Additionally, efforts are needed to examine age specific patterns of tobacco and alcohol use and co-use, particularly in relation to female breast and liver cancer where developmental windows of susceptibility or behavior change related to precancerous effects may be relevant.

Measurement and Analysis

This section discusses considerations for measuring exposure to tobacco and alcohol, including biomarkers of tobacco and alcohol use. The results of the epidemiological studies reviewed in this chapter and in chapters 2 and 3 emphasize the importance of measurement. Careful consideration of intended analyses, sources of bias, and fitness for purpose are needed for measure selection.¹⁷⁰ As discussed in chapter 2, surveillance or surveillance epidemiology focuses on the ongoing collection of data for planning, implementation, and evaluation of public health programs and action.¹⁷¹ In contrast, measurement of behavior for etiological studies focuses on estimating potential causal relationships between aspects of exposure and outcomes as well as controlling for potential confounding in the assessment of such relationships.¹⁷² Thus, longitudinal cohort studies could well include measures of tobacco and alcohol use

patterns, including those at different stages of the life course and correlates of tobacco and alcohol use, that may not be of immediate interest to surveillance epidemiology unless or until they are demonstrated to be critical determinants of future disease burden.

The amount, frequency, and duration of tobacco and alcohol use, as well as cessation of use, can affect cancer risk; for this reason, epidemiologic analyses should consider frequency of use, intensity of use, frequency of heavy use days, and variability of use over the life course. The most commonly used measures of alcohol consumption include quantity/frequency (QF) and graduated frequency (GF) approaches. The QF approach addresses the number of days drinking during some specified period (e.g., past year) and the average number of drinks on such days. The GF approach specifies categories of standard drinks consumed (e.g., 1–2 drinks) and facilitates comparisons across groups at the expense of some detail.¹⁷³ Table 4.5 lists examples of tobacco and alcohol use measures that are relevant or potentially relevant to assessing cancer risk.

Table 4.5 Selected Tobacco and Alcohol Use Measures Useful for Epidemiological Studies

Measure type	Tobacco	Alcohol
Current use	• Current use (not at all, some days, or every day) or use on at least 1 day in the past 30 days	• Past-month use or use in the last 30 days • Past-year use
Use frequency and intensity, including QF or GF approaches	• Cigarettes per day or other tobacco and nicotine products per day • Daily/nondaily use (cigarettes or other tobacco products) • Days per month used (cigarettes or other tobacco products) • Number of days of [tobacco product] use in the past 30 days • Number of cigarettes per day or other products on days when the respondent smokes • Ever daily smoking among those who smoke nondaily	• Frequency of alcohol consumption • Quantity of standard drinks^{a,b} per occasion • Volume consumed in the past month and past year (overall and by beverage type) • Frequency heavy episodic drinking or binge drinking (≥ 4 drinks for women or ≥ 5 drinks for men on an occasion) • Frequency of high-intensity drinking: 8+, 10+, 12+, or 15+ drinks per day or occasion • Maximum drinks consumed in 1 day in the past month and past year

Table 4.5 (continued)

Use history and lifetime use patterns	• Ever use (having ever smoked even a puff of a cigarette and having ever smoked 100 or more cigarettes in one's lifetime) • Age of initiation • Cigarettes per day during periods of regular use • Number of quit attempts resulting in abstinence for at least 24 hours ("Serious" quit attempts) • Age at longest successful quit attempt • Duration of smoking abstinence for longest quit attempt • Pack years (based on years smoked and average number of cigarettes per day) • Use of other tobacco products, including duration, frequency, and intensity • Time to first cigarette or first tobacco use	• Lifetime abstinence (cumulative periods of abstinence in one's lifetime) • Age of initiation • Age at which began regular drinking (for example, at least once a month for 6 months) • Former drinking • Age of cessation • Lifetime accumulated number of drinks • Frequency of lifetime heavy episodic drinking or binge drinking and during specific time periods/decades • If quit, reason for quitting
---------------------------------------	---	--

Note. GF = graduated frequency; QF = quantity/frequency.

^aOne U.S. standard drink contains 0.6 fluid ounces or 14 grams of ethanol. A standard drink is equivalent to 12 fluid ounces of beer at 5% alcohol by volume, 5 fluid ounces of wine at 12% alcohol by volume, and 1.5 fluid ounces of distilled spirits at 40% alcohol by volume.

^bModerate drinking is defined as up to 2 standard drinks/day for men and up to 1 standard drink/day for women.¹⁷⁴

Measurement of Frequency of Use, Intensity of Use, and Simultaneous Use

Research as of 2026 indicates a need for further efforts related to several aspects of tobacco and alcohol use including measures of drinking intensity, especially high intensity drinking, and lifetime patterns of tobacco and alcohol co-use, along with more detailed data on the characteristics and temporality of co-use. For example, near simultaneous co-use might have different exposure consequences than co-use on different occasions during the same day, week, or month, as well as high intensity drinking during different developmental stages of the life course (e.g., adolescence, pre- or post-menopause).

Measures of high intensity drinking days/occasions, intended to capture higher levels of impairment relevant to acute consequences of drinking, may also be relevant to cancer and other chronic disease risks. For example, a meta-analysis of case-control studies found that alcohol use intensity (drinks per day) was a greater risk factor for head and neck cancers than duration of alcohol use,⁷⁹ emphasizing the importance of measuring heavy episodic drinking, high intensity drinking, and maximum drinks in a day for cancer risk assessment. Many standardized surveys and other health studies do not consider changes in the number of cigarettes per day over time. However, diary and ecological momentary assessment studies suggest the number of cigarettes smoked per day varies from day to day.¹⁷⁵ Longitudinal studies also suggest that at least some individuals change their smoking patterns and the amount that they smoke over time, which may affect cancer risk.¹⁷⁵⁻¹⁷⁷ A growing literature on patterns of smoking examines those who smoke intermittently and fewer cigarettes, different cessation characteristics, and other aspects of smoking trajectories.¹⁷⁸⁻¹⁸³ For example, in a study of 24,613 men ages 50–69 who smoked and participated in an alpha-tocopherol and beta-carotene cancer prevention trial, reducing smoking intensity at an average 5 cigarettes per day per intervention year reduced lung cancer risk compared with smoking 20 cigarettes a day, but cessation had the largest reduction in risk.¹⁸⁴ More efforts are also needed to incorporate such patterns into etiological analyses and modeling

of population-level tobacco use and its consequences. For alcohol, a 2021 Australian prospective cohort study ($N = 226,162$) found a marginally increased risk of female breast cancer when alcohol intake was concentrated over time (i.e., the same amount of alcohol was consumed in 1–3 days versus 4–7 days).¹⁸⁵

Measures of simultaneous use of tobacco and alcohol could also be helpful for understanding cancer risk, particularly for upper aerodigestive tract cancers, for which a synergistic effect of these two substances is well documented. Broadly speaking, simultaneous use is defined as use at the same time; during simultaneous use, the effects of both substances could overlap and interact in important ways. However, the time periods involved, and the specific behaviors associated with “simultaneity” have not received much attention. Simultaneous use questions have rarely been included in epidemiologic studies, perhaps because researchers assume that alcohol drinking and tobacco smoking typically occur at the same time or in close time proximity. A study of 217 college students found that many people who smoke nondaily only smoke when drinking and that smoking is more appealing to them when drinking with greater re-enforcement of smoking and less attention to negative consequences.¹⁸⁶ One study of people who smoke nondaily ($N = 183$), grouped by those who reported long-term occasional smoking, early occasional smoking, and former daily smoking, found that these groups did not differ in alcohol co-use patterns.¹⁸⁷ Less than one-third of smoking sessions involved drinking, and 42% of drinking sessions involved smoking, with greater use amounts of both during co-use sessions. This indicates that attention is needed to co-use occurring on different time scales from simultaneous use to co-use over longer time scales such as in the same day, week, month, or year.

Measurement of Lifetime Exposure and Use Patterns

Life course measures of tobacco and alcohol co-use are also important for understanding cancer risk. Lifetime measures of tobacco use include the age of initiation, use frequency, use quantity per day/occasion in relevant periods of life (e.g., age decades or period of highest consumption), and aspects of cessation (e.g., age at cessation or longest successful cessation). These lifetime measures can be used to create estimates of accumulated use, such as pack years of cigarette smoking, calculated by multiplying the typical number of cigarette packs smoked in a day by the number of years the person has smoked. Identification of never drinking is also important for determining appropriate control groups. However, self-report of lifetime abstinence from alcohol is not perfect and misclassification based on self-report can be significant.^{188,189} Additionally, people who report lifetime abstinence from alcohol are known to have specific demographic and health related characteristics, which can result in bias if lifetime abstainers are used as a reference group.¹⁹⁰

Lifetime measures of accumulated alcohol intake are available in some prospective cohorts¹⁹¹; however, such data have not been used very widely in analyses of associations between tobacco and alcohol co-use and cancer risk. Some of these studies involve repeated measures over time, potentially improving validity, but others collect alcohol consumption in prior decades retrospectively.¹⁹² The latter format could result in recall bias and greater measurement error for more distally retrospective decades. More research is needed on the validity and reliability of such recalls and how to improve them, including by using electronic health record systems to document use.

Often, current drinking during the month or year of assessment is used to classify long-term drinking patterns, under the assumption that adult drinking patterns are stable over time.^{193,194} The past-year timeframe is typically preferred for measuring current alcohol use in prospective studies of alcohol-related outcomes, as this timeframe is thought to describe average drinking over seasons and other short-term variations and repeated assessments may not be feasible. Studies have shown that changing patterns commonly occur seasonally¹⁹⁵ and on a year-to-year basis,¹⁹⁴ with aging,¹⁹⁶⁻¹⁹⁸ due to life events,¹⁹⁹ and as a result of alcohol policy changes.²⁰⁰ More longitudinal studies with repeated assessment of alcohol use are needed.

By contrast, smoking behavior has been found to be relatively stable over time among those who smoke daily, but the literature regarding those who smoke less than daily is mixed regarding stability of smoking behavior.^{201,202} People who report nondaily smoking are an important group as they have the highest prevalence of alcohol use, including high-risk drinking behavior, compared with people who do not smoke (see chapters 2 and 3). In a study of 579 California young adults who smoked nondaily, alcohol use was associated with lower odds of abstinence.²⁰³ Moreover, it is important to note that adolescence to young adulthood is a period of experimentation and escalation of tobacco use, so the patterns of use can be unstable.²⁰³⁻²⁰⁶ These patterns may also be changing as the types of tobacco products available come into or out of the marketplace and with changes in regulation of where smoking is permitted and/or acceptable. Importantly, few studies have included lifetime measures for both tobacco and alcohol.

Measurement of Product Characteristics

Even more granular measures of tobacco and alcohol co-use may also be relevant to the influence of co-use on carcinogenesis. As discussed in chapter 5, all types of alcohol beverages contain ethanol, the major factor related to alcohol-related carcinogenesis, and the amount of ethanol consumed largely determines cancer risk. As discussed previously in this chapter, ABV can vary widely across alcohol products.^{207,208} Measures that identify the volume of beer, wine, and spirits consumed, as well as subtypes of higher percentage ABV beverages—such as malt liquor, strong beer, fortified wine, strong cocktails, shots, and straight spirits—could be informative. Under-reporting of total alcohol consumption could be greater for those at the highest levels of consumption of spirits; observational studies are more difficult because many people with higher levels of consumption consume several types of alcoholic beverages.

Despite the key role of ethanol in carcinogenesis, considerable research has examined the type of alcoholic beverage consumed and cancer risk, particularly for certain cancers. For example, the combined effects of tobacco and alcohol on risk could be sensitive to the type of alcohol consumed and to the precise timing of use, as these may influence salivary acetaldehyde levels and the oral microbiome.¹⁰⁸ Similarly, a study of esophageal cancer and alcohol consumption from France suggests additional risk related to consumption of apple brandy.²⁰⁹ However, all alcohol products cause increased risk of cancer and there does not appear to be a consistent difference in cancer risk based on the type of alcoholic beverage consumed (see also chapter 5).²¹⁰⁻²¹³

Methods and Measurement of Tobacco and Alcohol Consumption Across the Life Course

Epidemiological studies as well as health surveillance systems are deeply challenged by the need to consider respondent burden. This is a particular problem for studies that assess complex behaviors such as drinking and smoking. Greater efforts could be made to improve survey instruments for collecting lifetime consumption data, such as the use of graphical interfaces for online or smartphone-enabled data collection. Additionally, higher compensation for study participants or greater use of targeted cohorts focusing on specific exposures could reduce respondent burden by addressing only a few exposures in detail and including assessment of only the most critical covariates.

Study designs using detailed daily diaries that include timing of use, such as ecological momentary assessment studies which provide for real time assessment of the behaviors, could be used to measure simultaneous use. In addition, surveys can include follow-up questions on the use frequency of one substance (e.g., alcohol) about how often that substance was used together with the other substance (e.g., cigarettes) that the respondent had previously reported currently using. These follow-up questions have become more common in studies of alcohol and cannabis use and could be adapted for tobacco and alcohol.²¹⁴

Despite considerable efforts to develop reliable and valid measures of lifetime tobacco and alcohol use, there are inherent limitations to self-reported behavior, particularly if the behaviors occur less regularly, change over time, or must be recalled from the more distant past. All these factors are relevant to both tobacco and alcohol use, especially as intermittent and multiple tobacco product use has become more common, and levels of tobacco and alcohol use can change over time.

There have also been substantial efforts to identify biomarkers of longer-term exposure, including biochemical adducts,²¹⁵ DNA methylation,²¹⁶⁻²¹⁸ mosaic Y-chromosome loss,²¹⁹ and somatic mutation signatures.²²⁰ These integrative biomarkers reflect the molecular and physiological effects of exposure and thus can be considered to be both biomarkers of acute and long-term exposure and also intermediate markers of carcinogenesis and other disease processes. Such biomarkers are agnostic in that they do not rely on self-report and have been shown to be useful for assessing both current and former tobacco use. However, whether biomarkers can be widely deployed to overcome the limitations of self-reported assessment remains to be determined and is an active research area.

Biomarkers of Exposure to Tobacco

Cotinine, a by-product of nicotine metabolism which can be measured in blood, urine, or saliva, is the most commonly used biomarker of tobacco use. The half-life of cotinine averages 16 hours and thresholds have been established to detect active smoking (3–10 ng/ml for plasma) as well as for secondhand smoke exposure.^{221,222} Another commonly used biomarker of short-term exposure to tobacco smoke is the concentration of carbon monoxide (CO) in exhaled breath (or carboxyhemoglobin in blood). The half-life of CO is influenced by various factors but is typically in the range of about 4 hours. A cutpoint of 5–6 ppm in exhaled CO is typically recommended to distinguish a person who smokes from someone who is abstinent from smoking.²²¹ However, there is a limitation of using exhaled CO as a biomarker—it is not specific to tobacco smoking and may reflect exposure to other combustion products, such as cannabis

smoke, and common air pollutants, such as auto exhaust. Nicotine, a highly specific biomarker of tobacco use, can be measured directly in blood plasma; because of its short half-life (~2 hours) it is useful only for assessing short-term exposure.²²¹

The tobacco-specific biomarker, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a primary metabolite of the tobacco-specific nitrosamine NNK, is a biomarker of potential harm from tobacco. NNAL remains in the urine far longer than cotinine (NNAL half-life: 26–45 days; cotinine half-life: 16–18 hours) and is indicative of tobacco exposure from cigarettes, other tobacco products (e.g., smokeless tobacco, heated tobacco products) and secondhand smoke exposure.^{223–225} Other biomarkers of potential harm that assess exposure to specific carcinogens or carcinogenic processes, such as inflammation or oxidative stress, are also widely used in environmental epidemiology, tobacco regulatory science, and other fields.^{224,226} However, unlike NNAL, these biomarkers are not specific for tobacco. The minor tobacco alkaloids anabasine and anatabine are derived from tobacco leaf and can be used to determine exposure to products containing tobacco (e.g., cigarettes, cigars, smokeless tobacco, and others) in people using nicotine replacement therapy or using nicotine-containing ENDS to distinguish between exposure to products that do and do not contain tobacco.²²¹

Biomarkers of Exposure to Alcohol

Biomarkers currently in clinical and research use are sensitive to different levels of alcohol use and use over different time windows, ranging from the presence of ethanol itself in blood via blood alcohol concentration tests or exhalations to various biomarkers related to alcohol, such as phosphatidyl ethanol (PEth) and fatty acid ethyl ester (FAEE).²²⁷ FAEE is not correlated with level of use but can detect alcohol use within the past 24–99 hours. PEth is sensitive to consumption of about 50 grams ethanol per day up to 3 weeks after consumption ceases. Such tests have been used in randomized controlled trials²²⁸ and could potentially be useful in a clinical setting or to monitor adherence to cessation regimes. Shorter term measures of consumption may also be useful to validate self-reports. For example, a 2025 nested case-cohort study of Spanish men ages 55–80 and women ages 60–80 in the PREDIMED trial used urinary tartaric acid to validate self-report of wine consumption from food frequency questionnaires.²²⁹ However, more research is needed to identify more effective biomarkers.

For epidemiological studies, long term biomarkers of total alcohol consumption that are sensitive to lower levels of consumption are also needed to reduce measurement error related to self-report and refine estimates of risk at lower levels of alcohol consumption. Measures of liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are elevated with heavy drinking, but the degree of elevation is dependent on other aspects of the liver's response to alcohol and is reduced with reduced drinking.^{227,230} Biomarkers of long-term alcohol use might be found in genetic or epigenetic changes associated with exposure to alcohol and its metabolites, although more research is needed in this area.²³¹ The majority of research on biomarkers of alcohol use has involved short term markers such as metabolites of alcohol and alcohol related enzyme levels,^{232,233} and at the group level, several of these markers can distinguish between lower and higher levels of intake. However, none of these can distinguish between people who do not drink and sporadic or low daily intake consumers and none are able

to capture total consumption over multiple years. More research is needed to identify and validate markers of lifetime alcohol consumption, especially markers that are sensitive to lower levels of consumption. Such studies could be carried out in prospective cohort studies that included multiple self-report measures of alcohol consumption over time and recently collected blood or other biological samples.

Mendelian Randomized Studies of Alcohol and Tobacco

Genetic studies have also been used to evaluate whether tobacco or alcohol consumption are causally related to cancer risk at various sites.²³⁴⁻²⁴⁰ Such Mendelian randomization studies leverage genetic variants as tools in an attempt to causally evaluate whether exposures, such as tobacco and alcohol use, are independently associated with disease outcomes. In traditional observational epidemiologic studies, reverse causation, bias, and confounding are of substantial concern. In contrast, Mendelian randomization studies leverage Mendel's laws of inheritance, namely that genetic alleles are randomly assorted at conception, which is analogous to the randomization process of a clinical trial.²⁴¹ In Mendelian randomization studies, researchers aim to create genetic instrumental variables are created by identifying genetic variants that are specifically associated with exposures of interest²⁴² (e.g., tobacco use and alcohol intake). Associations of these instrumental variables and disease endpoints of interest are then evaluated. Mendelian approaches could be informative for clarifying unresolved associations, such as whether alcohol intake increases risk of lung cancer or whether smoking increases the risk of breast cancer. However, Mendelian randomization studies themselves require a number of assumptions, not all of which can be directly testable, and thus can also be affected by bias. To date, Mendelian randomization studies of alcohol consumption and lung cancer²³⁴⁻²³⁸ and smoking and breast cancer have been inconclusive,^{243,244} perhaps reflecting limited statistical power. Future research in this area is needed.

Measurement Needs Related to Health Disparities

High levels of tobacco and alcohol use as well as disparities in cancers related to tobacco and alcohol have been observed in some demographic groups such as American Indian or Alaska Native individuals and sexual minorities.^{53,245-248} However, great care must be taken not to interpret these studies as suggesting that all or most of the people in a demographic group have high levels of consumption (see chapter 3). These observations also highlight the importance of valid and reliable measurement of tobacco and alcohol use across diverse populations. Language, values, and social factors may influence self-report of tobacco and alcohol use behaviors.^{249,250} For example, in a cross-sectional study of 2,520 individuals analyzing data from the 1999–2002 National Health and Nutrition Examination Surveys, Everhart and colleagues (2009)²⁴⁹ reported that misclassification of tobacco use status was associated with both sex and acculturation status in Hispanic adults in the United States with greater levels of misclassification for men with lower levels of acculturation (almost 5%) compared to women with lower levels of acculturation (~1%). For alcohol use, prior use of alcohol and other substances was strongly related to disagreement between retrospective and prospective reporting of alcohol onset measures in a sample of 1,044 adolescents in Chicago.²⁵¹ Black and Hispanic military veterans are more likely to be diagnosed with alcohol use disorder compared to White veterans, even at the same reported levels of alcohol consumption²⁵²; such misclassification could bias epidemiological analyses relying on medical records. In addition, willingness to respond to surveys, ability to recall past

substance use (e.g., among older adults), and survey-specific factors leading to measurement error may differ by population group. More research is needed to identify and avoid differential misclassification of tobacco and alcohol use for epidemiological studies.

Worldwide, a 2010 report by the World Health Organization (WHO), *Equity, Social Determinants, and Public Health Programmes*,²⁵³ found that certain groups, including those of lower SES, had a higher prevalence of the use of tobacco products and experienced a higher burden of disease from that use. The report also found that, when looking at a macro-level at the relationship between alcohol and disease that, although populations with higher SES had higher percentages of people who drink, those with lower SES had a higher percentage of people who report heavy episodic drinking.²⁵³ Together these observations highlight the need for valid and reliable measurement of both consumption and health outcomes in different demographic groups.

Alcohol Harms and Socioeconomic Status

Several studies have examined the harm of alcohol in relation to SES. For example, Smith and colleagues (2024)²⁵⁴ examined associations of education and alcohol use with alcohol attributable hospitalization or death in a large ($N = 199,125$) cohort study in Canada. Levels of heavy alcohol consumption and alcohol volume were similar for people with lower and higher levels of education—but levels of hospitalization or death were disproportionately higher for people with lower SES and higher levels of consumption. This observation that people with lower SES exhibit greater harms from alcohol than those at higher SES with the same consumption levels has been called the alcohol harm paradox, and a growing number of studies have reported this pattern for several measures of SES and various health outcomes related to alcohol.²⁵⁵ For alcohol and cancer, very few studies have examined interactions between SES and alcohol; more analyses are needed.²⁵⁶

The synergistic effects of tobacco and alcohol in subpopulations were not addressed in the 2010 WHO report or in most studies of alcohol harms in relation to SES. These findings confirm the importance and need to accurately measure precise amounts of tobacco and alcohol consumed, as well as types of tobacco and alcohol products consumed, frequency, timing of consumption, and duration at a more granular level and over time to fully understand patterns of use of each product and to better understand how they relate to disease risk and how they interact with SES and its correlates.

Chapter Summary

Cigarette smoking has been causally linked to the development of cancer at multiple sites, including the oral cavity, pharynx, larynx, esophagus, lung (trachea and bronchus), stomach, liver, pancreas, kidney and ureter, bladder, cervix, colorectum, as well as acute myeloid leukemia. Currently, evidence also suggests an association between cigarette smoking and female breast cancer, however, consensus on this relationship has not been reached. The carcinogenicity of combusted tobacco products (e.g., cigarettes, cigars, and pipes) is attributed to the presence of more than 7,000 compounds, including more than 80 carcinogens, in tobacco smoke. The prevalence of cigarette smoking has been decreasing for decades; in 2024, 9.9% of

U.S. adults reported current use of cigarettes. However, youth and adult tobacco use now reflects the diversity of the tobacco product marketplace and polytobacco use has become increasingly common, especially among youth.

Alcohol consumption is the third most important modifiable risk factor for cancer in the United States. Conclusive evidence shows that alcohol consumption is causally linked to an increased risk of cancers of the oral cavity, pharynx, larynx, esophagus, colorectum, and liver, as well as female breast cancer; studies of a potential causal role for alcohol for other cancer sites is sparse or inconsistent. Alcohol consumption is also associated with a lower risk of kidney cancer and non-Hodgkin lymphoma. However, the potential benefit of this lower risk is vastly outweighed by alcohol's causal role in other cancers and other serious diseases. Ethanol, contained in all alcohol products, is the leading determinant of their cancer risk, although some differences in risk have been reported by specific alcohol products. The risk of alcohol-related cancers is substantially increased in people with aldehyde dehydrogenase deficiency, a genetic condition common in some populations, including people of Asian ancestry. As described in more detail in chapters 2 and 3, alcohol consumption differs significantly between men and women, and by other demographic factors such as race, age, and socioeconomic status.

Numerous studies have examined the potential for synergy between tobacco and alcohol and cancer risk (defined here as when the total effect is greater than the sum of the individual effect). Conclusive evidence for synergy between cigarette smoking and alcohol use has been shown for cancers of the aerodigestive tract (i.e., cancers of the oral cavity, pharynx, larynx, and esophagus). Few studies have addressed the potential for synergy between other tobacco products (e.g., smokeless tobacco, e-cigarettes) and alcohol use on cancer risk. Similarly, few studies have examined the potential for synergy between tobacco and alcohol use by demographic factors (age, sex, race, and/or ethnicity) and relevant health factors. For example, studies have shown that infection with human papilloma virus (HPV) weakens the synergy between tobacco and alcohol use and risk of oropharyngeal cancer. In addition, studies have examined the potential for synergy between tobacco and alcohol use for other cancer sites. For example, some studies suggest a possible synergistic interaction between tobacco and alcohol for cancer of the lung, liver, and female breast. Measurement is a critical component of studies to address the epidemiology of tobacco- and alcohol-associated cancer risk. Widely used measures of tobacco and alcohol use typically address frequency, intensity, duration, and cessation of use. Additional areas of special interest to studies of cancer risk include measuring simultaneous use of tobacco and alcohol, understanding lifetime substance consumption, and assessing how patterns of use may change over the lifespan. Given the wide range of alcoholic beverages and their variable alcohol content, measuring the volume of alcohol consumed is also important. Additionally, as the tobacco product marketplace continues to diversify, measures will be needed to assess the broad range of tobacco products.

Most surveys and epidemiologic studies rely on self-reported measures. However, self-reported measures have well known challenges, including the potential for research participants to be unwilling or unable to accurately report tobacco and/or alcohol use, which are stigmatized behaviors. Misclassification is a particular concern for case-control studies where people

diagnosed with cancer may recall their use more or less accurately than participants without cancer, but misclassification can also affect prospective cohort studies. Several biomarkers of tobacco and alcohol use are available to supplement or replace self-report; each of these biomarkers has limitations, and the field would benefit from additional tools to assess use. Finally, measures need to be valid and reliable across diverse populations, given the need to understand and address disparities in tobacco and alcohol use and cancers caused by tobacco and alcohol use.

Research Needs

Research needs concerning the relationship between tobacco and alcohol co-use and cancer risk involve a combination of measurement and analytical issues. For etiological studies of alcohol alone and tobacco and alcohol co-use, alcohol use is most commonly measured using quantity/frequency and graduated frequency approaches to estimate volume of alcohol intake. Fewer studies have examined patterns and changing patterns of alcohol intake from initiation throughout the life course, which is particularly important for cancers that may have developmental windows of susceptibility, such as female breast cancer.¹⁵⁷ Measures of tobacco and alcohol use over the life course increase respondent burden, a key cause of loss to follow-up or nonresponse in cohort studies²⁵⁷ as well as noncompletion of health surveys.^{258,259} For this reason, work is needed to further develop and refine a package of measures encompassing patterns of use and nonuse that minimize respondent burden and address both tobacco and alcohol. A few studies suggest that instruments such as the Lifetime Drink History Survey can capture data concerning alcohol use initiation and subsequent patterns of drinking over the life course.²⁶⁰⁻²⁶² However, more work is needed to refine such instruments and to understand their potential for bias and measurement error associated with different patterns of lifetime behavior as well as detailed aspects of co-use, such as simultaneous smoking and drinking.

Continued efforts to combine results from different cohorts and to harmonize estimates of tobacco and alcohol use for metanalytic or pooled analyses of associations between co-use and cancer risk are needed. Past analyses have often addressed tobacco and alcohol co-use and aerodigestive tract cancers because of the larger relative risks and population-attributable fractions for these cancers associated independently and synergistically with these exposures. Where relative risks and population-attributable fractions are lower, power to identify an interaction between tobacco and alcohol co-use and cancer can be limited because of the exceptionally large sample sizes needed for such analyses. Very large initiatives are needed, such as the Our Future Health study that aims to recruit 5 million participants in the United Kingdom,²⁶³ and pooling projects such as a 2025 study that examined the association of alcohol and pancreatic cancer pooled across 30 cohorts.⁸⁴

There are significant gaps in the literature concerning specific populations disproportionately affected by tobacco and alcohol co-use and relationship to cancer risk. Further research on the epidemiology of tobacco and alcohol co-use is needed in key populations including sexual minorities, Hispanic populations, American Indian and Alaska Native populations, and other demographic groups. Creative new approaches are needed for this work as sampling and other considerations related to small populations create significant study design challenges.²⁶⁴

More research is needed to address cancer risks associated with lower levels of alcohol consumption and intermittent (i.e., nondaily) cigarette smoking. The risks of nondaily smoking and lower levels of alcohol consumption are lower than the risks associated with daily cigarette smoking or heavier alcohol consumption, but they can still be substantial.²⁶⁵ Such studies could benefit from new analytical approaches as well as continued efforts at pooling studies to increase power.

Studies are needed to determine whether the use of e-cigarettes interacts with alcohol consumption to increase risk. Studies of e-cigarettes and alcohol in relation to cancer risk were not identified, and only a few studies have examined co-use of smokeless tobacco and alcohol in relation to cancer risk. Because of the large number of young people and adults co-using e-cigarettes and alcohol, and the wide variety of patterns of e-cigarette use, this is an important area for further research.

Studies are needed to better understand the potential cancer risk of co-use of smokeless tobacco and alcohol. Studies of co-use of smokeless tobacco and alcohol may benefit from being conducted among populations and/or countries where use of both smokeless tobacco and alcohol is common.

More experimental and epidemiological studies are needed to understand the effects of tobacco cessation and alcohol cessation or reduction, separately or together, on cancer risk. These could also inform the understanding of mechanisms linking increased risk associated with use. Such studies could also examine biomarkers of risk given the long latency of tobacco and alcohol caused cancer.

In addition, more epidemiological studies that examine associations between co-use of specific alcohol/tobacco product types are needed. This is especially important as new product types are introduced to the market and where aspects of their formulation or patterns of use might influence risk.

Concerning measurement, more efforts are needed to improve biomarkers, especially of long-term use, and to harmonize measures across cohort studies. Further research on biomarkers of exposure over longer time periods could strengthen epidemiological studies of tobacco and alcohol co-use. Behavioral and etiological studies are needed in subpopulations that experience health disparities or are most vulnerable to co-use of tobacco and alcohol. Identification of additional biomarkers of exposure, especially markers related to long term alcohol consumption, could strengthen etiological studies and evaluation of interventions. Biomarkers of tobacco and alcohol exposure are an important adjunct to self-report. For tobacco use, the availability of serum markers of current or recent tobacco exposure has strengthened exposure assessment and inference. Short-term (current blood alcohol content) and medium-term (consumption over the past weeks) biomarkers of alcohol consumption are available,²²⁷ but markers of lifetime consumption such as epigenetic changes, especially those relevant for lower levels of drinking, could potentially improve risk estimates.

Conclusions

1. **Tobacco and alcohol use independently cause multiple types of cancer, and even low levels of use increase the risk for specific cancers.** Smoking one or fewer cigarettes per day is known to increase the risk of numerous cancers. For alcohol, the risk of female breast cancer increases at less than one drink per day, and head and neck cancer risk increases with one drink per day and possibly at lower levels of consumption.
2. **Strong evidence exists for a synergistic increase in risk of squamous cancers of the head, neck, and esophagus caused by tobacco and alcohol co-use.** Numerous studies conducted in several countries over many years find that co-use of tobacco and alcohol, especially when use levels are high, results in synergistic increase in risk of head and neck and esophageal cancers. Limited evidence is available to determine whether there is a synergistic increase in cancer risk due to tobacco and alcohol co-use for several other cancer sites. For example, there have been mixed results for studies examining synergistic effects of tobacco and alcohol exposures on female breast cancer risk.
3. **Increased risk of head and neck cancers caused by alcohol use in people with aldehyde dehydrogenase 2 (ALDH2) deficiency, an autosomal recessive disorder that reduces the rate of metabolism of acetaldehyde, provides strong evidence for the causal relationship and underlying biological mechanism linking alcohol to head and neck cancers.** ALDH2 deficiency is especially common in people of East Asian ancestry, resulting in the alcohol flushing syndrome. Continued high prevalence of alcohol use in East Asian populations, especially among men, leads to a strong opportunity for intervention at the clinical and population level.
4. **Improved measurement would strengthen studies of the effect of tobacco and alcohol co-use on cancer risk.** Improving and implementing standardized measures of lifetime tobacco and alcohol exposure (including measures of frequency and duration of use, initiation, cessation, and product types used) are needed to strengthen the evidence base. Developing longer-term biomarkers of exposure and effect for tobacco and alcohol is also a significant gap in the currently available research tools; such biomarkers will advance understanding of co-use risks.
5. **Tobacco cessation reduces the risk of numerous cancers, and alcohol reduction or cessation reduces the risk of cancers of the aerodigestive tract.** As of 2026, few studies have addressed the effects of quitting or reducing both tobacco and alcohol use on cancer risk. Overall, the synergistic increases in risk of head, neck, and esophageal cancers and the potential for synergistic increases in risk for other cancers provide strong support for further developing and implementing interventions to address the co-use of tobacco and alcohol.

Appendix 4A Literature Search Strategy

The literature search included three phases: (1) identify cancer types causally associated with tobacco, (2) identify cancer types causally associated with alcohol, and (3) identify synergy between tobacco and alcohol in the causal pathways of the identified cancer types in phases one and two. To identify studies since 2010 (since the publication of IARC monographs in 2010 and 2012),^{1,2} searches were conducted in PubMed in 2023 to identify studies of the synergy between alcohol, tobacco, and the following cancer sites: oral cavity, pharynx, esophagus, stomach, colorectal, liver, pancreas, larynx, lung, bronchus, skin melanoma, female breast, cervix uteri, corpus uterus, ovary, prostate, testis, urinary bladder, kidney, renal pelvis, brain, thyroid, Hodgkin lymphoma, non-Hodgkin lymphomas, myeloma, and leukemias. These sites were chosen based on specific cancer sites examined in the IARC reports.^{1,2} Search strings used terms for each cancer site in combination with the following search terms: [tobacco or nicotine or cigarette] and [alcohol or “alcohol use” or drink*] and [synergy OR synergistic OR “interaction” OR “joint effect” OR “joint effects” OR “multiplicative effect” OR “amplified effect” OR “synergistic”] and [cancer OR neoplasm*]. Reference lists of relevant articles were also reviewed to identify important studies published before 2010. Relevant articles (including notable studies published prior to 2010) are described in a narrative format in the chapter and in Table 4.4 and Appendix 4B. Additional studies published after 2023 were incorporated into the chapter based on their relevance.

Appendix 4B Select Studies Examining Synergy Between Tobacco and Alcohol Use and Cancer

Cancer type	Study	Study design	Sample	Results
Lung	Brenner et al. 2019 ¹³⁸	Pooled analysis	Data from International Lung Cancer Consortium and Synergy Consortium Study. 22 participating studies: North America (11), Europe (8), Asia (3), and European Prospective Investigation into Cancer; 19,149 cases, 362,340 controls	- Interaction analysis between smoking and drinking suggested lung cancer risk was associated with higher levels of smoking, with an interaction observed for those in the highest smoking and alcohol consumption groups: effect estimate deviated from that expected on the additive scale (aOR = 11.23, 95% CI = 10.29–12.26, ≥ 20 grams/day alcohol, ≥ 10 pack years). - Test for multiplicative interaction between alcohol consumption and smoking intensity was also significant ($p < .001$). - Positive interaction between high pack years of smoking and elevated levels of drinking.
Lung	Viner et al. 2019 ¹³⁹	Cohort study	Alberta, Canada; 2001–2017; 6,607 participants (2,370 cancer cases, of which 210 were lung cancer)	Lung cancer risks were significantly elevated compared to non-smokers for men (aHR = 10.16, 95% CI = 4.29–24.04) and women (aHR = 20.05, 95% CI = 10.92–36.70) who smoked 20 pack years or more, but there was no significant synergistic interaction between tobacco and alcohol use on lung cancer risk ($p = .81$)

Appendix 4B (continued)

Cancer type	Study	Study design	Sample	Results
Liver	Aglago et al. 2025 ¹⁴⁹	Nested case-control	10 European countries; recruited 1992–2000; 450,112 participants (255 liver cancer cases; 108 used in analysis)	- Positive relationship between smoking and HCC risk: Log-transformed cotinine, one standard deviation increments: aOR = 1.35, 95% CI = 1.11–1.63. Log-transformed nicotine, one standard deviation increments: aOR = 2.13, 95% CI = 1.28–3.56. Self-reported current versus never smoking: aHR = 2.46, 95% CI = 1.77–3.43. Self-reported former smoking versus never smoking: aHR = 1.31, 95% CI = 0.93–1.83. - Positive relationship between alcohol and HCC risk: Log-transformed 2-hydroxy-3-methylbutyric acid, one standard deviation increments: aOR = 3.04, 95% CI = 1.31–7.04. Compared with self-reported light drinking: self-reported never drinking aHR = 1.35, 95% CI = 0.59–3.10; moderate/never heavy drinking aHR = 0.94; 95% CI = 0.56–1.59; former drinking aHR = 3.20, 95% CI = 1.70–6.03; periodic heavy drinking (based on lifetime intake of >40 grams/day in women, 60 grams/day in men, reported at 1 or more assessment points) aHR = 1.98, 95% CI = 1.11–3.54; always heavy drinking (based on lifetime intake of >40 grams/day in women, >60 grams/day in men, reported at all assessment points)(M. Jenab, Ph.D., personal communication, September 2, 2025) aHR = 5.51, 95% CI = 2.39–12.7; unknown aHR = 1.79, 95% CI = 0.80–4.03. - Synergy indices for self-reported smoking and alcohol use behaviors (synergy index = 1.27, 95% CI = 0.98–1.66), and smoking and alcohol biomarkers (synergy index for 2-hydroxy-3-methylbutyric acid and cotinine = 1.59, 95% CI = 0.58–4.33; synergy index for 2-hydroxy-3-methylbutyric acid and nicotine = 1.36, 95% CI = 0.60–3.10), were not significant.
Liver	Bui et al. 2024 ¹⁴⁶	Case-control	South Korea; 2009–2019; 15,352 cancer cases (92,112 controls)	- Among men, there was an additive effect for current smoking and current alcohol consumption on liver cancer risk, relative excessive risk due to interaction (RERI = 0.28 [95% CI, 0.15–0.40]), and a multiplicative interaction (multiplicative aOR = 1.20 [95% CI, 1.07–1.34]). When examining by smoking and alcohol use intensity, there was an additive effect for light-to-moderate drinking (0.1–0.28 grams/day) and heavy smoking (>20 pack years), on liver cancer risk, RERI = 0.34 (95% CI, 0.16–0.51) and a multiplicative interaction (synergy index = 2.75 [95% CI = 1.85–3.66]; multiplicative aOR = 1.28 [95% CI = 1.11–1.49]). - Among women, there was no significant interaction between smoking and alcohol consumption on liver cancer risk.

Appendix 4B (continued)

Cancer type	Study	Study design	Sample	Results
Liver	Kuper et al. 2000 ¹⁴⁵	Case-control	Athens, Greece; 1995–1998; 333 cancer cases (360 controls)	• Positive, dose–response relationship between smoking and liver cancer risk (aOR for <2 packs/day = 1.6 [95% CI, 0.8–2.9]; aOR for ≥2 packs/day = 2.5 [95% CI, 1.1–5.5]; trend $p = .03$). • Alcohol consumption of >40 glasses per week had a positive but nonsignificant association with liver cancer risk (aOR = 1.9, 95% CI = 0.9–2.9). • Heavy smoking (≥2 packs/day) and heavy drinking (≥40 glasses/week) had a multiplicative association with liver cancer risk (aOR = 9.6 for both exposures [95% CI, 3.4–27.5]).
Liver	Pirie et al. 2013 ¹⁶⁹	Cohort study	United Kingdom; 1996–2011; 1.2 million women	• Among women who smoked versus those who never smoked, sensitivity analyses to examine those who did not drink alcohol or consumed <3 units of alcohol per week: Liver cancer mortality adjusted RR = 1.43 (95% CI 1.11–1.85). • Alcohol consumption attenuated the association between tobacco use and liver cancer, but association remained significant.
Liver	Marrero et al. 2005 ¹⁴³	Case-control	United States; 2002–2003; 70 cancer cases (70 cirrhosis controls and 70 controls with no liver disease)	• Hepatocellular cases (HCC) compared to cirrhosis controls: Cigarette smoking of ≥20 pack years was associated with increased risk of HCC (aOR = 4.9, 95% CI = 2.2–10.6) compared to never smoking. • HCC cases compared to cirrhosis controls: Alcohol consumption of ≥1,500 grams per year was associated with increased risk of HCC (aOR = 5.7, 95% CI = 2.4–13.7) compared to never alcohol use. • HCC cases compared to cirrhosis controls: Exposure to both smoking and alcohol was associated with increased risk of HCC (aOR = 7.2, 95% CI = 2.2–14.1) compared to smoking alone (aOR = 2.5, 95% CI = 1.7–15.0) or alcohol alone (aOR = 1.4, 95% CI = 1.1–4.0), with a synergistic index of 3.3 (95% CI, 1.8–5.7). • HCC cases compared to cirrhosis controls: The presence of 3 risk factors (alcohol, smoking, and obesity), compared to only 2 risk factors, was associated with increased risk of HCC (aOR = 7.4, 95% CI = 2.1–14.6), with a synergistic index of 1.6 (95% CI, 1.1–4.3).

Appendix 4B (continued)

Cancer type	Study	Study design	Sample	Results
Breast (female)	Gaudet et al. 2013 ¹⁶²	Cohort study	United States; 1992–2007; 73,388 women (3,721 invasive breast cancer cases)	- Alcohol consumption did not confound associations with smoking status, although neither current nor former smoking were associated with risk among those who reported never drinking (p for interaction = .11). - Association between active smoking and breast cancer incidence was not attenuated by the inclusion of alcohol intake in the multivariate model. - Association was statistically significant only in those who reported current and formers drinking in analyses that stratified on alcohol consumption, although the CIs for the association in those who reported never drinking were wide. - No synergistic effect reported.
Breast (female)	Gaudet et al. 2017 ¹⁵⁵	Pooled analysis	14 cohort studies; 934,681 (36,030 invasive breast cancer cases)	- People who currently drank 2 or more drinks per day and who formerly smoked (aHR = 1.33, 95% CI = 1.19–1.49) or currently smoked (aHR = 1.32, 95% CI = 1.16–1.49) were at slightly greater risk than expected under a multiplicative model (expected aHRs = 1.22 and 1.22, respectively). - People who currently drank ≥ 3 drinks per day and smoked >10 years prior to first birth (aHR = 1.85, 95% CI = 1.55–2.21) were at noticeably greater risk than expected under the multiplicative model (expected aHR = 1.43). - Results support a synergistic relationship between smoking initiation and adult alcohol drinking and increased breast cancer risk.
Breast (female)	Gram et al. 2005 ¹⁶³	Cohort study	Norwegian/Swedish Cohort Study; 1991–2000; 102,098 women	- Study found that women who initiate smoking prior to menarche or a first birth and continue to smoke for at least 20 years have a small increase in breast cancer risk relative to never smokers. - People who did not drink experienced a similar increase in risk as people who drank. - No synergistic effect reported.
Breast (female)	Hamajima et al. 2002 ¹⁶⁴	Collaborative reanalysis	Global; Collaborative Group on Hormonal Factors in Breast Cancer; 58,515 cases with invasive breast cancer; 95,067 controls	- Relationship between smoking and breast cancer was confounded by alcohol: when comparing 22,255 women with breast cancer and 40,832 controls who reported drinking no alcohol, smoking was not associated with breast cancer (versus never smoking, adjusted RR for ever-smoking = 1.03, 95% CI = 0.98–1.07, and for current smoking adjusted RR = 0.99, 95% CI = 0.92–1.05). - No synergistic effect reported.
Breast (female)	Jones et al. 2017 ¹⁵⁸	Longitudinal cohort study	United Kingdom; 2003–2013; 102,927 women (1,815 breast cancer cases)	No significant interaction between smoking and drinking on breast cancer risk (p = .41)

Appendix 4B (continued)

Cancer type	Study	Study design	Sample	Results
Breast (female)	Knight et al. 2017 ¹⁵⁹	Case-control study	United States, Canada, Denmark—Women's Environmental, Cancer, and Radiation Epidemiology Study; 2001–2004, 2009–2012; 1,521 cases (contralateral breast cancer); 2,212 controls (unilateral breast cancer)	- Interaction between current drinking and smoking was statistically significant ($p = .008$), whereas the interaction between any drinking and smoking history was not ($p = .76$). - The consumption of cigarettes and alcohol at the time of first diagnosis had the strongest association with increased contralateral breast cancer risk. - Women who drink and smoke following diagnosis continue to be at increased risk.
Breast (female): <i>BRCA</i> , <i>BRCA2</i> mutations	Li et al. 2020 ¹⁶⁰	Prospective and retrospective cohort analyses	21 centers in Western countries; 9,845 women (9,232 for retrospective and 3,886 for prospective)	In the retrospective analysis, ever alcohol and ever smoking (i.e., at least 1 glass per month for 1 year and at least 1 pack of cigarettes per month for 1 year; aHR = 1.43, 95% CI = 1.13–1.81; $p = .003$) was associated with increased synergistic breast cancer risk for <i>BRCA2</i> mutation carriers.
Breast (female)	Pirie et al. 2013 ¹⁶⁹	Cohort study	United Kingdom; 1996–2011; 1.2 million women	- Among women who smoked versus those who never smoked, sensitivity analyses to examine those who did not drink alcohol or consumed <3 units of alcohol per week: Breast cancer mortality RR: 1.06 (95% CI, 0.95–1.18) among women who consumed little to no alcohol. - Alcohol consumption attenuated many associations between cigarette smoking and breast cancer (no longer significant).
Breast (female)	Viner et al. 2019 ¹³⁹	Cohort study	Alberta, Canada; 2001–2017; 26,607 participants (2,370 cancer cases, of which 483 were breast cancer)	- A "U-shaped" multiplicative interaction was observed for breast cancer ($p = .05$) when cigarettes and alcohol were used in combination—moderate alcohol consumption and minimal cigarette smoking were associated with lower cancer incidence. - This interaction rapidly changes in a multiplicative fashion when alcohol consumption and pack years increase.

Appendix 4B (continued)

Cancer type	Study	Study design	Sample	Results
Breast (female)	Zeinomar et al. 2019 ¹⁶¹	Secondary data analysis of cohort study	United States, Canada, Australia; 10.4 years; 17,435; 1,009 incident breast cancer cases	- Significant 3-way interaction between familial risk profile, alcohol consumption, and cigarette smoking (interaction $p = .01$). - Among women who were regular drinkers, there was a significant multiplicative interaction ($p = .005$) between familial risk profile and smoking status (current versus never) on breast cancer risk (aHR = 1.39, 95% CI = 1.13–1.71), largely driven by women with a very high familial risk profile. 30% increased overall breast cancer risk for women at the 95th percentile of familial risk profile (5-year BOADICEA > 6.55%) who reported currently smoking at baseline and regularly drinking (aHR = 1.30, 95% CI = 0.99–1.71).
Thyroid	Kitahara et al. 2012 ¹⁶⁶	Pooled analysis, 5 prospective studies	United States; 746,097 people at baseline; 89,527 incident thyroid cases	- Compared to never smoking and nondrinking, current smoking and drinking one or more drinks per week was associated with 36% reduced risk (joint aHR = 0.64, 95% CI = 0.47–0.86). - The joint aHR was slightly weaker than the aHR for current smoking among people who did not drink alcohol (aHR = 0.46, 95% CI = 0.29–0.73) and similar to that observed for people who reported never smoking and reported ≥ 1 drink per week (aHR = 0.70, 95% CI = 0.56–0.87). - The relationship for the joint association of smoking and drinking appears sub-multiplicative (p for interaction = .004).
Thyroid	Yeo et al. 2022 ¹⁶⁷	Cohort study	Korea; 2009; 9,699,104 people	- Statistically significant interaction found between smoking and alcohol consumption on thyroid cancer risk (p interaction < .001), with differences in risk by current smoking (never/former/current) and levels of alcohol consumption (none/mild/moderate/heavy), range of aHRs (versus never smoking and nondrinking) = 0.62–0.92. - Findings suggested a submultiplicative interaction slightly lower than expected from the independent effects from tobacco or alcohol use.
Prostate	Viner et al. 2019 ¹³⁹	Cohort study	Alberta, Canada; 2001–2017; 26,607 participants (2,370 cancer cases, of which 401 were prostate cancer)	3-way interaction model showed an additive, not a synergistic, effect between alcohol as a continuous variable (grams/day) and pack years consumed for prostate cancer. - Differences were significant for men (aHR = 10.16, 95% CI = 4.29–24.04) and women (aHR = 20.05, 95% CI = 10.92–36.70) among those who smoked 20 pack years or more.

Note. aHR = adjusted hazard ratio; aOR = adjusted odds ratio; CI = confidence interval; HCC = hepatocellular carcinoma; RERI = relative excess risk due to interaction; RR = risk ratio.

References

1. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Alcohol Consumption and Ethyl Carbamate. Lyon (FR): International Agency for Research on Cancer; 2010. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 96.) Available from: <https://www.ncbi.nlm.nih.gov/books/NBK326568>.
2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Personal Habits and Indoor Combustions. Lyon (FR): International Agency for Research on Cancer; 2012. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 100E.) Available from: <https://www.ncbi.nlm.nih.gov/books/NBK304391>.
3. U.S. Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014. Printed with corrections, January 2014.
4. World Cancer Research Fund International/American Institute for Cancer Research. Diet, nutrition, physical activity and cancer: a global perspective; continuous update project expert report. 2018. [cited 2026 Mar 27]. Available from: <https://www.wcrf.org/wp-content/uploads/2024/10/Alcoholic-Drinks.pdf>.
5. Hashibe M, Brennan P, Chuang SC, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev*. 2009;18(2):541-50. doi:10.1158/1055-9965.Epi-08-0347.
6. Jun S, Park H, Kim UJ, et al. Cancer risk based on alcohol consumption levels: a comprehensive systematic review and meta-analysis. *Epidemiol Health*. 2023;45:e2023092. doi:10.4178/epih.e2023092.
7. Burton R, Fryers PT, Sharpe C, et al. The independent and joint risks of alcohol consumption, smoking, and excess weight on morbidity and mortality: a systematic review and meta-analysis exploring synergistic associations. *Public Health*. 2024;226:39-52. doi:10.1016/j.puhe.2023.10.035.
8. Schwartz S. Modern epidemiologic approaches to interaction: applications to the study of genetic interactions. Genes, behavior, and the social environment: Moving beyond the nature/nurture debate. National Academies Press (US); 2006.
9. VanderWeele TJ, Knol MJ. A tutorial on interaction. *Epidemiol Methods*. 2014;3(1):33-72.
10. Lash TL, VanderWeele TJ, Haneuse S, Rothman KJ, editors. *Modern epidemiology*. 4th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2021.
11. Andersson T, Alfredsson L, Källberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. *Eur J Epidemiol*. 2005;20(7):575-9. doi:10.1007/s10654-005-7835-x.
12. Kalilani L, Atashili J. Measuring additive interaction using odds ratios. *Epidemiol Perspect Innov*. 2006;3:5. doi:10.1186/1742-5573-3-5.
13. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Alcohol Drinking. Lyon (FR): International Agency for Research on Cancer; 1988. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 44) Available from: <https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Alcohol-Drinking-1988>.
14. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Smokeless Tobacco and Some Tobacco-specific N-Nitrosamines. Lyon (FR): International Agency for Research on Cancer; 2007. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 89.) Available from: <https://www.ncbi.nlm.nih.gov/books/NBK326497>.
15. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco Smoke and Involuntary Smoking. Lyon (FR): International Agency for Research on Cancer; 2004. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 83.) Available from: <https://www.ncbi.nlm.nih.gov/books/NBK316407/>.
16. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Reduction or Cessation of Alcoholic Beverage Consumption. Lyon (FR): International Agency for Research on Cancer; 2024. (IARC Handbooks of Cancer Prevention, Vol. 20A). Available from: <https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Reduction-Or-Cessation-Of-Alcoholic-Beverage-Consumption-2024>.
17. Ali FRM, Seaman EL, Crane E, Schillo B, King BA. Trends in U.S. e-cigarette sales and prices by nicotine strength, overall and by product and flavor type, 2017-2022. *Nicotine Tob Res*. 2023;25(5):1052-1056. doi:10.1093/ntr/ntac284.

18. Jackler RK, Ramamurthi D. Nicotine arms race: JUUL and the high-nicotine product market. *Tob Control*. 2019;28(6):623-628. doi:10.1136/tobaccocontrol-2018-054796.
19. World Health Organization. WHO report on the global tobacco epidemic 2021: addressing new and emerging products. 2021 [cited 2026 Mar 27]. Available from: <https://www.who.int/publications-detail-redirect/9789240032095>.
20. Ling PM, Kim M, Egbe CO, Patanavanich R, Pinho M, Hendlin Y. Moving targets: how the rapidly changing tobacco and nicotine landscape creates advertising and promotion policy challenges. *Tobacco Control*. 2022;31(2):222-228. doi:10.1136/tobaccocontrol-2021-056552.
21. Jernigan D, Ross CS. The alcohol marketing landscape: alcohol industry size, structure, strategies, and public health responses. *J Stud Alcohol Drugs Suppl*. 2020;Suppl 19(Suppl 19):13-25. doi:10.15288/jsads.2020.s19.13.
22. Albers AB, Siegel M, Ramirez RL, Ross C, DeJong W, Jernigan DH. Flavored alcoholic beverage use, risky drinking behaviors, and adverse outcomes among underage drinkers: results from the ABRAND Study. *Am J Pub Health*. 2015;105(4):810-815.
23. Rossheim ME, Thombs DL, Treffers RD. High-alcohol-content flavored alcoholic beverages (supersized alcopops) should be reclassified to reduce public health hazard. *Am J Drug Alcohol Abuse*. 2018;44(4):413-417. doi:10.1080/00952990.2018.1460375.
24. Food and Drug Administration. E-cigarettes authorized by the FDA. [cited 2026 Mar 27]. Available from: <https://digitalmedia.hhs.gov/tobacco/hosted/Authorized-E-Cig-July2025.pdf>.
25. Food and Drug Administration. Searchable tobacco products database. [cited 2026 Mar 27]. Available from: <https://www.accessdata.fda.gov/scripts/searchtobacco>.
26. Ali FRM, Diaz MC, Armour BS, Crane E, Tynan MA, Marynak KL. Trends in U.S. e-cigarette sales measured in milligrams of nicotine, 2019-2024. *Am J Prev Med*. 2025;68(6):1173-1178. doi:10.1016/j.amepre.2025.02.007.
27. Marynak KL, Wang X, Borowiecki M, et al. Nicotine Pouch Unit Sales in the US, 2016 -2020. *JAMA*. 2021;326(6):566-568. doi:10.1001/jama.2021.10366.
28. Kerr WC, Stockwell T. Understanding standard drinks and drinking guidelines. *Drug and Alcohol Review*. 2012;31(2): 200-5. doi:10.1111/j.1465-3362.2011.00374.x
29. Demers-Potvin E, Gaucher-Holm A, Hobin E, et al. Nutrition cues on ready-to-drink alcoholic beverage containers sold in grocery stores in Québec City, Canada. *Preventive Medicine Reports*. 2023;32(102164). doi:10.1016/j.pmedr.2023.102164.
30. Sinha A. The best canned cocktails. *New York Times*. 2025 Dec 18. Available from: <https://www.nytimes.com/wirecutter/reviews/best-canned-cocktails>.
31. Rossheim ME, Yurasek AM, Greene KM, et al. The Federal Trade Commission's mandated Four Loko labeling fails to facilitate accurate estimation of alcohol content by college students. *Am J Drug Alcohol Abuse*. 2020;46(4):430-7. doi:10.1080/00952990.2019.1671438.
32. Siegel S. The Four-Loko effect. *Perspect Psychol Sci*. 2011;6(4):357-62. doi:10.1177/1745691611409243.
33. National Institute on Alcohol Abuse and Alcoholism. What is a standard drink [Internet]? 2025 [cited 2026 Mar 27]. Available from: <https://www.niaaa.nih.gov/alcohols-effects-health/what-standard-drink>.
34. Atkinson AM, Meadows BR, Emslie C, Lyons A, Sumnall HR. 'Pretty in Pink' and 'Girl Power': an analysis of the targeting and representation of women in alcohol brand marketing on Facebook and Instagram. *Int J Drug Policy*. 2022;101:103547. doi:10.1016/j.drugpo.2021.103547.
35. Spivey JD, Lee JGL, Smallwood SW. Tobacco policies and alcohol sponsorship at lesbian, gay, bisexual, and transgender pride festivals: time for intervention. *Am J Public Health*. 2018;108(2):187-188. doi:10.2105/ajph.2017.304205.
36. Alcohol and Tobacco Tax and Trade Bureau. Health claims in advertising – mitigating health consequences. 2022 [cited 2026 Mar 27]. Available from: <https://content.govdelivery.com/accounts/USTTB/bulletins/3107f19>.
37. Dwivedi YK, Ismagilova E, Hughes DL, et al. Setting the future of digital and social media marketing research: perspectives and research propositions. *Int J Inf Manage*. 2021;59:102168.
38. National Cancer Institute. *The Role of the Media in Promoting and Reducing Tobacco Use*. Tobacco Control Monograph No. 19. NIH Publication No. 07-6242. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2008.
39. Radoš Krnel S, Levičnik G, van Dalen W, Ferrarese G, Tricas-Sauras S. Effectiveness of regulatory policies on online/digital/internet-mediated alcohol marketing: a systematic review. *J Epidemiol Glob Health*. 2023;13(1): 115-128. doi:10.1007/s44197-023-00088-2.

40. Kelley K. Alcoholic beverage consumption statistics and trends 2023. Pennsylvania State University; 2023 [cited 2026 Mar 27]. Available from: <https://web.archive.org/web/20250428161423/https://extension.psu.edu/alcoholic-beverage-consumption-statistics-and-trends-2023>.
41. Marbin J, Balk SJ, Gribben V, Groner J. Health disparities in tobacco use and exposure: a structural competency approach. *Pediatrics*. 2021;147(1). doi:10.1542/peds.2020-040253.
42. Cecconi C, Adams R, Cardone A, et al. Generational differences in healthcare: the role of technology in the path forward. *Front Public Health*. 2025;13:1546317. doi:10.3389/fpubh.2025.1546317.
43. National Cancer Institute. SEER*Explorer: An interactive website for SEER cancer statistics. 2024 [cited 2026 Mar 27]. Available from: <https://seer.cancer.gov/statistics-network/explorer>.
44. U.S. Department of Health and Human Services. *Smoking Cessation. A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2020.
45. U.S. National Cancer Institute. *Treating Smoking in Cancer Patients: An Essential Component of Cancer Care*. National Cancer Institute Tobacco Control Monograph 23. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2022.
46. National Toxicology Program. National Toxicology Report, Report on Carcinogens, 15th Edition. 2021 [cited 2026 Mar 27]. Available from: <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc>.
47. Islami F, Marlow EC, Thomson B, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States, 2019. *CA Cancer J Clin*. 2024. doi:10.3322/caac.21858.
48. Safiri S, Nejadghaderi SA, Abdollahi M, et al. Global, regional, and national burden of cancers attributable to tobacco smoking in 204 countries and territories, 1990-2019. *Cancer Med*. 2022;11(13):2662-78. doi:10.1002/cam4.4647.
49. U.S. Department of Health and Human Services. *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2006.
50. U.S. Department of Health and Human Services. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.
51. Jamal A, Agaku IT, O'Connor E, King BA, Kenemer JB, Neff L. Current cigarette smoking among adults--United States, 2005-2013. *MMWR Morb Mortal Wkly Rep*. 2014;63(47):1108-12.
52. National Center for Health Statistics. Percentage of current cigarette smoking for adults aged 18 and over, United States, 2019-2024. [cited 2026 Mar 27]. Available from: https://wwwn.cdc.gov/NHISDataQueryTool/SHS_adult/index.html.
53. U.S. Department of Health and Human Services. *Eliminating Tobacco-Related Disease and Death: Addressing Disparities—A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2024.
54. Centers for Disease Control and Prevention. Tobacco product use among adults - United States, 2022. [cited 2026 Mar 27]. Available from: <https://www.cdc.gov/tobacco/media/pdfs/2024/09/cdc-osh-ncis-data-report-508.pdf>.
55. U.S. National Cancer Institute. *A Socioecological Approach to Addressing Tobacco-Related Health Disparities*. National Cancer Institute Tobacco Control Monograph 22. NIH Publication No. 17-CA-8035A. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2017.
56. Babor TF, Casswell S, Graham K, et al. *Alcohol: no ordinary commodity: research and public policy*. Oxford University Press; 2022.
57. U.S. National Cancer Institute and World Health Organization. *The Economics of Tobacco and Tobacco Control*. National Cancer Institute Tobacco Control Monograph 21. NIH Publication No. 16-CA-8029A. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; and Geneva, CH: World Health Organization; 2016.
58. Bandi P, Minihan AK, Siegel RL, Islami F, Nargis N, Jemal A, Fedewa SA. Updated review of major cancer risk factors and screening test use in the United States in 2018 and 2019, with a focus on smoking cessation. *Cancer Epidemiol Biomarkers Prev*. 2021;30(7):1287-1299. doi:10.1158/1055-9965.Epi-20-1754.

59. Akl EA, Gaddam S, Gunukula SK, Honeine R, Jaoude PA, Irani J. The effects of waterpipe tobacco smoking on health outcomes: a systematic review. *International journal of epidemiology*. 2010;39(3):834-57. doi:10.1093/ije/dyq002.
60. National Cancer Institute. *Cigars: Health Effects and Trends*. Tobacco Control Monograph No. 9. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 1988
61. World Health Organization. Advisory note: waterpipe tobacco smoking: health effects, research needs and recommended actions by regulators, 2nd edition. 2015 [cited 2026 Mar 27]. Available from: <https://www.who.int/publications/i/item/advisory-note-waterpipe-tobacco-smoking-health-effects-research-needs-and-recommended-actions-by-regulators-2nd-ed>.
62. WHO Study Group on Tobacco Product Regulation. Advisory note: waterpipe tobacco smoking: health effects, research needs and recommended actions by regulators. 2005. Geneva: World Health Organization.
63. Centers for Disease Control and Prevention. Smoking and tobacco use - hookahs. 2024 [cited 2026 Mar 27]. Available from: <https://www.cdc.gov/tobacco/other-tobacco-products/hookahs.html>.
64. Primack BA, Carroll MV, Weiss PM, et al. systematic review and meta-analysis of inhaled toxicants from waterpipe and cigarette smoking. *Public Health Rep*. 2016;131(1):76-85. doi:10.1177/003335491613100114.
65. Etemadi A, Poustchi H, Chang CM, et al. Urinary biomarkers of carcinogenic exposure among cigarette, waterpipe, and smokeless tobacco users and never users of tobacco in the Golestan Cohort Study. *Cancer Epidemiol Biomarkers Prev*. 2019;28(2):337-347. doi:10.1158/1055-9965.Epi-18-0743.
66. Darawshy F, Abu Rmeileh A, Kuint R, Berkman N. Waterpipe smoking: a review of pulmonary and health effects. *Eur Respir Rev*. 2021;30(160). doi:10.1183/16000617.0374-2020.
67. Patil S, Mahuli AV, Warnakulasuriya S. Effects of smoking shisha, cancer risk, and strategies for prevention of shisha habit. *J Oral Biol Craniofac Res*. 2022;12(4):439-443. doi:10.1016/j.jobcr.2022.05.008.
68. Byhamre ML, Araghi M, Alfredsson L, et al. Swedish snus use is associated with mortality: a pooled analysis of eight prospective studies. *International journal of epidemiology*. 2021;49(6):2041-50. doi:10.1093/ije/dyaa197.
69. National Cancer Institute and Centers for Disease Control and Prevention. *Smokeless Tobacco and Public Health: A Global Perspective*. Bethesda, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Institutes of Health, National Cancer Institute. NIH Publication No. 14-7983; 2014.
70. Taylor KA, Sharma E, Edwards KC, et al. Longitudinal pathways of exclusive and polytobacco cigarette use among youth, young adults and adults in the USA: findings from the PATH Study Waves 1-3 (2013-2016). *Tob Control*. 2020;29(Suppl 3):s139-s146. doi:10.1136/tobaccocontrol-2020-055630.
71. King JL, Reboussin D, Cornacchione Ross J, Wiseman KD, Wagoner KG, Sutfin EL. Polytobacco use among a nationally representative sample of adolescent and young adult e-cigarette users. *J Adolesc Health*. 2018;63(4):407-412. doi:10.1016/j.jadohealth.2018.04.010.
72. Jamal A, Park-Lee E, Birdsey J, et al. Tobacco product use among middle and high school students - National Youth Tobacco Survey, United States, 2024. *MMWR Morb Mortal Wkly Rep*. 2024;73(41):917-924. doi:10.15585/mmwr.mm7341a2.
73. Mattingly DT, Zavala-Arciniega L, Hirschtick JL, Meza R, Levy DT, Fleischer NL. Trends in exclusive, dual and polytobacco use among U.S. adults, 2014-2019: results from two nationally representative surveys. *Int J Environ Res Public Health*. 2021;18(24). doi:10.3390/ijerph182413092.
74. Samet JM, Chiu WA, Coglian V, et al. The IARC monographs: updated procedures for modern and transparent evidence synthesis in cancer hazard identification. *J Natl Cancer Inst*. 2020;112(1):30-37. doi:10.1093/jnci/djz169.
75. Rumgay H, Shield K, Charvat H, et al. Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study. *Lancet Oncol*. 2021;22(8):1071-1080. doi:10.1016/S1470-2045(21)00279-5.
76. Esser MB, Sherk A, Liu Y, Henley SJ, Naimi TS. Reducing alcohol use to prevent cancer deaths: estimated effects among U.S. adults. *Am J Prev Med*. 2024;66(4):725-729. doi:10.1016/j.amepre.2023.12.003.
77. Freedman ND, Abnet CC, Leitzmann MF, Mouw T, Subar AF, Hollenbeck AR, Schatzkin A. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am J Epidemiol*. 2007;165(12):1424-33. doi:10.1093/aje/kwm051.
78. Sohi I, Rehm J, Saab M, et al. Alcoholic beverage consumption and female breast cancer risk: A systematic review and meta-analysis of prospective cohort studies. *Alcohol Clin Exp Res (Hoboken)*. 2024;48(12):2222-2241. doi:10.1111/acer.15493.

79. Di Credico G, Polesel J, Dal Maso L, et al. Alcohol drinking and head and neck cancer risk: the joint effect of intensity and duration. *Br J Cancer*. 2020;123(9):1456-1463. doi:10.1038/s41416-020-01031-z.
80. Jun S, Park H, Kim UJ, et al. Cancer risk based on alcohol consumption levels: a comprehensive systematic review and meta-analysis. *Epidemiol Health*. 2023;45:e2023092. doi:10.4178/epih.e2023092.
81. Chuang SC, Lee YC, Wu GJ, Straif K, Hashibe M. Alcohol consumption and liver cancer risk: a meta-analysis. *Cancer Causes Control*. 2015;26(9):1205-31. doi:10.1007/s10552-015-0615-3.
82. Park H, Shin SK, Joo I, Song DS, Jang JW, Park JW. Systematic review with meta-analysis: low-level alcohol consumption and the risk of liver cancer. *Gut Liver*. 2020;14(6):792-807. doi:10.5009/gnl19163.
83. Deng W, Jin L, Zhuo H, Vasiliou V, Zhang Y. Alcohol consumption and risk of stomach cancer: a meta-analysis. *Chem Biol Interact*. 2021;336:109365. doi:10.1016/j.cbi.2021.109365.
84. Naudin S, Wang M, Dimou N, et al. Alcohol intake and pancreatic cancer risk: an analysis from 30 prospective studies across Asia, Australia, Europe, and North America. *PLoS Med*. 2025;22(5):e1004590. doi:10.1371/journal.pmed.1004590.
85. Gandini S, Masala G, Palli D, et al. Alcohol, alcoholic beverages, and melanoma risk: a systematic literature review and dose-response meta-analysis. *Eur J Nutr*. 2018;57(7):2323-2332. doi:10.1007/s00394-018-1613-5.
86. Hong S, Khil H, Lee DH, Keum N, Giovannucci EL. alcohol consumption and the risk of prostate cancer: a dose-response meta-analysis. *Nutrients*. 2020;12(8). doi:10.3390/nu12082188.
87. Rumgay H, Murphy N, Ferrari P, Soerjomataram I. Alcohol and cancer: epidemiology and biological mechanisms. *Nutrients*. 2021;13(9). doi:10.3390/nu13093173.
88. Tramacere I, Pelucchi C, Bonifazi M, et al. Alcohol drinking and non-Hodgkin lymphoma risk: a systematic review and a meta-analysis. *Ann Oncol*. 2012;23(11):2791-2798. doi:10.1093/annonc/mds013.
89. Al-Bayati O, Hasan A, Pruthi D, Kaushik D, Liss MA. Systematic review of modifiable risk factors for kidney cancer. *Urol Oncol*. 2019;37(6):359-371. doi:10.1016/j.urolonc.2018.12.008.
90. Bellocco R, Pasquali E, Rota M, et al. Alcohol drinking and risk of renal cell carcinoma: results of a meta-analysis. *Ann Oncol*. 2012;23(9):2235-2244. doi:10.1093/annonc/mds022.
91. Cheng G, Xie L. Alcohol intake and risk of renal cell carcinoma: a meta-analysis of published case-control studies. *Arch Med Sci*. 2011;7(4):648-57. doi:10.5114/aoms.2011.24135.
92. Psaltopoulou T, Sergentanis TN, Ntanasis-Stathopoulos I, Tzanninis IG, Tsilimigras DI, Dimopoulos MA. Alcohol consumption and risk of hematological malignancies: a meta-analysis of prospective studies. *Int J Cancer*. 2018;143(3):486-495. doi:10.1002/ijc.31330.
93. Cerdá M, Johnson-Lawrence VD, Galea S. Lifetime income patterns and alcohol consumption: investigating the association between long- and short-term income trajectories and drinking. *Soc Sci Med*. 2011;73(8):1178-85. doi:10.1016/j.socscimed.2011.07.025.
94. Collins SE. Associations between socioeconomic factors and alcohol outcomes. *Alcohol Res*. 2016;38(1):83-94.
95. Devaux M, Sassi F. Social disparities in hazardous alcohol use: self-report bias may lead to incorrect estimates. *Eur J Public Health*. 2016;26(1):129-34. doi:10.1093/eurpub/ckv190.
96. Chaloupka FJ, Grossman M, Saffer H. The effects of price on alcohol consumption and alcohol-related problems. *Alcohol Res Health*. 2002;26(1):22-34.
97. Klatsky AL, Armstrong MA, Kipp H. Correlates of alcoholic beverage preference: traits of persons who choose wine, liquor or beer. *Br J Addict*. 1990;85(10):1279-89. doi:10.1111/j.1360-0443.1990.tb01604.x.
98. Sharma A, Sinha K, Vandenberg B. Pricing as a means of controlling alcohol consumption. *Br Med Bull*. 2017;123(1):149-158. doi:10.1093/bmb/ldx020.
99. Patrick ME, Terry-McElrath YM, Miech RA, Keyes KM, Jager J, Schulenberg JE. Alcohol use and the COVID-19 pandemic: historical trends in drinking, contexts, and reasons for use among U.S. adults. *Soc Sci Med*. 2022;301:114887. doi:10.1016/j.socscimed.2022.114887.
100. Kerr WC, Lui CK, Ye Y, Li L, Greenfield T, Karriker-Jaffe KJ, Martinez P. Long-term trends in beverage-specific drinking in the National Alcohol Surveys: differences by sex, age, and race and ethnicity. *Alcohol Clin Exp Res (Hoboken)*. 2024;48(7):1322-1335. doi:10.1111/acer.15335.
101. Winn RA, Tossas KY, Doubeni C. Commentary: some water in the data desert: the Cancer Intervention and Surveillance Modeling Network's capacity to guide mitigation of cancer health disparities. *J Natl Cancer Inst Monogr*. 2023;2023(62):167-172. doi:10.1093/jncimonographs/lgad032.
102. Alcácer MA, Marques-Lopes I, Fajó-Pascual M, Foncillas JP, Carmona-Torre F, Martínez-González MA. Alcoholic beverage preference and dietary pattern in Spanish university graduates: the SUN cohort study. *Eur J Clin Nutr*. 2008;62(10):1178-86. doi:10.1038/sj.ejcn.1602833.

103. Barefoot JC, Grønbaek M, Feaganes JR, McPherson RS, Williams RB, Siegler IC. Alcoholic beverage preference, diet, and health habits in the UNC Alumni Heart Study. *Am J Clin Nutr.* 2002;76(2):466-72. doi:10.1093/ajcn/76.2.466.
104. Paschall M, Lipton RI. Wine preference and related health determinants in a U.S. national sample of young adults. *Drug Alcohol Depend.* 2005;78(3):339-44. doi:10.1016/j.drugalcdep.2004.12.004.
105. Gapstur SM, Bouvard V, Nathán ST, et al. The IARC perspective on alcohol reduction or cessation and cancer risk. *N Engl J Med.* 2023;389(26):2486-2494. doi:10.1056/NEJMSr2306723.
106. Centers for Disease Control and Prevention. Tobacco and cancer. Available from: <https://www.cdc.gov/cancer/risk-factors/tobacco.html>.
107. Li Y, Hecht SS. Carcinogenic components of tobacco and tobacco smoke: a 2022 update. *Food Chem Toxicol.* 2022;165:113179. doi:10.1016/j.fct.2022.113179.
108. Stornetta A, Guidolin V, Balbo S. Alcohol-derived acetaldehyde exposure in the oral cavity. *Cancers (Basel).* 2018;10(1). doi:10.3390/cancers10010020.
109. Ratna A, Mandrekar P. Alcohol and cancer: mechanisms and therapies. *Biomolecules.* 2017;7(3). doi:10.3390/biom7030061.
110. Nieminen MT, Salaspuro M. Local Acetaldehyde-an essential role in alcohol-related upper gastrointestinal tract carcinogenesis. *Cancers (Basel).* 2018;10(1). doi:10.3390/cancers10010011.
111. Salaspuro M. Interrelationship between alcohol, smoking, acetaldehyde and cancer. *Novartis Found Symp.* 2007;285:80-9; discussion 89-96, 198-9. doi:10.1002/9780470511848.ch6.
112. Talhout R, Opperhuizen A, van Amsterdam JG. Role of acetaldehyde in tobacco smoke addiction. *Eur Neuropsychopharmacol.* 2007;17(10):627-36. doi:10.1016/j.euroneuro.2007.02.013.
113. King L, Aplin R, Gill C, Naimi T. A state-of-the-science review of alcoholic beverages and polycyclic aromatic hydrocarbons. *Environ Health Perspect.* 2024;132(1):16001. doi:10.1289/ehp13506.
114. Tóth ME, Vigh L, Sántha M. Alcohol stress, membranes, and chaperones. *Cell Stress Chaperones.* 2014;19(3):299-309. doi:10.1007/s12192-013-0472-5.
115. Harada S, Agarwal DP, Goedde HW. Aldehyde dehydrogenase deficiency as cause of facial flushing reaction to alcohol in Japanese. *Lancet.* 1981;2(8253):982. doi:10.1016/s0140-6736(81)91172-7.
116. Montel RA, Munoz-Zuluaga C, Stiles KM, Crystal RG. Can gene therapy be used to prevent cancer? Gene therapy for aldehyde dehydrogenase 2 deficiency. *Cancer Gene Ther.* 2022;29(7):889-896. doi:10.1038/s41417-021-00399-1.
117. Sim W, Pan JT, Chua CWX, Fong KY, Wong SH, Lee B, Oon HH. Association between alcohol flushing syndrome and cancer: a systematic review and meta-analysis. *Ann Acad Med Singap.* 2024;53(7):420-434. doi:10.47102/annals-acadmedsg.2023351.
118. Chen CH, Ferreira JC, Gross ER, Mochly-Rosen D. Targeting aldehyde dehydrogenase 2: new therapeutic opportunities. *Physiol Rev.* 2014;94(1):1-34. doi:10.1152/physrev.00017.2013.
119. Chang JS, Hsiao J-R, Chen C-H. ALDH2 polymorphism and alcohol-related cancers in Asians: a public health perspective. *J Biomed Sci.* 2017;24(1):19. doi:10.1186/s12929-017-0327-y.
120. Boccia S, Hashibe M, Galli P, et al. Aldehyde dehydrogenase 2 and head and neck cancer: a meta-analysis implementing a Mendelian randomization approach. *Cancer Epidemiol Biomarkers Prev.* 2009;18(1):248-54. doi:10.1158/1055-9965.EPI-08-0462.
121. Yokoyama A, Muramatsu T, Ohmori T, Higuchi S, Hayashida M, Ishii H. Esophageal cancer and aldehyde dehydrogenase-2 genotypes in Japanese males. *Cancer Epidemiol Biomarkers Prev.* 1996;5(2):99-102.
122. Salaspuro V, Salaspuro M. Synergistic effect of alcohol drinking and smoking on in vivo acetaldehyde concentration in saliva. *Int J Cancer.* 2004;111(4):480-3. doi:10.1002/ijc.20293.
123. Cance JD, Talley AE, Morgan-Lopez A, Fromme K. Longitudinal conjoint patterns of alcohol and tobacco use throughout emerging adulthood. *Subst Use Misuse.* 2017;52(3):373-382. doi:10.1080/10826084.2016.1228677.
124. Gubner NR, Delucchi KL, Ramo DE. Associations between binge drinking frequency and tobacco use among young adults. *Addict Behav.* 2016;60:191-6. doi:10.1016/j.addbeh.2016.04.019.
125. Brooks PJ, Enoch MA, Goldman D, Li TK, Yokoyama A. The alcohol flushing response: an unrecognized risk factor for esophageal cancer from alcohol consumption. *PLoS Med.* 2009;6(3):e50. doi:10.1371/journal.pmed.1000050.
126. Saunders GRB, McGue M, Iacono WG, Vrieze S. Longitudinal effects and environmental moderation of ALDH2 and ADH1B gene variants on substance use from age 14 to 40. *Dev Psychopathol.* 2022;34(5):1856-1864. doi:10.1017/s0954579422000712.

127. Forman D, Yang M, Chien R, et al. ALDH2 deficiency and alcohol intake in the U.S.: opportunity for precision cancer prevention. *Cancer Epidemiol Biomarkers Prev*. 2025. doi:10.1158/1055-9965.Epi-24-1296.
128. Castellsagué X, Muñoz N, De Stefani E, Victora CG, Castelletto R, Rolón PA, Quintana MJ. Independent and joint effects of tobacco smoking and alcohol drinking on the risk of esophageal cancer in men and women. *Int J Cancer*. 1999;82(5):657-64.
129. Mello FW, Melo G, Pasetto JJ, Silva CAB, Warnakulasuriya S, Rivero ERC. The synergistic effect of tobacco and alcohol consumption on oral squamous cell carcinoma: a systematic review and meta-analysis. *Clin Oral Investig*. 2019;23(7):2849-2859. doi:10.1007/s00784-019-02958-1.
130. Pelucchi C, Gallus S, Garavello W, Bosetti C, La Vecchia C. Cancer risk associated with alcohol and tobacco use: focus on upper aero-digestive tract and liver. *Alcohol Res Health*. 2006;29(3):193-8.
131. Brown LM, Hoover RN, Greenberg RS, et al. Are racial differences in squamous cell esophageal cancer explained by alcohol and tobacco use? *J Natl Cancer Inst*. 1994;86(17):1340-5. doi:10.1093/jnci/86.17.1340.
132. Auguste A, Deloumeaux J, Joachim C, et al. Joint effect of tobacco, alcohol, and oral HPV infection on head and neck cancer risk in the French West Indies. *Cancer Med*. 2020;9(18):6854-6863. doi:10.1002/cam4.3327
133. Oh HY, Seo S-S, Kim MK, et al. Synergistic effect of viral load and alcohol consumption on the risk of persistent high-risk human papillomavirus infection. *PLOS ONE*. 2014;9(8):e104374. doi:10.1371/journal.pone.0104374.
134. Oh HY, Kim MK, Seo S, et al. Alcohol consumption and persistent infection of high-risk human papillomavirus. *Epidemiology and Infection*. 2015;143(7):1442-1450. doi:10.1017/S0950268814002258.
135. Schabath MB, Thompson ZJ, Egan KM, et al. Alcohol consumption and prevalence of human papillomavirus (HPV) infection among US men in the HPV in Men (HIM) study. *Sex Transm Infect*. 2015;91(1):61-7. doi:10.1136/sextrans-2013-051422.
136. Mirabello L, Clarke MA, Nelson CW, et al. The intersection of HPV epidemiology, genomics and mechanistic studies of HPV-mediated carcinogenesis. *Viruses*. 2018;10(2). doi:10.3390/v10020080.
137. Garcia TA, Litt DM, Davis KC, Norris J, Kaysen D, Lewis MA. growing up, hooking up, and drinking: a review of uncommitted sexual behavior and its association with alcohol use and related consequences among adolescents and young adults in the United States. *Front Psychol*. 2019;10:1872. doi:10.3389/fpsyg.2019.01872.
138. Brenner DR, Fehring G, Zhang ZF, et al. Alcohol consumption and lung cancer risk: a pooled analysis from the International Lung Cancer Consortium and the SYNERGY study. *Cancer Epidemiol*. 2019;58:25-32. doi:10.1016/j.canep.2018.10.006.
139. Viner B, Barberio AM, Haig TR, Friedenreich CM, Brenner DR. The individual and combined effects of alcohol consumption and cigarette smoking on site-specific cancer risk in a prospective cohort of 26,607 adults: results from Alberta's Tomorrow Project. *Cancer Causes Control*. 2019;30(12):1313-1326. doi:10.1007/s10552-019-01226-7.
140. García-Lavandeira JA, Ruano-Ravina A, Barros-Dios JM. Alcohol consumption and lung cancer risk in never smokers. *Gac Sanit*. 2016;30(4):311-7. doi:10.1016/j.gaceta.2016.03.017.
141. Bandera EV, Freudenheim JL, Vena JE. Alcohol consumption and lung cancer: a review of the epidemiologic evidence. *Cancer Epidemiol Biomarkers Prev*. 2001;10(8):813-21.
142. Fehring G, Brenner DR, Zhang ZF, et al. Alcohol and lung cancer risk among never smokers: a pooled analysis from the international lung cancer consortium and the SYNERGY study. *Int J Cancer*. 2017;140(9):1976-1984. doi:10.1002/ijc.30618.
143. Marrero JA, Fontana RJ, Fu S, Conjeevaram HS, Su GL, Lok AS. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. *J Hepatol*. 2005;42(2):218-24. doi:10.1016/j.jhep.2004.10.005.
144. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology*. 2004;127(5 Suppl 1):S35-50. doi:10.1053/j.gastro.2004.09.014.
145. Kuper H, Tzonou A, Kaklamani E, et al. Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. *Int J Cancer*. 2000;85(4):498-502.
146. Bui TT, Park E, Kang HY, Oh JK. Combined effects of smoking and alcohol consumption on the risk of liver cancer according to metabolic syndrome: a nested case-control study in South Korea. *Int J Cancer*. 2024;155(4):654-665. doi:10.1002/ijc.34935.
147. European Association for the Study of the Liver. EASL Clinical practice guidelines: management of alcohol-related liver disease. *J Hepatol*. 2018;69(1):154-181. doi:10.1016/j.jhep.2018.03.018.
148. U.S. Department of Veterans Affairs. Avoidance of alcohol for patients with cirrhosis [Internet]. [cited 2026 Mar 27]. Available from: <https://www.hepatitis.va.gov/cirrhosis/cirrhosis-alcohol.asp>.

149. Aglago EK, Ramos I, Keski-Rahkonen P, et al. Alcohol and smoking habits in association with hepatocellular carcinoma risk. *Int J Cancer*. Aug 15 2025;157(4):644-657. doi:10.1002/ijc.35401.
150. Freudenheim JL. Alcohol's effects on breast cancer in women. *Alcohol Res*. 2020;40(2):11. doi:10.35946/arcr.v40.2.11.
151. Dorgan JF, Baer DJ, Albert PS, et al. Serum hormones and the alcohol-breast cancer association in postmenopausal women. *J Natl Cancer Inst*. 2001;93(9):710-5. doi:10.1093/jnci/93.9.710.
152. U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.
153. U.S. Department of Health and Human Services. *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2006.
154. Scala M, Bosetti C, Bagnardi V, Possenti I, Specchia C, Gallus S, Lugo A. Dose-response relationships between cigarette smoking and breast cancer risk: a systematic review and meta-analysis. *J Epidemiol*. 2023;33(12):640-648. doi:10.2188/jea.JE20220206.
155. Gaudet MM, Carter BD, Brinton LA, et al. Pooled analysis of active cigarette smoking and invasive breast cancer risk in 14 cohort studies. *International journal of epidemiology*. 2017;46(3):881-893. doi:10.1093/ije/dyw288.
156. Liu Y, Nguyen N, Colditz GA. Links between alcohol consumption and breast cancer: a look at the evidence. *Womens Health (Lond)*. 2015;11(1):65-77. doi:10.2217/whe.14.62.
157. Fordyce L, Berrigan D, Srinivasan S. Social determinants of health and the environmental exposures: a promising partnership. In Waters M, Hughes C, editors. *Translational Toxicology and Therapeutics: Windows of Developmental Susceptibility and Cancer*. Wiley and Sons; 2018:295-414.
158. Jones ME, Schoemaker MJ, Wright LB, Ashworth A, Swerdlow AJ. Smoking and risk of breast cancer in the Generations Study cohort. *Breast Cancer Res*. 2017;19(1):118. doi:10.1186/s13058-017-0908-4.
159. Knight JA, Fan J, Malone KE, et al. Alcohol consumption and cigarette smoking in combination: A predictor of contralateral breast cancer risk in the WECARE study. *Int J Cancer*. 2017;141(5):916-924. doi:10.1002/ijc.30791.
160. Li H, Terry MB, Antoniou AC, et al. Alcohol consumption, cigarette smoking, and risk of breast cancer for BRCA1 and BRCA2 mutation carriers: results from the BRCA1 and BRCA2 Cohort Consortium. *Cancer Epidemiol Biomarkers Prev*. 2020;29(2):368-378. doi:10.1158/1055-9965.EPI-19-0546.
161. Zeinomar N, Knight JA, Genkinger JM, et al. Alcohol consumption, cigarette smoking, and familial breast cancer risk: findings from the Prospective Family Study Cohort (ProF-SC). *Breast Cancer Res*. 2019;21(1):128. doi:10.1186/s13058-019-1213-1.
162. Gaudet MM, Gapstur SM, Sun J, Diver WR, Hannan LM, Thun MJ. Active smoking and breast cancer risk: original cohort data and meta-analysis. *J Natl Cancer Inst*. 2013;105(8):515-25. doi:10.1093/jnci/djt023.
163. Gram IT, Braaten T, Terry PD, Sasco AJ, Adami HO, Lund E, Weiderpass E. Breast cancer risk among women who start smoking as teenagers. *Cancer Epidemiol Biomarkers Prev*. 2005;14(1):61-6.
164. Hamajima N, Hirose K, Tajima K, et al. Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer*. 2002;87(11):1234-45. doi:10.1038/sj.bjc.6600596.
165. Spillane S, Shiels MS, Best AF, et al. Trends in alcohol-induced deaths in the United States, 2000-2016. *JAMA Netw Open*. 2020;3(2):e1921451. doi:10.1001/jamanetworkopen.2019.21451.
166. Kitahara CM, Linet MS, Beane Freeman LE, et al. Cigarette smoking, alcohol intake, and thyroid cancer risk: a pooled analysis of five prospective studies in the United States. *Cancer Causes Control*. 2012;23(10):1615-24. doi:10.1007/s10552-012-0039-2.
167. Yeo Y, Shin DW, Han K, et al. Smoking, alcohol consumption, and the risk of thyroid cancer: a population-based Korean cohort study of 10 million people. *Thyroid®*. 2022;32(4):440-448. doi:10.1089/thy.2021.0675.
168. La Greca A, Grau L, Arbet J, Liao LM, Sosa JA, Haugen BR, et al. Anthropometric, dietary, and lifestyle factors and risk of advanced thyroid cancer: the NIH-AARP diet and health cohort study. *Clin Endocrinol (Oxf)*. 2023;99(6):586-597. doi:10.1111/cen.14970.
169. Pirie K, Peto R, Reeves GK, Green J, Beral V, Million Women Study. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. *Lancet*. 2013;381(9861):133-41. doi:10.1016/S0140-6736(12)61720-6.

170. Gmel G, Shield KD, Rehm J. Tools for estimating alcohol consumption. In: Boyle P, Boffetta P, Lowenfels AB, Burns H, Brawley O, Zatonski W, Rehm J, editors. *Alcohol: Science, Policy and Public Health*. Oxford University Press; 2013.
171. Centers for Disease Control and Prevention. Introduction to public health surveillance [Internet]. [cited 2026 Mar 27]. Available from: <https://www.cdc.gov/training-publichealth101/php/training/introduction-to-public-health-surveillance.html>.
172. Hendershot T, Pan H, Haines J, et al. Using the PhenX Toolkit to add standard measures to a study. *Curr Protoc Hum Genet*. 2015;86:1.21.1-1.21.17. doi:10.1002/0471142905.hg0121s86.
173. Dawson DA. Methodological issues in measuring alcohol use. *Alcohol Res Health*. 2003;27(1):18-29.
174. Centers for Disease Control and Prevention. About standard drink sizes 2025. [cited 2026 Mar 27]. Available from: https://www.cdc.gov/alcohol/standard-drink-sizes/index.html#cdc_generic_section_2-standard-alcohol-drink-sizes.
175. Hughes JR, Shiffman S, Naud S, Peters EN. Day-to-day variability in self-reported cigarettes per day. *Nicotine Tob Res*. 2017;19(9):1107-1111. doi:10.1093/ntr/ntx057.
176. Krishnan N, Berg CJ, Elmi AF, Klemperer EM, Sherman SE, Abroms LC. Trajectories of ENDS and cigarette use among dual users: analysis of waves 1 to 5 of the PATH Study. *Tob Control*. 2024;33(e1):e62-e68. doi:10.1136/tc-2022-057405.
177. Mayer M, Shin YE, Baker L, et al. a longitudinal analysis of respiratory illness and tobacco use transitions. *Am J Prev Med*. Feb 2023;64(2):175-183. doi:10.1016/j.amepre.2022.08.010.
178. Brook JS, Balka E, Zhang C, Pahl K, Brook DW. Adolescent academic adjustment factors and the trajectories of cigarette smoking from adolescence to the mid-thirties. *Int J Ment Health*. Spring 2011;40(1):7-21. doi:10.2753/imh0020-7411400101.
179. Kotz D, Fidler J, West R. Very low rate and light smokers: smoking patterns and cessation-related behaviour in England, 2006-11. *Addiction*. 2012;107(5):995-1002. doi:10.1111/j.1360-0443.2011.03739.x.
180. Kvaavik E, von Soest T, Pedersen W. Nondaily smoking: a population-based, longitudinal study of stability and predictors. *BMC Public Health*. 2014;14:123. doi:10.1186/1471-2458-14-123.
181. Johnson AL, Villanti AC, Williams V, et al. Smoking trajectory classes and impact of social smoking identity in two cohorts of U.S. young adults. *Emerg Adulthood*. 2019;7(4):258-269. doi:10.1177/2167696818763949.
182. Costello DM, Dierker LC, Jones BL, Rose JS. Trajectories of smoking from adolescence to early adulthood and their psychosocial risk factors. *Health Psychol*. 2008;27(6):811-8. doi:10.1037/0278-6133.27.6.811.
183. Gutiérrez-Torres DS, Reyes-Guzman C, Mayer M, Prutzman YM, Freedman ND. Quit attempts and use of cessation aids among U.S. adults who smoke nondaily. *Am J Prev Med*. 2024. doi:10.1016/j.amepre.2024.11.004.
184. Gutiérrez-Torres DS, Kim S, Albanes D, Weinstein SJ, Inoue-Choi M, Albert PS, Freedman ND. Changes in smoking use and subsequent lung cancer risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *J Natl Cancer Inst*. 2024 Jun 7;116(6):895-901. doi: 10.1093/jnci/djae012.
185. Sarich P, Canfell K, Egger S, Banks E, Joshy G, Grogan P, Weber MF. Alcohol consumption, drinking patterns and cancer incidence in an Australian cohort of 226,162 participants aged 45 years and over. *Br J Cancer*. 2021;124(2):513-523. doi:10.1038/s41416-020-01101-2.
186. McKee SA, Hinson R, Rounsaville D, Petrelli P. Survey of subjective effects of smoking while drinking among college students. *Nicotine Tob Res*. 2004;6(1):111-7. doi:10.1080/14622200310001656939.
187. Campbell ML, Bozec LJ, McGrath D, Barrett SP. Alcohol and tobacco co-use in nondaily smokers: an inevitable phenomenon? *Drug and Alcohol Review*. 2012;31(4):447-450. doi:10.1111/j.1465-3362.2011.00328.x.
188. Ekholm O, Bloomfield K, Thygesen LC. Alcohol habits and alcohol-related health conditions of self-defined lifetime abstainers and never binge drinkers. *Alcohol Clin Exp Res (Hoboken)*. 2024;48(10):1905-14. doi:10.1111/acer.15433.
189. Rehm J, Irving H, Ye Y, Kerr WC, Bond J, Greenfield TK. Are lifetime abstainers the best control group in alcohol epidemiology? On the stability and validity of reported lifetime abstinence. *Am J Epidemiol*. 2008;168(8):866-71. doi:10.1093/aje/kwn093.
190. Kerr WC, Lui CK, Williams E, Ye Y, Greenfield TK, Lown EA. Health risk factors associated with lifetime abstinence from alcohol in the 1979 National Longitudinal Survey of Youth Cohort. *Alcohol Clin Exp Res*. 2017;41(2):388-98. doi:10.1111/acer.13302.
191. Bell S, Britton A. Reliability of a retrospective decade-based life-course alcohol consumption questionnaire administered in later life. *Addiction*. 2015;110(10):1563-73.

192. Klipstein-Grobusch K, Slimani N, Krogh V, et al. Trends in self-reported past alcoholic beverage consumption and ethanol intake from 1950 to 1995 observed in eight European countries participating in the European Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr.* 2002;5(6b):1297-310. doi:10.1079/phn2002406.
193. Kerr WC, Fillmore KM, Bostrom A. Stability of alcohol consumption over time: evidence from three longitudinal surveys from the United States. *J Stud Alcohol.* 2002;63(3):325-33. doi:10.15288/jsa.2002.63.325.
194. Puka K, Buckley C, Mulia N, et al. Behavioral stability of alcohol consumption and socio-demographic correlates of change among a nationally representative cohort of U.S adults. *Addiction.* 2023;118(1):61-70.
195. Cho YI, Johnson TP, Fendrich M. Monthly variations in self-reports of alcohol consumption. *J Stud Alcohol.* March 2001;62(2):268-272.
196. Kerr WC, Greenfield TK, Ye Y, Bond J, Rehm J. Are the 1976-1985 birth cohorts heavier drinkers? Age-period-cohort analyses of the National Alcohol Surveys 1979-2010. *Addiction.* 2013;108(6):1038-1048. doi:10.1111/j.1360-0443.2012.04055.x.
197. Keyes KM, Miech R. Age, period, and cohort effects in heavy episodic drinking in the US from 1985 to 2009. *Drug Alcohol Depend.* 2013;132(1):140-148. doi:10.1016/j.drugalcdep.2013.01.019.
198. Patrick ME, Terry-McElrath YM, Lanza ST, Jager J, Schulenberg JE, O'Malley PM. Shifting age of peak binge drinking prevalence: historical changes in normative trajectories among young adults aged 18 to 30. *Alcohol Clin Exp Res.* 2019;43(2):287-298. doi:10.1111/acer.13933.
199. Keyes KM, Hatzenbuehler ML, Hasin DS. Stressful life experiences, alcohol consumption, and alcohol use disorders: the epidemiologic evidence for four main types of stressors. *Psychopharmacology (Berl).* 2011;218(1):1-17. doi:10.1007/s00213-011-2236-1.
200. Grossman ER, Kerr WC, Toomey TL. The role of law and policy in reducing deaths attributable to alcohol to reach healthy people's substance abuse goals in the United States. 2020 [cited 2026 Mar 27]. Available from: https://wayback.archive-it.org/5774/20220415185147/https://www.healthypeople.gov/sites/default/files/SA_report_2020-05-13_508_0.pdf.
201. Bondy SJ, Victor JC, Diemert LM, et al. Transitions in smoking status over time in a population-based panel study of smokers. *Nicotine Tob Res.* 2013;15(7):1201-10. doi:10.1093/ntr/nts259.
202. Weinberger AH, Pilver CE, Mazure CM, McKee SA. Stability of smoking status in the U.S. population: a longitudinal investigation. *Addiction.* 2014;109(9):1541-53. doi:10.1111/add.12647.
203. Doran N, Myers M, Luczak S, Trim R, Strong D, Tully L. Non-daily cigarette smoking: stability and transition to abstinence in young Adults. *Nicotine Tob Res.* 2023;25(1):151-158. doi:10.1093/ntr/ntac189.
204. Klein EG, Bernat DH, Lenk KM, Forster JL. Nondaily smoking patterns in young adulthood. *Addict Behav.* 2013;38(7):2267-72. doi:10.1016/j.addbeh.2013.03.005.
205. Robertson L, Iosua E, McGee R, Hancox RJ. Nondaily, low-rate daily, and high-rate daily smoking in young adults: a 17-year follow-up. *Nicotine Tob Res.* 2016;18(5):943-9. doi:10.1093/ntr/ntv167.
206. Schweizer CA, Roesch SC, Khoddam R, Doran N, Myers MG. Examining the stability of young-adult alcohol and tobacco co-use: a latent transition analysis. *Addict Res Theory.* 2014;22(4):325-335.
207. Kerr WC, Greenfield TK, Tujague J, Brown SE. A drink is a drink? Variation in the alcohol contained in beer, wine, and spirits drinks in a U.S. methodological sample. *Alcohol Clin Exp Res.* 2005;29(11):2015-2021. doi:10.1097/01.alc.0000187596.92804.bd.
208. Kerr WC, Patterson D, Koenen MA, Greenfield TK. Alcohol content variation of bar and restaurant drinks in Northern California. *Alcohol Clin Exp Res.* 2008;32(9):1623-1629. doi:10.1111/j.1530-0277.2008.00741.x.
209. Tuyns AJ, Péquignot G, Abbatucci JS. Oesophageal cancer and alcohol consumption; importance of type of beverage. *Int J Cancer.* 1979;23(4):443-7. doi:10.1002/ijc.2910230402.
210. Baan R, Straif K, Grosse Y, et al. Carcinogenicity of alcoholic beverages. *Lancet Oncol.* 2007;8(4):292-3. doi:10.1016/s1470-2045(07)70099-2.
211. Rehm J, Shield K. Alcohol consumption. In: Stewart B, Wild C, eds. *World Cancer Report 2014*. International Agency for Research on Cancer, World Health Organization; 2014.
212. Boffetta P, Hashibe M. Alcohol and cancer. *Lancet Oncol.* 2006;7(2):149-56. doi:10.1016/s1470-2045(06)70577-0.
213. Turati F, Garavello W, Tramacere I, et al. A meta-analysis of alcohol drinking and oral and pharyngeal cancers: results from subgroup analyses. *Alcohol Alcohol.* 2013;48(1):107-18. doi:10.1093/alcalc/ags100.
214. Subbaraman MS, Kerr WC. Simultaneous versus concurrent use of alcohol and cannabis in the National Alcohol Survey. *Alcohol Clin Exp Res.* 2015;39(5):872-879. doi:10.1111/acer.12698.

215. Ma B, Stepanov I, Hecht SS. Recent studies on DNA adducts resulting from human exposure to tobacco smoke. *Toxics*. 2019;7(1). doi:10.3390/toxics7010016.
216. Ambatipudi S, Cuenin C, Hernandez-Vargas H, et al. Tobacco smoking-associated genome-wide DNA methylation changes in the EPIC study. *Epigenomics*. 2016;8(5):599-618. doi:10.2217/epi-2016-0001.
217. Guida F, Sandanger TM, Castagné R, et al. Dynamics of smoking-induced genome-wide methylation changes with time since smoking cessation. *Hum Mol Genet*. 2015;24(8):2349-59. doi:10.1093/hmg/ddu751.
218. Huang BZ, Binder AM, Quon B, et al. Epigenome-wide association study of total nicotine equivalents in multiethnic current smokers from three prospective cohorts. *Am J Hum Genet*. 2024;111(3):456-472. doi:10.1016/j.ajhg.2024.01.012.
219. Zhou W, Machiela MJ, Freedman ND, et al. Mosaic loss of chromosome Y is associated with common variation near TCL1A. *Nat Genet*. 2016;48(5):563-8. doi:10.1038/ng.3545.
220. Alexandrov LB, Ju YS, Haase K, et al. Mutational signatures associated with tobacco smoking in human cancer. *Science*. 2016;354(6312):618-22. doi:10.1126/science.aag0299.
221. Benowitz NL, Bernert JT, Foulds J, et al. Biochemical Verification of Tobacco Use and Abstinence: 2019 Update. *Nicotine Tob Res*. 2020;22(7):1086-1097. doi:10.1093/ntr/ntz132.
222. Gutiérrez-Torres DS, Wang L, Blount BC, et al. Concentrations of cotinine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in U.S. non-daily cigarette smokers. *Cancer Epidemiol Biomarkers Prev*. 2021;30(6):1165-1174. doi:10.1158/1055-9965.Epi-20-1601.
223. Bernert JT, Pirkle JL, Xia Y, Jain RB, Ashley DL, Sampson EJ. Urine concentrations of a tobacco-specific nitrosamine carcinogen in the U.S. population from secondhand smoke exposure. *Cancer Epidemiol Biomarkers Prev*. 2010;19(11):2969-77. doi:10.1158/1055-9965.Epi-10-0711.
224. Hatsukami DK, Hecht SS, Hennrikus DJ, Joseph AM, Pentel PR. Biomarkers of tobacco exposure or harm: application to clinical and epidemiological studies. 25-26 October 2001, Minneapolis, Minnesota. *Nicotine Tob Res*. 2003;5(3):387-96. doi:10.1080/1462220031000094222.
225. Mahabee-Gittens EM, Matt GE, Merianos AL. High levels of the carcinogenic tobacco-specific nitrosamine NNAL and associated findings in children of smokers: a case series. *Biomark Insights*. 2022;17:11772719221118868. doi:10.1177/11772719221118868.
226. Chang CM, Cheng YC, Cho TM, Mishina EV, Del Valle-Pinero AY, van Bommel DM, Hatsukami DK. Biomarkers of potential harm: summary of an FDA-sponsored public workshop. *Nicotine Tob Res*. 2019;21(1):3-13. doi:10.1093/ntr/ntx273.
227. Harris JC, Leggio L, Farokhnia M. Blood biomarkers of alcohol use: a scoping review. *Curr Addict Rep*. 2021;8(4):500-508. doi:10.1007/s40429-021-00402-7.
228. Egholm JWM, Pedersen B, Oppedal K, et al. Minor effect of patient education for alcohol cessation intervention on outcomes after acute fracture surgery: a randomized trial of 70 patients. *Acta Orthop*. 2022;93:424-431. doi:10.2340/17453674.2022.2482.
229. Domínguez-López I, Lamuela-Raventós RM, Razquin C, et al. Urinary tartaric acid as a biomarker of wine consumption and cardiovascular risk: the PREDIMED trial. *Eur Heart J*. 2025;46(2):161-172. doi:10.1093/eurheartj/ehae804.
230. Fakhari S, Waszkiewicz N. Old and new biomarkers of alcohol abuse: narrative review. *J Clin Med*. 2023;12(6). doi:10.3390/jcm12062124.
231. Luo A, Jung J, Longley M, et al. Epigenetic aging is accelerated in alcohol use disorder and regulated by genetic variation in APOL2. *Neuropsychopharmacology*. 2020;45(2):327-336. doi:10.1038/s41386-019-0500-y.
232. Loftfield E, Stepien M, Viallon V, et al. Novel biomarkers of habitual alcohol intake and associations with risk of pancreatic and liver cancers and liver disease mortality. *J Natl Cancer Inst*. 2021;113(11):1542-1550. doi:10.1093/jnci/djab078.
233. Trius-Soler M, Praticò G, Gürdeniz G, et al. Biomarkers of moderate alcohol intake and alcoholic beverages: a systematic literature review. *Genes Nutr*. 2023;18(1):7. doi:10.1186/s12263-023-00726-1.
234. Bouajila N, Domenighetti C, Aubin HJ, Naassila M. Alcohol consumption and its association with cancer, cardiovascular, liver and brain diseases: a systematic review of Mendelian randomization studies. *Front Epidemiol*. 2024;4:1385064. doi:10.3389/fepid.2024.1385064.
235. Chen C, Hu Q, Wang J, et al. Habitual consumption of alcohol with meals and lung cancer: a Mendelian randomization study. *Ann Transl Med*. 2021;9(3):263. doi:10.21037/atm-20-3063.
236. Im PK, Yang L, Kartsonaki C, et al. Alcohol metabolism genes and risks of site-specific cancers in Chinese adults: An 11-year prospective study. *Int J Cancer*. 2022;150(10):1627-1639. doi:10.1002/ijc.33917.

237. King C, Mulugeta A, Nabi F, Walton R, Zhou A, Hyppönen E. Mendelian randomization case-control PheWAS in UK Biobank shows evidence of causality for smoking intensity in 28 distinct clinical conditions. *EClinicalMedicine*. 2020;26:100488. doi:10.1016/j.eclinm.2020.100488.
238. Larsson SC, Carter P, Kar S, Vithayathil M, Mason AM, Michaëlsson K, et al. Smoking, alcohol consumption, and cancer: a mendelian randomisation study in UK Biobank and international genetic consortia participants. *PLoS Med*. 2020;17(7):e1003178. doi:10.1371/journal.pmed.1003178.
239. Liu Y, Liu C, Li X, He J, Zhou Q, Chen Y, Tang J. The association of tobacco use on gastrointestinal cancers: a secondary dataset analysis of the Global Burden of Disease Study 2021 and Mendelian randomization. *Tob Induc Dis*. 2026;24doi:10.18332/tid/215178.
240. Yang F, Chen X, Wei R, Lv P, Alhoot MA. Causal association of smoking and laryngeal cancer: a Mendelian randomization study. *Tob Induc Dis*. 2025;23doi:10.18332/tid/209744.
241. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32(1):1-22. doi:10.1093/ije/dyg070.
242. Burgess S, Small DS, Thompson SG. A review of instrumental variable estimators for Mendelian randomization. *Stat Methods Med Res*. 2017;26(5):2333-2355. doi:10.1177/0962280215597579.
243. Dimou N, Yarmolinsky J, Bouras E, et al. Causal effects of lifetime smoking on breast and colorectal cancer risk: mendelian randomization study. *Cancer Epidemiol Biomarkers Prev*. 2021;30(5):953-964. doi:10.1158/1055-9965.Epi-20-1218.
244. Park HA, Neumeyer S, Michailidou K, et al. Mendelian randomisation study of smoking exposure in relation to breast cancer risk. *Br J Cancer*. 2021;125(8):1135-1145. doi:10.1038/s41416-021-01432-8.
245. Chartier K, Caetano R. Ethnicity and health disparities in alcohol research. *Alcohol Res Health*. 2010;33(1-2):152-60.
246. Rosario M, Corliss HL, Everett BG, Reisner SL, Austin SB, Buchting FO, et al. Sexual orientation disparities in cancer-related risk behaviors of tobacco, alcohol, sexual behaviors, and diet and physical activity: pooled Youth Risk Behavior Surveys. *Am J Public Health*. 2014;104(2):245-54. doi:10.2105/ajph.2013.301506.
247. Voltzke KJ, Lee YA, Zhang ZF, et al. Racial differences in the relationship between tobacco, alcohol, and the risk of head and neck cancer: pooled analysis of U.S. studies in the INHANCE Consortium. *Cancer Causes Control*. 2018;29(7):619-630. doi:10.1007/s10552-018-1026-z.
248. Zavala VA, Bracci PM, Carethers JM, et al. Cancer health disparities in racial/ethnic minorities in the United States. *Br J Cancer*. 2021;124(2):315-332. doi:10.1038/s41416-020-01038-6.
249. Everhart J, Ferketich AK, Browning K, Wewers ME. Acculturation and misclassification of tobacco use status among Hispanic men and women in the United States. *Nicotine Tob Res*. 2009;11(3):240-7. doi:10.1093/ntr/ntn030.
250. Chen MS, Jr., Guthrie R, Moeschberger M, Wewers ME, Anderson J, Kuun P, Nguyen H. Lessons learned and baseline data from initiating smoking cessation research with Southeast Asian adults. *Asian Am Pac Isl J Health*. 1993;1(2):194-214.
251. Livingston MD, Xu X, Komro KA. Predictors of recall error in self-report of age at alcohol use onset. *J Stud Alcohol Drugs*. Sep 2016;77(5):811-8. doi:10.15288/jsad.2016.77.811.
252. Vickers-Smith R, Justice AC, Becker WC, et al. Racial and ethnic bias in the diagnosis of alcohol use disorder in veterans. *Am J Psychiatry*. 2023;180(6):426-436. doi:10.1176/appi.ajp.21111097.
253. Blas E, Sivasankara Kurup A, editors. *Equity, social determinants and public health programmes*. Geneva: World Health Organization; 2010.
254. Smith BT, Warren CM, Andreacchi AT, Schwartz N, Hobin E. The joint effect of education and alcohol use on 100% alcohol-attributable hospitalization or death in Canada. *Epidemiology*. 2024;35(1):64-73. doi:10.1097/ede.0000000000001674.
255. Probst C, Kilian C, Sanchez S, Lange S, Rehm J. The role of alcohol use and drinking patterns in socioeconomic inequalities in mortality: a systematic review. *Lancet Public Health*. 2020;5(6):e324-e332. doi:10.1016/S2468-2667(20)30052-9.
256. Boyd J, Sexton O, Angus C, Meier P, Purshouse RC, Holmes J. Causal mechanisms proposed for the alcohol harm paradox-a systematic review. *Addiction*. 2022;117(1):33-56. doi:10.1111/add.15567.
257. Teague S, Youssef GJ, Macdonald JA, et al. Retention strategies in longitudinal cohort studies: a systematic review and meta-analysis. *BMC Med Res Methodol*. 2018;18(1):151. doi:10.1186/s12874-018-0586-7.
258. Stussman B, Dahlhamer J, Simile C. How interviewer strategies relate to contact and cooperation in the National Health Interview Survey, 2004. [cited 2026 Mar 27]. Available from: https://nces.ed.gov/FCSM/pdf/2005FCSM_Stussman_Dahlhamer_Simile_VIB.pdf.
259. Lavrakas PJ. *Encyclopedia of survey research methods*. SAGE Publications; 2008.

260. Skinner HA, Sheu WJ. Reliability of alcohol use indices. The Lifetime Drinking History and the MAST. *J Stud Alcohol*. 1982;43(11):1157-70. doi:10.15288/jsa.1982.43.1157.
261. Koenig LB, Jacob T, Haber JR. Validity of the lifetime drinking history: a comparison of retrospective and prospective quantity-frequency measures. *J Stud Alcohol Drugs*. 2009;70(2):296-303. doi:10.15288/jsad.2009.70.296.
262. Greenfield TK, Nayak MB, Bond J, Kerr WC, Ye Y. Test-retest reliability and validity of life-course alcohol consumption measures: the 2005 National Alcohol Survey follow-up. *Alcohol Clin Exp Res*. 2014;38(9):2479-87. doi:10.1111/acer.12480.
263. Cook MB, Sanderson SC, Deanfield JE, Reddington F, Roddam A, Hunter DJ, Ali R. Our Future Health: a unique global resource for discovery and translational research. *Nat Med*. 2025;31(3):728-730. doi:10.1038/s41591-024-03438-0.
264. Srinivasan S, Moser RP, Willis G, Riley W, Alexander M, Berrigan D, Kobrin S. Small is essential: importance of subpopulation research in cancer control. *Am J Public Health*. 2015;105 Suppl 3(Suppl 3):S371-3. doi:10.2105/ajph.2014.302267.
265. Inoue-Choi M, Christensen CH, Rostron BL, Cosgrove CM, Reyes-Guzman C, Apelberg B, Freedman ND. Dose-response association of low-intensity and nondaily smoking with mortality in the United States. *JAMA Netw Open*. 2020;3(6):e206436. doi:10.1001/jamanetworkopen.2020.6436.

This page left blank intentionally.