A Blueprint for the Primary Prevention of Cancer: Targeting Established, Modifiable Risk Factors

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Abstract: In the United States, it is estimated that more than 1.7 million people will be diagnosed with cancer, and more than 600,000 will die of the disease in 2018. The financial costs associated with cancer risk factors and cancer care are enormous. To substantially reduce both the number of individuals diagnosed with and dying from cancer and the costs associated with cancer each year in the United States, government and industry and the public health, medical, and scientific communities must work together to develop, invest in, and implement comprehensive cancer control goals and strategies at the national level and expand ongoing initiatives at the state and local levels. This report is the second in a series of articles in this journal that, together, describe trends in cancer rates and the scientific evidence on cancer prevention, early detection, treatment, and survivorship to inform the identification of priorities for a comprehensive cancer control plan. Herein, we focus on existing evidence about established, modifiable risk factors for cancer, including prevalence estimates and the cancer burden due to each risk factor in the United States, and established primary prevention recommendations and interventions to reduce exposure to each risk factor.

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An ounce of prevention is worth a pound of cure.

Benjamin Franklin

Introduction
In the United States, it is estimated that more than 1.7 million people will be diagnosed with cancer and more than 600,000 will die of the disease in 2018.1 In 2010, the cost of cancer care in the United States was more than $124 billion, and this cost is expected to rise to at least $157 billion in 2020.2 To substantially reduce both the number of individuals diagnosed with and dying from cancer and the costs associated with cancer each year in the United States, government and industry as well as the public health, medical, and scientific communities must work together to develop, invest in, and implement comprehensive cancer control goals and strategies at the national level and expand ongoing state and local level initiatives. This report is the second in a series of articles in this journal that, together, describe trends in cancer incidence and mortality rates and the scientific evidence on cancer prevention, early detection, treatment, and survivorship to inform the identification of priorities for cancer control goals and strategies in the United States.

Herein, we focus on existing evidence about established, modifiable risk factors for cancer, including prevalence estimates and the cancer burden due to each risk factor in the United States, as well as established primary prevention interventions and/or recommendations to reduce exposure to each risk factor. Indeed, international variation in the cancer burden, changes in the risk observed in migrant studies, and the dramatic rise in cancer incidence and mortality rates from 1900 to 1991 in the
United States provide evidence that a substantial fraction of cancer is preventable. Furthermore, numerous modifiable risk factors for specific types of cancer have been identified, and exposure to many of these risk factors can be reduced by established cancer prevention interventions. To set priorities, the medical and public health communities need to know the fraction of cancer cases and deaths that might be reduced through prevention interventions. A population-attributable fraction (PAF) is the percentage of cases (or deaths) in the population attributable to a specific exposure or susceptibility factor and thus represents the fraction of disease in a population that could be prevented if the factor was reduced to the theoretical minimal risk (eg, elimination of cigarette smoking). Recently, Islami et al estimated that 42% of all cancers diagnosed and 45% of all cancer deaths in 2014 among individuals aged 30 years and older in the United States were attributable to major, potentially modifiable risk factors, including cigarette smoking, secondhand smoke, alcohol intake, excess body weight, consumption of red and processed meat, low consumption of fruits/vegetables, low dietary fiber, low dietary calcium, physical inactivity, ultraviolet (UV) radiation exposure, and 6 cancer-associated infections.

In May 2013, the World Health Organization (WHO) Global Action Plan for the Prevention and Control of Noncommunicable Diseases (NCDs) (2013-2020) was endorsed by the World Health Assembly. In May 2017, the Assembly endorsed an update, Best Buys and Other Recommended Interventions, which includes cost-effective recommendations and suggestions that focus on reducing tobacco use, the harmful use of alcohol, promoting healthy diets and physical activity, and (specifically for cancer) vaccination against oncogenic viruses, screening, and early detection. This WHO Global Action Plan and other prevention initiatives provide a foundation for developing a US national comprehensive cancer control plan that includes primary cancer prevention interventions that have proven to effectively reduce exposure or susceptibility to known cancer risk factors affecting the general population.

**Tobacco Products**

Tobacco use remains the leading cause of cancer, cardiovascular disease, and NCDs worldwide. Combustible tobacco products include cigarettes, cigars, pipes, and waterpipes. Historically, the most common types of noncombustible tobacco products included chewing tobacco and snuff. However, the landscape of tobacco products has changed markedly over the past decade with the introduction of noncombustible, electronic nicotine delivery systems (ENDS), such as electronic cigarettes (e-cigarettes). The annual direct health care costs of tobacco in the United States are estimated to be $170 billion, and tobacco use results in $156 billion in lost productivity.

**Active and Secondhand Smoke Exposure**

Since the 1930s, cigarettes have been the most common type of tobacco product used in the United States. Although smoking rates declined steadily since they peaked in the middle of the 20th century, there remain nearly 40 million adult smokers (Fig. 1). The demographic profile of today’s smoker also has changed. Until smoking was widely recognized as a health hazard, starting in the mid-1950s, smoking prevalence among groups defined by education and/or income was relatively similar. However, those

![FIGURE 1. Trends in the Prevalence of Current Cigarette Smoking Among Adults Aged 18 Years and Older in the United States From 1965 to 2016.](image-url)
with more education and higher income have been more responsive to educational messages about the health risks of smoking. Today, tobacco use is more prevalent among persons with lower educational attainment and/or lower income; within vulnerable populations, such as individuals with mental illness or addiction to other substances; within the Lesbian, Gay, Bisexual, Transgender (LGBT) community; and within certain racial or ethnic groups. In 2016, 23.1% of individuals who had a high school education or less smoked, compared with only 6.5% of those who had a college degree. Among individuals whose income was below the poverty line, smoking prevalence was 25%; however, among those well above (400%) the poverty line, smoking prevalence was 10%. Enhanced efforts to reach groups that are more likely to smoke are needed to further reduce the prevalence of tobacco use.

Tobacco and tobacco smoke contain more than 8000 chemical compounds, and, among these, the International Agency for Research on Cancer (IARC) has identified more than 70 as human and/or animal carcinogens. The cancers caused by smoking include lung, oral cavity, nasopharynx, oropharynx, hypopharynx, nasal cavity and accessory sinuses, larynx, esophagus, kidney, urinary bladder, ureter, liver, pancreas, stomach, ovary, cervix, colon, and rectum as well as myeloid leukemia. In the United States, tobacco smoking (active and secondhand smoke) caused an estimated 19.4% of all cancers diagnosed (n = 304,880) and 29.6% of all cancer deaths (n = 173,670) in 2014. Tobacco control can prevent more cancer deaths than any other primary (or secondary) prevention strategy. Smoking prevalence has declined in the United States from a high of 55% of adult men in 1955 to 17.5% in 2016 and from a high of 35% of adult women in 1965 to 13.5% in 2016. More than one-half of the 26% decline in cancer mortality rates that began in 1991 is because of this decline in smoking prevalence.

Much of the reduction in tobacco use is attributed to population-level strategies for both preventing initiation among nonusers and increasing cessation among users. Among the most effective of these strategies is increasing taxes on tobacco products, thus helping to increase prices, which is particularly effective for preventing initiation by young people, because it makes these products less affordable. A 10% increase in price typically leads to a 4% to 8% decrease in consumption, with greater declines among youth and/or those with lower incomes. In the United States, federal, state, and (in some cases) local governments can apply excise taxes on tobacco products. Although the federal government raised the cigarette tax from $0.39 to $1.01 per pack in 2009, tax rates vary considerably because of the wide variation in state and local tobacco taxes. State taxes are as low as $0.17 per pack in Missouri and as high as $4.35 in New York State. Some cities, including Chicago and New York City, apply additional municipal taxes and, consequently, have among the most expensive cigarettes in the United States. The WHO recommends that excise taxes comprise 70% of the price of a tobacco product, but this percentage is less than 50% in more than 40 US states. Over time, reaching the modest recommendation of the WHO would prevent millions of youth from starting smoking and prompt millions of smokers to quit in the United States.

There is overwhelming evidence that smoke-free public place and workplace policies protect people from harmful secondhand tobacco smoke. Such laws have resulted in a reduction in cardiovascular events and overall mortality rates, although there is mixed evidence that such policies promote cessation among existing smokers. With the emergence of definitive evidence in the 1970s and 1980s about the harm caused by secondhand tobacco smoke exposure, a movement for nonsmokers’ rights emerged, and policymakers in a growing number of localities and states began to establish public smoking restrictions. There has been less success in passing smoke-free legislation at the national level, with the only major victory occurring in 1987 when the US Congress passed the first smoke-free law for domestic commercial airline flights of 2 hours or less, later expanding the law to all domestic airline flights starting in 1990. Today, only 50% of the US population live in jurisdictions covered by policies that guarantee 100% smoke-free workplaces, restaurants, and bars. With little prospect of a comprehensive national smoke-free policy, smoke-free proponents will need to continue to work locally, particularly in jurisdictions that have lagged behind.

The tobacco industry effectively uses marketing to convince individuals—particularly youth—to try tobacco and to encourage current tobacco users to continue using. The US government banned tobacco advertising on television and radio in 1971 but has been very slow to expand on these efforts. The Master Settlement Agreement in 1998 banned outdoor advertising (eg, billboards) and advertising on public transportation in the 46 states that signed it. Despite these efforts, the marketing of tobacco products comprises the vast preponderance of tobacco manufacturers’ expenditures. While practices such as direct mail advertisements, point-of-sale displays, and some types of free distribution of tobacco products continue, the core marketing strategy of US tobacco companies is price discounting. This strategy not only helps tobacco companies attract new customers with very low prices but also mitigates the effects of excise taxation. The US Federal Trade Commission reports that, although cigarette sales declined from 2014 to 2015,
marketing expenditures increased from $8.03 billion to $8.24 billion, and approximately two-thirds of these expenditures were for price discounting. Advocacy for a comprehensive ban on price discounting must be a core strategy for future tobacco control.

Health warnings are particularly effective in increasing public awareness and communicating the harms of tobacco use as well as decreasing initiation among youth. US studies demonstrate that graphic warning labels on tobacco packaging would be an important measure to reduce tobacco use. However, the United States lags behind much of the world in implementing effective warning labels. Current regulations do not meet the basic WHO Framework Convention on Tobacco Control standard of warnings that cover at least 50% of the pack, let alone the new gold standard pioneered by Australia of plain, standardized packaging of tobacco products with numerous rotating, graphic warnings. Currently in the United States, as enacted in 1984, there are 4 rotating, text-only warnings that cover 30% of one side of the pack in a small and inconspicuous font. The warnings do not reference basic health issues related to tobacco use and smoking, such as nicotine addiction and the lethality of secondhand smoke to bystanders. The Family Smoking Prevention and Tobacco Control Act mandated that the US Food and Drug Administration (FDA) develop and require graphic warnings covering the top one-half of the front and back of cigarette packs and 20% of cigarette advertising by June 2011. After a First Amendment-based legal challenge to the FDA, the US Court of Appeals for the Sixth Circuit upheld the law’s requirement for graphic warnings, but the FDA has yet to issue new warning labels. In October 2016, the American Cancer Society (ACS) and the ACS Cancer Action Network joined partners in a lawsuit seeking a court order requiring the FDA to satisfy its statutory obligation. As of August 2018, the lawsuit is pending.

Quitting tobacco use benefits individuals of any age. Smoking on average causes the loss of more than a decade of life, but cessation before age 40 years typically can return 9 of those years. More than two-thirds of all smokers in the United States indicate an interest in quitting tobacco, and more than one-half (approximately 20 million) attempt to quit each year; however, only about 1.4 million (7%) succeed in quitting. Government policies and the public health/clinical communities’ promotion and facilitation efforts could markedly assist would-be quitters. The FDA has approved 5 nicotine-replacement therapies (NRTs) and 2 non-nicotine medications to aid in smoking cessation, and policies and efforts by health providers to maximize their use through counseling and support should be improved. First, the public health community and government must encourage cessation of all combustible tobacco products as a cornerstone of their tobacco control efforts. Second, smoking cessation should be a central part of routine primary care, because health care providers are not only on the frontline of care but are typically a trusted source of information and advice. In 2015, 57% of smokers who visited a health care setting in the previous year were advised to quit, and less than one-third of those smokers received one or more of the FDA-approved cessation aids. Moreover, during their last quit attempt, less than 5% reported using the current gold-standard treatment combination of counseling and an FDA-approved cessation aid. Third, FDA-approved cessation aids need to be more accessible, which can be facilitated by reducing their cost and improving insurance coverage (ie, adding subscribers and, for many plans, providing cessation coverage for longer periods of time). Moreover, additional cessation efforts need to focus on vulnerable/at-risk populations, such as individuals with behavioral health disorders (mental illness and/or substance use disorders), individuals who are homeless or living in public housing, and the LGBT population. The continuing high prevalence of cigarette smoking among vulnerable subpopulations is one of the most pressing challenges facing the tobacco control community. More financial and program support for promising, novel interventions and new attempts to reach these populations with established, effective interventions are crucial for reducing tobacco use disparities.

Smokeless Tobacco

There are various smokeless tobacco products, most of which are used by placing the product between the cheek or lip and the gum. Those most commonly used in the United States include moist snuff and chewing tobacco. Nationwide, about 3% of adults use smokeless tobacco, whereas 6% (an estimated 900,000) of high school students and 1.8% (an estimated 210,000) of middle school students were current users of smokeless tobacco in 2015. There is wide variation in use by race and ethnicity: for example, 16% of American Indian and Alaskan Native adults use smokeless tobacco. Although most experts agree that smokeless tobacco use causes significantly less harm and fewer deaths compared with smoking, it still poses risk, causing cancers of the oral cavity, esophagus, and pancreas. Indeed, more than 30 carcinogens have been identified in smokeless tobacco products available in the United States. Conventional wisdom in the United States generally has discouraged smokeless tobacco as a smoking cessation tool because it is more harmful than NRTs. Further study is needed on who is using these products, how they use them, under what circumstances, and what factors encourage use.
conditions, and whether there is evidence of a gateway effect to combustible tobacco.

As with cigarettes, the US FDA regulates the manufacture, import, packaging, labeling, advertising, promotion, sale, and distribution of smokeless tobacco products. As part of its regulatory mandate, in 2010, the FDA required that smokeless tobacco packaging and advertisements prominently display warnings including that, “This product can cause mouth cancer.” In 2017, the FDA also issued a proposed rule to limit N-nitrosonornicotine (NNN), a known carcinogen, in smokeless tobacco products—the first time FDA had used its authority to require a standard for tobacco products. The agency projected that, over a 20-year period, the proposed rule would prevent nearly 13,000 new oral cancer diagnoses and 2220 oral cancer deaths.44 Overall, the public health community should examine more actively the potential for regulating tobacco product standards as a tool to mitigate harm.

Emerging Tobacco-Control Issues

Hookah (or “waterpipe”) smoking among youth in the United States increased significantly over the past decade. Hookah smoking involves the combustion of tobacco—usually mixed with a molasses-like sweetener and/or other flavor additives—and inhaling the smoke after it passes through water. From the combusted tobacco, a hookah delivers nicotine and other chemicals similar to those in cigarette smoke, and the amount of smoke inhaled during a typical hookah session (75 liters) is many times greater than the amount of smoke inhaled from a single cigarette (600 mL), resulting in inhalation of far greater amounts of tar and carbon monoxide than smoking a cigarette.45

The US Centers for Disease Control and Prevention’s (CDC’s) National Youth Tobacco Survey indicated that, from 2013 to 2014, current hookah use among high school students rose from 5.2% to 9.4% and, among middle school students, it rose from 1.1% to 2.5%.40 The 2014 Monitoring the Future Survey found that 23% of US 12th grade students had used a hookah at least once in the past year, and the prevalence was higher among boys (25%) than among girls (21%).46

A key public health challenge is that many young hookah smokers are poorly informed about the nature of the product and incorrectly believe that hookah smoking is less harmful than cigarette smoking.47 Therefore, the public health community needs to educate clinicians, regulators, and the broader public—especially young people—about the risks of hookah smoking and exposure to secondhand hookah smoke. Because the harm from hookah smoking can be similar to that of cigarette smoking, the WHO recommends that hookah smoking fall under the same regulations.48 Currently, most jurisdictions in the United States overlook hookah in their tobacco control efforts, which must change to be in concert with the sensible recommendations of the WHO.

Like the hookah, the use of ENDS, commonly referred to as “vaping,” has become increasingly popular, particularly among youth. ENDS is a heterogeneous group of products that heat a liquid, typically largely propylene glycol and/or vegetable glycerin often mixed with nicotine, flavor additive, and other constituents, producing an inhalable aerosol. A commonly used ENDS product is the e-cigarette. A 2014 Population Assessment of Tobacco and Health study indicated that 5.5% of adults reported being current e-cigarette users, among whom 42.2% reported infrequent use, 36.5% reported moderate use, and 21.3% reported daily use.49 According to the National Youth Tobacco Survey, the use of e-cigarettes increased among middle school and high school students from 2011 to 2015.40 In 2015, 5.3% of middle school and 16% of high school students reported e-cigarette use in the past 30 days; whereas, in 2016, a Population Assessment of Tobacco and Health study indicated that ENDS use dropped to 11.3% among high school students.50

There is a wide range of views about the health effects of ENDS use, both in the general population and among those in the public health and medical communities. Some view ENDS primarily as another harmful tobacco product, and they do not focus on distinctions between the use of ENDS and the use of cigarettes and/or they have grave concerns that ENDS are making tobacco more socially acceptable again. In contrast, others view ENDS as a potential quitting tool and an opportunity to reduce harm to individuals who are unwilling or unable to quit using products with nicotine. To evaluate the net public health benefit of ENDS, it is necessary to consider at least the following: 1) the harm from using ENDS, 2) the influence of ENDS on adult cigarette cessation, and 3) youth initiation of ENDS, leading either to long-term ENDS use or to eventual combustible tobacco use. Major recent reviews concluded that the exclusive use of current-generation ENDS is likely to be significantly less harmful than using combustible tobacco products (with or without concurrent use of ENDS),51,52 but there are not yet sufficient data to evaluate the long-term health effects of using ENDS. Although carcinogens, including tobacco-specific nitrates, are found in ENDS aerosol, the levels are significantly lower than those in tobacco smoke,53 and there are considerably fewer toxicants in ENDS aerosol compared with tobacco smoke.54 However, because of the wide heterogeneity in ENDS products in the marketplace, and because there are many new products entering the marketplace with few
restrictions, it is difficult to claim that the existing research addresses all ENDS products.

There is limited evidence that e-cigarettes help some individuals to quit. In a recent comprehensive review of ENDS and quitting, Malas et al state that the limited evidence currently available appears to indicate that e-cigarettes might be potentially useful in helping to quit cigarette smoking. A 2016 Cochrane review concluded that, based on evidence from 2 trials, e-cigarettes help individuals stop smoking over the long term compared with placebo e-cigarettes; however, those authors graded the evidence as low because of the limited number of trials, the low event rates, and the wide confidence intervals around the estimates.

It is reasonable to assume that, when ENDS use results in quitting all tobacco products or switching completely from combustible tobacco products to ENDS, then ENDS use reduces the risk of tobacco-attributable morbidity and death. However, it is also possible that ENDS use may cost some lives, because ENDS use among users of combustible tobacco products (ie, “dual use”) might interfere with attempts to quit combustible tobacco products. While there is some expectation of a short to medium duration of dual use during the transition from one product to the other, or on the way to quitting altogether, long-term dual use does not appear to be a favorable outcome. A recent study using medium-term biomarkers demonstrated significant reductions in exposure to tobacco-related toxicants among complete switchers from cigarettes to either ENDS or NRT, but not among dual users. Recent surveillance data demonstrate a potentially troubling pattern wherein the majority of adult ENDS users are using both ENDS and combustibles, although the precise patterns of use are unclear (eg, whether it is an actual transition or long-term dual use).

A gateway effect of ENDS users initiating combustible tobacco use as a direct consequence of using ENDS remains a significant concern, particularly regarding youth. There is evidence in youth that the initiation of e-cigarette use is associated with an increased likelihood of subsequently initiating conventional cigarette use. However, it is unclear whether this association is causal, and it is difficult to disentangle the factors that cause a young person to try different tobacco products, because many eventual combustible users who initiated ENDS use might have ended up as combustible tobacco users even in the absence of ENDS. A randomized controlled trial (RCT) would provide the most definitive answer about whether this association is causal. However, it is unethical to assign a nonuser to tobacco use. Our understanding of this association may be improved by future observational studies that measure ENDS use in detail, including the type of device and e-liquid, and that comprehensively identify and control for factors that predispose individuals to use combustible products.

To harness the potential of using ENDS to help smokers who cannot or will not quit nicotine, significant and effective public education efforts and, more importantly, guidance to clinicians are critically necessary to avoid unintended consequences. The first emphatic message from the public health community should be that no one—especially young people—should initiate any type of tobacco use, combustible or otherwise. The second message should be that current combustible users should quit, preferably using a combination of FDA-approved cessation aids (eg, NRTs) and counseling. Would-be quitters need to understand that the process can be lengthy, with multiple quit attempts, and should receive sustained support. If quitting smoking is not possible, then the follow-up message to these users should be to stop using combustible tobacco products altogether, although preferably still with a clear goal of eventually using no tobacco at all. More research is needed into the risks posed by ENDS, their potential utility in helping smokers quit, and the potential use of ENDS as a harm-reduction tool.

To further complicate the tobacco products landscape, there is a new class of products, called “heat-not-burn” (HNB), in which processed tobacco is heated in a device, but to a lower temperature than in cigarettes (although higher than that in ENDS), generating an inhalable aerosol. Preliminary evidence suggests that HNB products are less harmful than cigarettes but more harmful than e-cigarettes. HNB products generate some of the same carcinogens found in cigarette smoke. The tobacco industry is now aggressively marketing HNB products in more than 25 countries. Although it is not yet available in the United States, in 2017, one tobacco manufacturer applied to the FDA for an HNB product to be approved as a Modified-Risk Tobacco Product—the official indication that the product is less harmful. As of May 2018, the application is still under review; however, in January 2018, the FDA’s Tobacco Products Scientific Advisory Committee counseled that the applicant had not proven that HNB use reduces harm compared with cigarette smoking. With so much concern and uncertainty surrounding ENDS products, which are less harmful, it is difficult to conceptualize a role for HNB in cessation or harm reduction at this time.

In July 2017, the FDA announced that it would develop a new comprehensive plan for tobacco and nicotine regulation in the United States that focuses on the central role played by nicotine in all tobacco products and the growing potential for shifting smokers either entirely off tobacco products or, when necessary, to those tobacco products that pose the lowest risk. The most ambitious strategy announced by
the FDA is its pursuit of a product standard requiring the reduction of nicotine content of combustible tobacco products to minimal or nonaddictive levels. Rendering cigarettes and other combustible tobacco products nonaddictive holds the promise of weaning the majority of smokers off of the most lethal form of tobacco use, which could lead to unprecedented public health gains.

As the FDA develops its tobacco/nicotine control strategies, the public health community must continue to promote the main interventions elucidated above. The intervention with the greatest potential to save lives is to increase tobacco taxes, which remain low throughout most of the United States, and the full public health potential of this intervention has yet to be fully realized.

Alcohol Consumption
Alcoholic beverages have been consumed by humans for thousands of years for religious, social, and cultural reasons.62 Globally, spirits, wine, and beer are the most commonly consumed types of alcoholic beverages, respectively, although, in some parts of the world, locally or home-produced beverages contribute significantly to daily consumption.63 In the United States, a standard alcoholic beverage contains 14 grams of ethanol, the primary form of alcohol in alcoholic beverages, which are contained in approximately 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of distilled spirits. Harmful alcohol drinking has numerous adverse health effects, including, for example, intentional and unintentional injuries, violence, acute alcohol poisoning, cirrhosis, social disruption, fetal alcohol syndrome, and (as discussed below) at least 7 types of cancer. Furthermore, alcohol drinking is a leading preventable cause of death in the United States.64

In the United States, 50.7% of the population aged 12 years or older reported current (ie, in the past 30 days) alcohol consumption in 2016.65 Although there was little overall change in the prevalence of current consumption from 2002 to 2016, among adolescents aged 12 to 17 years, the prevalence decreased markedly from 17.6% in 2002 to 9.2% in 2016, with only a modest decrease over time among young adults aged 18 to 25 years (ie, from 60.5% in 2000 to 57.1% in 2016). Overall, about 24.2% of the population were binge drinkers (ie, drank at least 5 or more alcoholic beverages on the same occasion on at least a single day in the past 30 days), and approximately 6% were heavy alcohol drinkers (ie, drank 5 or more alcoholic beverages on the same occasion on 5 or more days in the past 30 days).65 There are complex disparities in the prevalence of alcohol consumption. For example, for both men and for women, the prevalence of alcohol abstinence is higher among Hispanics, blacks, Asians, and Native Americans than among non-Hispanic whites; however, among current drinkers, the prevalence of heavy weekly drinking is highest among Native Americans, and the prevalence of heavy daily drinking is highest among Hispanic men.66 In addition, the economic burden of alcohol drinking misuse in the United States was approximately $249 billion dollars in 2010.67

The consumption of alcoholic beverages was first classified as carcinogenic to humans in 1987 by an expert working group convened by the IARC.68 This working group found the evidence for causality to be sufficient for cancers of the upper aerodigestive tract (UADT) (ie, oral cavity, pharynx, larynx, esophagus) and the liver. However, no conclusions were made about the carcinogenicity of ethanol or other constituents of alcoholic beverages. In 2007, a second IARC expert working group reaffirmed that alcohol consumption causes UADT and liver cancer, and they expanded the list of cancers for which there was sufficient evidence of causality to include colorectal and female breast cancers; that group also found for the first time that “ethanol in alcoholic beverages” is carcinogenic to humans.69 A 2009 IARC working group confirmed the previous conclusions and added that both ethanol and acetaldehyde—the primary metabolite of ethanol ingestion—associated with the consumption of alcoholic beverages are a cause of cancers of the UADT.15 More recently, a 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Continuous Update Project (CUP) report noted evidence that consumption of 3 or more drinks per day probably increases the risk of stomach cancer.70 Although there is variability by cancer type, broadly, the carcinogenic effects of ethanol found in alcoholic beverages and acetaldehyde involve DNA and protein damage and aduct formation, oxidative stress, inhibition of DNA repair, cell death and hyper-regeneration, nutritional malabsorption, changes in DNA methylation, metabolic effects, and (for breast cancer) increased estrogen levels.71,72 In addition, carcinogenic contaminants can be introduced during alcoholic beverage production.

Alcoholic beverage consumption is a major contributor to cancer among women (6.4%) and men (4.8%).4 In 2014, among men and women combined, an estimated 40.9% of oral cavity/pharynx cancers, 23.2% of larynx cancers, 21.6% of liver cancers, 21% of esophageal cancers, and 12.8% of colorectal cancers were attributed to alcohol consumption. Notably, among women, alcohol intake is one of the major modifiable risk factors for breast cancer, accounting for 16.4% (ie, 39,060) of all cases.4 Although there has been sufficient evidence that alcohol consumption causes multiple types of cancer for at least 3 decades, that a substantial number of cancer cases are attributed to its consumption in the United States, and that reducing harmful
alcoholic beverage consumption is one of the WHO “best buys” for reducing NCDs, and public awareness is low about the carcinogenicity of alcohol and its primary metabolite, acetaldehyde. Furthermore, fewer than one-half of the US CDC-funded comprehensive cancer control plans specify goals, objectives, or strategies for alcohol control. To address gaps in alcohol control in the United States, several national health organizations, such as the American Society for Clinical Oncology, and the American Medical Association, have published statements indicating their support for recommendations to reduce the harmful use of alcoholic beverages.

The US Community Preventive Services Task Force’s (CPSTF) Guide to Community Preventive Services, and the WHO “best buys” recommend several evidence-based strategies to reduce the harmful use of alcohol. Similar to those to reduce the use of tobacco products, these strategies include increasing the unit price of alcohol by increasing excise taxes, including those at the federal, state, or local levels. Indeed, there is substantial evidence that increasing the price of alcohol through excise taxes reduces both consumption and adverse health outcomes caused by alcohol, including motor vehicle crashes, violence, and cirrhosis, which is an important cause of liver cancer.

Other strategies to reduce the harmful use of alcohol include: regulating the density of alcohol retail outlets through licensing or zoning processes; enforcing dram shop, or commercial host, liability laws that hold alcohol retail establishments liable for injuries or harms caused by illegal service to intoxicated or underage customers; maintaining limits on the days that alcohol can legally be sold in retail outlets; maintaining limits on the hours that alcohol can legally be sold where it is consumed on premise; enhancing the enforcement of laws prohibiting sales to minors, including increasing compliance checks at alcohol retailers (such as bars, restaurants, and liquor stores); enacting and enforcing bans or comprehensive restrictions on exposure to alcohol advertising (across multiple types of media); enacting and enforcing drinking-driving laws and blood alcohol concentration limits via checkpoints; restricting or banning promotions of alcoholic beverages in connection with sponsorships and activities that target youth; and providing consumer information about, and labeling, alcoholic beverages to indicate alcohol-related harm.

The US CPSTF recommends against the privatization of retail alcohol sales. The American Society for Clinical Oncology also noted their support for the elimination of marketing alcoholic beverages in the form of “pinkwashing,” a term that refers to the action of supporting or exploiting the breast cancer cause, including the promotion of products with known or suspected links to cancer, for profit or public relations purposes.

For individuals, the ACS recommends that those who do drink alcohol limit consumption to no more than a single drink per day for women and 2 drinks per day for men. However, because of the evidence that alcohol consumption, even at low amounts, increases risk of some types of cancer, including breast cancer, to prevent cancer, the AICR recommends not drinking alcohol. To help individuals reduce consumption, the US Preventive Services Task Force recommends alcohol screening and behavioral counseling interventions in primary care settings to identify those (including pregnant women) whose alcohol consumption does not meet the criteria for alcohol dependence but places them at higher risk of alcohol-related harms.

### Body Fatness, Dietary Factors, and Physical Activity

#### Excess Body Fatness

Excess body fatness is largely a result of energy imbalance because of excess energy intake (from both food and drink) and, to a lesser extent, low energy expenditure, although inherited genetic factors and changes in metabolism with age also play roles. The dietary factors most consistently associated with a high risk of excess body fatness include sugar-sweetened beverages, “fast-foods,” and a “Western-type” diet (ie, high in free sugars, meat, and fat); whereas foods containing dietary fiber and a “Mediterranean type” diet reduce risk. In addition, aerobic physical activity, including walking, is associated with a lower risk of excess body fatness, whereas sedentary behaviors and greater screen time are associated with a higher risk.

The most accurate measures of excess body fatness include computed tomography (CT), magnetic resonance imaging, and dual-energy x-ray absorptiometry; however, their application in large population studies and in many clinical settings is limited by high costs and logistical challenges. Body mass index (BMI) is a standard measurement of weight relative to height (kg/m²) that correlates relatively well with dual-energy x-ray absorptiometry measures of body fatness among adults, with some attenuation of the correlation in older age groups. On the basis of the WHO classification for adults, overweight is defined as a BMI from 25.0 to 29.9 kg/m², and obesity is defined as a BMI of 30 kg/m² or greater. Obesity can be divided further into...
class 1 (BMI, 30.0-34.9 kg/m²), class 2 (BMI, 35.0-39.9 kg/m²), and class 3 (BMI, ≥ 40.0 kg/m²). The obesity epidemic is now well recognized, and recent estimates from 2015 and 2016 indicate that 39.6% of American adults were obese, and the prevalence was higher among women (41.1%) than among men (37.9%). The prevalence of obesity varies nearly 4-fold among racial/ethnic groups; it is lowest among non-Hispanic Asian adults (12.7%), followed by non-Hispanic white (37.9%), Hispanic (46.8%), and non-Hispanic black (47.0%) adults. Moreover, in 2015 and 2016, 20.6% of adolescents aged 12 to 19 years, 18.4% of children aged 6 to 11 years, and 13.9% of children aged 2 to 5 years were obese. The medical care costs of obesity in 2008 were estimated to be $147 billion, and, if the obesity epidemic in the United States is not curbed, these costs will increase.

In the mid-20th century, epidemiologic studies began to document associations of excess body fatness (assessed as BMI or other measures) with a higher risk of being diagnosed with or dying from specific types of cancer. In 2000, the IARC convened an expert working group to review the scientific evidence on excess body fatness and cancer risk. The group reported that the evidence for causality in humans was sufficient for cancers of the female breast (postmenopausal), endometrium, kidney (renal cell), esophagus (adenocarcinoma), colon, and rectum. A second expert working group convened by the IARC in 2016 expanded the list of cancers caused by excess body fatness to also include cancers of the gastric cardia, liver, gallbladder, pancreas, ovary, and thyroid as well as multiple myeloma and meningioma. In addition, the WCRF/AICR CUP on prostate cancer has reported probable evidence that excess body fatness increases the risk of advanced, high-grade, or fatal prostate cancer. Notably, the WCRF/AICR CUP reports convincing evidence that weight gain increases the risk of postmenopausal breast cancer. Despite some findings that weight loss might be associated with a lower risk of cancer, the second IARC expert working group found that the evidence on weight loss and cancer risk, from both observational and bariatric surgery studies, was insufficient to evaluate. Excess adiposity can contribute to a procarcinogenic environment through several carcinogenic pathways involved in metastases, inflammation, oxidative stress, cell proliferations and angiogenesis, and inhibition of apoptosis/cell death. Research also demonstrates that the gut microbiome might play an important role in many obesity-related carcinogenic pathways.

In the United States, approximately, 7.8% of incident cancer cases in 2014 were attributed to excess body fatness, second only to cigarette smoking. The PAF was higher among women (10.9% of cases) than among men (4.8% of cases). Among women, 60.3% of corpus uteri cancer and, among men and women combined, greater than 30% of gallbladder, liver, and kidney/renal cancers as well as esophageal adenocarcinoma were attributed to excess body fatness. Despite clear evidence that excess body fatness contributes substantially to cancer risk, the full impact of the obesity epidemic on the cancer burden, including the long-term effect of obesity that begins in childhood, is yet to be completely understood.

Dietary Factors
The role of diet in relation to chronic disease risk has been of considerable interest for thousands of years. Most evidence comes from observational studies conducted since the latter one-half of the 20th century. Measuring usual diet in large study populations is challenging, and most studies rely on food frequency questionnaires to assess dietary intake of numerous foods, beverages, and other key nutritional factors.

The human diet is complex and comprises a variety of constituents that are often highly correlated and thus difficult to tease apart. Moreover, the food supply is constantly changing. Finally, early life dietary exposures are likely to be relevant to later development of cancer, but evidence remains limited. As a result, current cancer prevention guidelines emphasize diet during adulthood. Despite these complexities of assessing diet and cancer risk, consistent findings from numerous studies have informed dietary guidelines for cancer prevention published by major cancer organizations such as the ACS and the WCRF/AICR. Generally, these guidelines recommend consuming at least 5 servings of fruit and vegetables per day, choosing whole grains over refined grains, and limiting red and processed meat intake. However, the typical US diet falls far short of dietary recommendations for cancer prevention. For example, only 16% of adults consumed 3 or more servings of fruit and vegetables per day in 2015. Although whole grain consumption in adults improved from 0.72 ounce-equivalents per day in 2001 and 2002 to 0.99 ounce-equivalents per day for adults in 2011, the proportion of grains that are whole grain is less than 10% for all Americans. Total meat intake in the United States doubled from 1907 to 2007. Despite an increase in poultry intake since the 1950s, in 2003 and 2004, red meat still comprised 58% of all meat consumed in the United States, and 28% of red meat was processed. Estimated unprocessed red meat and processed meat intake did not change from 1999 and 2000 to 2011 and 2012.

Evidence on associations of dietary factors with cancer risk has evolved over time as results from newer, high-quality studies have been published. Despite the initial promise, derived largely from case-control studies in the 1980s and 1990s, that high fruit and vegetable...
consumption may be associated with a lower risk of cancer, prospective studies generally found weaker associations. In the latest review of the evidence, the WCRF/AICR CUP concluded that greater fruit and nonstarchy vegetable consumption probably lowers the risk of some types of UADT cancers. In addition, the WCRF/AICR CUP showed that foods high in dietary fiber and whole grains, probably decrease the risk of colorectal cancer.

Fruits and vegetables contain numerous constituents that influence carcinogenesis, including vitamins, phytochemicals, and dietary fiber. Numerous RCTs of the effects of specific nutrients and phytochemicals (ie, vitamin E, selenium, β-carotene and vitamin C) on cancer outcomes suggest that high doses of these agents are unlikely to lower cancer risk and may even cause harm. It is possible that high-dose, isolated forms of individual plant constituents used in RCTs may have unexpected physiological effects compared with those found in food. Similarly, dietary fiber supplements have not reduced the risk of colorectal polyp recurrence. A possible exception is for supplemental calcium. The WCRF/AICR have judged the that there is probable evidence that supplemental calcium lowers colorectal cancer risk, although the results from RCTs on the effects of calcium supplementation in relation to colorectal polyp recurrence are mixed.

In 2015, the IARC classified processed meat (eg, hot dogs, bacon, sausage, deli meats, etc) as a carcinogen based on sufficient evidence in humans for colorectal cancer and classified unprocessed red meat (eg, beef, pork, lamb) as a probable carcinogen based on limited evidence in humans in relation to colorectal cancer and on strong mechanistic evidence. The WCRF/AICR CUP indicates that the association between processed meats and colorectal cancer is convincing and that the association between red meat and colorectal cancer is probable. For each 100 grams of red meat or 50 grams of processed meat consumed per day, the risk of colorectal cancer increases by 17% and 18%, respectively. Potential biologic mechanisms underlying the associations of red and processed meats with colorectal cancer risk include oxidative DNA damage from the formation of nitrosamines in the gut catalyzed by heme iron and the formation of heterocyclic aromatic amines (HCA or HAA) and polycyclic aromatic hydrocarbons (PAHs) during high-heat cooking of meat.

Recognizing the complexity of diet and potential for the additive and interactive effects of dietary constituents on health, research on overall diet patterns has become increasingly common. Consumption of a mostly plant-based dietary pattern rich in vegetables, fruit, and whole grains and limited in processed and red meat, such as that recommended by the ACS and the WCRF/AICR, as well as other largely plant-based, healthy diet patterns, have been associated with lower cancer incidence and mortality.

Recently, Islami et al estimated that, for all incident cancer cases, the PAF for the combination of low calcium, fiber, and fruit and vegetable intake and high red and processed meat intake was 4.2% among men and women combined. However, there was considerable variation across specific dietary factors and types of cancer. For incident colorectal cancer, the PAF was 5.4% for high red meat consumption, 8.2% for high processed meat, and 10.3% and 4.9% for low dietary fiber and calcium consumption, respectively. Low fruit and vegetable consumption was attributed to 17.6% and 17.4% of oral cavity/pharynx and larynx cancers, respectively. Because the role of early life dietary exposures is still largely unknown, and many dietary hypotheses are unresolved and/or difficult to test, the percentage of cancers attributable to diet may continue to rise beyond such estimates as these issues are resolved.

Physical Activity

Physical activity is defined as any movement of the body produced by skeletal muscles that results in the expenditure of energy. Various domains have been used to define physical activity, including household, occupational, and leisure time. Physical activity can be further characterized by intensity, frequency, and duration. Numerous methods of estimating physical activity, including calorimetry, physiologic measures, and mechanical and electronic monitors, can be useful in clinical or small studies. In large epidemiologic studies, job classifications and surveys are most often used to assess physical activity; the reliability and validity of these surveys varies by intensity of activity, with vigorous activities most reliably reported. While various methods have been used to quantify physical activity across different domains, the majority of epidemiologic evidence is based on self-reported leisure-time physical activity.

In the United States, physical activity guidelines, including those specifically for cancer prevention, recommend that adults should engage in at least 150 minutes per week of moderate-intensity aerobic physical activity (eg, brisk walking), or 75 minutes per week of vigorous-intensity activity (eg, jogging), or an equivalent combination. In 2016, approximately 51.7% of all US adults met this recommendation for aerobic activity, although men (56.1%) were more likely than women (49.1%) to meet the recommendation, as were non-Hispanic whites (56.2%) compared with non-Hispanic blacks (44.4%) and Hispanics (44.3%). In 2002, the IARC reported sufficient evidence in humans that physical activity decreases the risk of colon and

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breast cancer. Since then, the WCRF/AICR CUP has expanded on this conclusion, noting convincing evidence that all types and intensities of physical activity decrease the risk of colon cancer and probably decrease the risk of endometrial and postmenopausal breast cancers. More recently, the 2018 WCRF/AICR CUP added that only vigorous activity probably decreases the risk of premenopausal breast cancer. In 2018, the US Physical Activity Guidelines Advisory Committee released a scientific summary report citing strong evidence for associations between physical activity and lower risk of colon and breast cancer, but they also found moderate evidence that physical activity is associated with reduced risks of other cancers, including kidney, endometrial, bladder, and stomach (cardia) cancers as well as esophageal adenocarcinoma. Physical activity may reduce cancer risk through its role in weight control and by modulating insulin resistance, inflammation, immune function, and circulating sex steroid hormones.

Islami et al estimated that 2.9% of all incident cancer cases in the United States in 2014 were attributable to low physical activity. However, the PAF because of low physical activity was greater among women (4.4%) than among men (1.5%). The PAFs also varied considerably by cancer type; for incident cancer cases, the highest PAF was for corpus uteri cancer (26.7%), followed by 6.3% for colorectal cancer (among men and women combined), and the lowest PAF was for female breast cancer (3.9%). As additional cancer types are determined to be causally associated with low amounts of physical activity, the total number of cancer cases attributed to low physical activity will continue to rise.

Primary Prevention Interventions to Improve Healthy Eating and Active Living

In the United States, an estimated 13.9% of cancers among men and 22.4% among women in 2014 were attributable to the combination of excess body weight, poor diet, physical inactivity, and alcohol consumption. Reversing the obesity epidemic and increasing the prevalence of healthy eating and active living hold considerable potential for reducing cancer incidence and mortality rates. Achieving this potential will require a comprehensive approach, including evidence-based, primary prevention interventions that target communities and individuals and are implemented using strategies similar to those outlined in the social-ecologic model for food intake and activity decisions, as illustrated in the by the US Department of Agriculture Dietary Guidelines for Americans 2015–2018 (Fig. 2) and in a new policy framework described by the WCRF International (Fig. 3). Both of these models recognize that change must occur across multiple sectors (e.g., government, public health, clinical, industry) and in different settings (e.g., home, school, work).

Numerous organizations have developed guidelines for individuals, health care professionals, and policy makers about healthy eating and active living behavior choices for cancer prevention. For example, for over 2 decades, the ACS has published cancer prevention guidelines (with periodic updates) on nutrition, physical activity, and weight control. The most recent ACS Guidelines on Nutrition and Physical Activity for Cancer Prevention, published in 2012, included recommendations for both individuals and communities. Broadly, the recommendations for individual choices include: 1) achieve and maintain a healthy weight throughout life; 2) adopt a physically active lifestyle; 3) consume a healthy diet, with an emphasis on plant foods; and 4) if you drink alcohol, limit consumption. The potential benefits of health behaviors consistent with the ACS guidelines were demonstrated in several large, prospective epidemiologic studies published over the past decade. Scores reflecting overall adherence to the 4 recommendations were associated with a lower risk of total cancer incidence, cancer mortality, and, recently, survival from colorectal cancer. For specific types of cancer, one study found that greater adherence was associated with statistically significantly lower risks of oral, esophageal, stomach, small intestine, colon, rectum, liver, gallbladder, pancreas, bladder, kidney, and lung cancers as well as leukemia and Hodgkin lymphoma; and, among women, adherence also was associated with a significantly lower risk of breast and endometrial cancer. Similar associations also were reported for racially/ethnically diverse and low-income study populations.

The 2012 ACS Guidelines on Nutrition and Physical Activity for Cancer Prevention also recognize that individual choices occur within the context of the larger environment and that community-level efforts are necessary to facilitate the adoption and maintenance of healthy lifestyles. Thus, the ACS guidelines call for public, private, and community organizations to work collaboratively at the national, state, and local levels to implement policy and environmental changes to: 1) increase access to affordable, healthy foods in communities, worksites, and schools and decrease access to and marketing of foods and beverages of low nutritional value, particularly to youth; and 2) provide safe, enjoyable, and accessible environments for physical activity in schools and worksites and for transportation and recreation in communities.

Community-level and individual-level strategies for promoting the consumption of healthful foods, physical activity, and achieving a healthy weight have been described in the WHO “best buys” for reducing NCDs and in the
CDC 2009 Recommendations for Community Strategies and Measurement to Prevent Obesity in the United States. Most recently, a new WCRF framework (Fig. 3) was developed that addresses policies important for diet, physical activity, and breast feeding (recognizing that these influence body fatness) as well as alcohol consumption that are important for supporting adherence to cancer prevention recommendations.

In general, the strategies described by all of these organizations for healthy eating, active living, and weight control focus on: promoting and improving the availability of affordable healthy foods and beverages, particularly in public service venues and in underserved areas; supporting healthy food and beverage choices; encouraging physical activity and limiting sedentary activity among children and youth; creating safe communities that support physical activity; and encouraging communities to form partnerships to address obesity. The enhancement and/or implementation of nutrition and physical activity education and counseling in different settings (eg, schools and workplaces) and as part of primary health care services also are recommended.

Sugar-sweetened beverage consumption consistently has been associated with weight gain, overweight, and obesity. Thus, in recognition of the growing obesity epidemic among adults and youth in the United States, and consistent with the effectiveness of raising tobacco taxes on reducing the use of tobacco products, an important policy intervention to reduce the consumption of sugar-sweetened beverages is the implementation of excise taxes on these products (commonly referred to as soda-taxes). Although findings are not yet conclusive, experience derived from early adopters, such as those in Mexico and in Berkley, California, demonstrate raising taxes that increased prices was associated with a reduction in sales and consumption of sodas. This preliminary evidence is promising and justifies expanding soda taxation policies while conducting careful longitudinal evaluation of their health effects.
Infectious Agents

Eleven pathogens have classified as human carcinogens by the IARC, including: one bacterium (*Helicobacter pylori*); 7 viruses (hepatitis B virus [HBV], hepatitis C virus [HCV], human papillomavirus [HPV], Epstein-Barr virus [EBV], human immunodeficiency virus-1 [HIV-1], Kaposi sarcoma herpes virus [KSHV], and human T-cell leukemia virus type 1 [HTLV-1]); and 3 parasites (*Opisthorchis viverrini*, *Clonorchis sinensis*, and *Schistosoma hematobium*). Two additional agents have been classified as probable carcinogens: Merkel cell polyomavirus and *Plasmodium falciparum*. The biologic mechanisms by which infectious agents lead to cancer can include both direct (eg, EBV directly transforms human lymphocytes) and/or indirect (such as immune system depletion [eg, HIV] or chronic immune stimulation [eg, HCV]) effects. Each of the cancer-associated pathogens listed above causes at least one type of cancer, and in many cases, several types. In the United States, an estimated 4% of human cancers are attributed to infectious agents annually, and for several types of cancer, infectious agents are the dominant known risk factors.

**Helicobacter pylori**

In the last century, improvements in sanitation, living conditions, and antibiotic use were credited with a large decrease in the seroprevalence of *H. pylori*, the only bacteria known to cause human cancer, and subsequent reductions in gastric cancer incidence and mortality rates in the United States. Despite this progress, in the United States, the prevalence of *H. pylori* infection is still over 30%, and it caused approximately one-third (31.2%) of gastric cancers in 2014. Importantly, both *H. pylori* infection prevalence and gastric cancer incidence are significantly higher in African Americans, Latinos, and Asian Americans compared with non-Hispanic whites. Reasons for these disparities are unclear.

**FIGURE 3**. A World Cancer Research Fund International Policy Framework That Addresses Diet, Physical Activity, Breast Feeding, and Alcohol Consumption. This framework recognizes 3 broad policy domains, including 1) health enhancing environments, 2) systems change, and 3) behavior change communication must be included in efforts to address and support cancer preventive behavior change. This material has been reproduced from the World Cancer Research Fund/American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Cancer: A Global Perspective. Continuous Update Project Expert Report 2018. London, UK: WCRF International; 2018. wcrf.org/dietandcancer/contents. Accessed May 8, 2018.
Human Papillomavirus
In the United States, the most common infectious cause of cancer is HPV.4 According to the CDC, more than 79 million Americans are currently infected with genital HPV, and approximately 14 million, mostly teens and young adults, become newly infected each year. Almost every person will acquire an HPV infection at some time in their life. Every year in the United States, an estimated 19,470 women and 9,520 men are diagnosed with a cancer caused by HPV. All cervical cancers, as well as most anal (88.2%), vaginal (64.6%), and penile (56.9%) cancers, are attributed to HPV. HPV also is a major risk factor for oropharyngeal cancer.4

The first 2 HPV vaccines were introduced in 2006, and both protected against the 2 HPV types collectively thought to be responsible for 70% of all cervical cancers, HPV16 and HPV18.139 In 2014 a new HPV vaccine was approved by the FDA that targets 9 types of HPV (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) and is now the gold-standard, recommended vaccine in the United States.140 The 9-valent vaccine is given in 2 or 3 doses, depending on the age at first vaccination. Current recommendations advise HPV vaccination for girls and boys at age 11 or 12 years, but as early as age 9 years and as late as 26 years for females and 21 years for males.140 A recent study published in The Lancet estimated that the 9-valent vaccine is 97.4% effective, meaning it would have prevented about 90% of the HPV-related cancers today if the vaccine had been available when these patients were in adolescence.141

The HPV vaccine, in combination with an aggressive, evidence-based screening program, has the potential to eliminate cervical cancer. To achieve this goal, however, use of this vaccine must be increased. The latest estimates from the US CDC indicate that, as of 2016, only 60% of teens aged 13 to 17 years (65% of girls, 56% of boys) had received at least one dose of the HPV vaccine, and only 43% were up to date on all the recommended doses of HPV vaccine.142 Pediatricians and other clinicians should seek opportunities to improve vaccination rates among their patients. Examples of strategies that may help increase uptake of the HPV vaccine include: bundling of the HPV vaccine on the same visit as other vaccination; offering quick, nurse-only visits for second and third doses of the vaccine; routine reminders sent to unvaccinated patients; and preparation of succinct, accurate, and empathetic answers to parents’ commonly asked questions.143 In contrast to the United States, countries such as Australia and England have achieved higher rates of HPV vaccine series completion, largely through school-based vaccination programs.144,145 Australia in particular is a world leader in HPV vaccination, as it was one of the first countries to implement a fully government-funded, population-based HPV vaccination program.146 Vaccination rates have continued to improve annually in Australia, and, in 2015 and 2016, the prevalence of fully vaccinated girls and boys aged 15 years was 80.1% and 74.1%, respectively.147 These high rates of coverage have produced population-level reductions in HPV infections, and the sharpest declines in HPV-associated outcomes have occurred in countries with school-based vaccination delivery.144 Although access to HPV vaccination in the United States is nearly exclusively limited to the clinical setting, local pharmacist-led HPV vaccination efforts148 and school-located vaccination programs149 have been shown to be effective in this country and could help improve vaccine coverage rates if implemented more broadly.

Through gender-neutral HPV vaccination, evidence-based cancer screening, and treatment of precancerous lesions, cervical cancer can and should become a thing of the past. Indeed, in May 2018, the WHO Director General called for a global coordinated action to eliminate cervical cancer, advocating that the private sector along with nongovernmental organizations should commit to the cause.150 The ACS has extended this global call to action to include all HPV-related cancers, starting with cervical cancer.151 Similarly, all 70 National Cancer Institute-designated cancer center directors and leaders of other US cancer organizations have endorsed a similar statement.152

Hepatitis B Virus
Before 1982, an estimated 200,000 to 300,000 individuals in the United States were infected annually with HBV, which is an established cause of liver cancer, including approximately 20,000 children. No practical method of pre-exposure prophylaxis for HBV existed, and the only postexposure prophylaxis available was injection with hepatitis B immune globulin.153 In 1982, the HBV vaccine became the first vaccine to prevent a major human cancer (ie, liver cancer), and the WHO has recommended HBV vaccination since 1992.154 The HBV vaccine is 95% effective in preventing HBV infection155 and is given in 3 doses over the first 18 months of life, including ideally just after birth.156 Because of vaccination (along with changes in risk-reduction behaviors among at-risk populations in response to the HIV/acquired immunodeficiency syndrome epidemic), a marked decline in acute HBV infections has occurred in the United States since the 1990s. The decline has been greatest among children born since 1991, when routine vaccination of children was first recommended. The number of reported cases of HBV infections dropped to 3218 in 2016. Of note, the CDC estimates that, after adjustment for underascertainment and underreporting, the true incidence of acute hepatitis B cases is closer to 20,900.
Likewise, approximately 850,000 individuals were known to have chronic HBV as of 2011 and 2012, but the CDC estimates that the true prevalence is more than 2 million men and women.\textsuperscript{157} Since 2014, the rate of new HBV infections increased slightly, which is likely because of increasing injection drug use.

Historically, some of the highest rates of both chronic HBV infection and liver cancer in the United States (and the world) were among Alaskan Natives.\textsuperscript{158} In 1984, an extremely successful infant HBV vaccination program, coupled with a population screening program, reduced the incidence of both acute, symptomatic HBV and liver cancer to near zero among Alaskans aged ≤20 years.\textsuperscript{159} No cases of liver cancer among persons younger than 20 years have occurred in Alaska since 1999. The goal of eliminating HBV is within reach—as of 2016, coverage with 3 doses of hepatitis B vaccine for infants was estimated at 84% globally.\textsuperscript{153} To eliminate HBV transmission, high vaccine-coverage rates must be sustained among infants, children, and adolescents, and programs to vaccinate adults at high risk for HBV infection must be expanded.

**Hepatitis C Virus**

In the United States, an estimated 3.5 million people are infected with HCV,\textsuperscript{157} among whom 80% are Baby Boomers (ie, individuals born between 1945 and 1965). Unlike HBV, there is no vaccine for HCV. Thus, the US CDC recommends all individuals in the Baby Boomer birth cohort should be screened for HCV, although only 12.8% of adults in this birth cohort have been screened.\textsuperscript{160} Most of the new cases of HCV are occurring in young, white injection drug users living in rural areas. Notably, HCV causes approximately 24.2% of liver cancers in the United States, and the incidence rate of hepatocellular carcinoma has tripled over the last decade,\textsuperscript{157} in part because of an increased prevalence of chronic HCV infection.

In 2014, a new type of HCV treatment was approved by the FDA. These new pharmaceuticals, called direct-acting antiviral (DAA) drugs, completely changed the outlook for patients infected with HCV. With DAAs, HCV infections can be cured, thus preventing cancers and reducing costs associated with HCV infection. They also have the potential to significantly impact the HCV epidemic. Unlike many other new drugs, however, cost\textsuperscript{7} and limited access among select groups (such as those with minimal fibrosis or active substance abuse problems) have been barriers to this treatment.\textsuperscript{161} Expanding efforts to screen all at-risk individuals for HCV infection and increase access to treatment define emerging opportunities for the prevention of an important cause of liver cancer in the United States.\textsuperscript{162,163}

**Epstein-Barr Virus**

EBV is the most prevalent oncogenic pathogen, with an estimated >90% of adults infected with the virus worldwide; it is usually spread through saliva and is best known as the major cause of infectious mononucleosis, although most people experience mild or no symptoms after being infected with EBV.\textsuperscript{164} EBV is an established cause of several types of cancer, including Burkitt lymphoma, Hodgkin lymphoma, and nasopharyngeal cancers.\textsuperscript{7} Reactivation, rather than initial infection, of EBV may be the critical factor in the relationship between this virus and cancer risk.\textsuperscript{135} Although there is no currently licensed vaccine to prevent EBV infection, research to develop a vaccine is ongoing.\textsuperscript{165}

**Human Immunodeficiency Virus**

Although the prevalence of HIV in the United States is declining (down 5% between 2011 and 2015), approximately 40,000 people were diagnosed with the infection in 2016.\textsuperscript{166} Gay and bisexual men, particularly black men, had the highest rates of new HIV infection in the United States.\textsuperscript{167} Although there is no known cure or vaccine for HIV infection, effective antiviral treatments extend the lives of those who are infected. The impact of HIV on carcinogenesis is because of its profound immunosuppressive effects, and, thus, it acts as a co-carcinogen for other oncogenic viruses.\textsuperscript{136} One such co-infectious agent is KSHV. In the United States, the prevalence of KSHV is approximately 7% in the general population, and, like HIV, the prevalence of KSHV is highest among gay men.\textsuperscript{135} Kaposi sarcoma is a cancer for which the infectious agent is considered a necessary cause.\textsuperscript{4} Another HIV co-infection is HTLV-1, a cause of adult T-cell lymphoma. Although the prevalence of HTLV-1 is low in the United States,\textsuperscript{168} its impact should not be underestimated, because there is currently no available treatment intervention for acute or chronic HTLV-1 infection.

Overall, although vaccination against oncogenic infectious agents is among the most feasible and effective forms of cancer prevention, other strategies of infection control also can be important components of preventing the transmission of oncogenic infections and perhaps reducing disparities in the prevalence of infection. These strategies include, but are not limited to, treatment of infections, sanitation, needle-exchange programs, vigilant screening of donated blood and organs, promoting responsible sexual practices, and educating health care workers on the handling of bodily fluids.

**UV Radiation From the Sun and Indoor Tanning Devices**

UV radiation includes wavelengths from 10 nm to 400 nm, but only UVA (320–400 nm) and UVB (280–320 nm) are
significant causes of cancer. UV exposure from the sun is ubiquitous in the environment; however, there are other sources of UV radiation, the most common of which are indoor tanning devices, including tanning beds, tanning booths, and sunlamps. Large epidemiologic studies have assessed UV exposure using surveys which ask participants to recall their place of residence at different times of life, sun tanning, sunburns, time outdoors at different times of life, and indoor tanning.

Although indoor tanning has declined somewhat in the United States in recent years, it remains a significant exposure. In 2015, the estimated prevalence of indoor tanning at least once during the last 12 months was about 4% among US adults, with the highest prevalence (20%) among non-Hispanic white females aged 18 to 21 years. Among high school students in the 2015 Youth Risk Behavior Survey, the past-year prevalence of indoor tanning was 7% overall and 15% among non-Hispanic white females.

UV radiation from the sun causes cutaneous melanoma, as well as squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the skin. Both “intermittent” sun exposure (eg, from sunbathing or vacationing in sunny places) and a history of sunburns have been associated with higher risk of cutaneous melanoma in meta-analyses of epidemiologic studies. In a meta-analysis of 16 studies with information on the number of sunburns, an increase of 5 sunburns per decade was associated with an almost 3 higher risk of cutaneous melanoma. Sunburns have consistently been associated with higher risk of BCC and somewhat less consistently associated with risk of SCC. Indoor tanning is also an established cause of melanoma. In a meta-analysis of studies with information on the number of tanning sessions, having had more than 10 tanning sessions was associated with a 34% increased risk of cutaneous melanoma. UV radiation from the sun and from indoor tanning causes skin cancer by damaging DNA and possibly also through other mechanisms, including immunosuppression.

Preventing excessive exposure to UV radiation is important, because more than 9000 men and women die each year from melanoma in the United States alone. Recent estimates indicate that approximately 95% of all cutaneous melanoma cases in the United States may be attributable to UV radiation exposure from the sun and indoor tanning. This estimate of the PAF assumes that melanoma incidence among those in the general population with minimal UV exposure can be approximated by the relatively low incidence rates in US blacks, because UV is a much less important risk factor in the black population. Although the exact PAF is uncertain, it is clear that the large proportion of melanoma cases in the United States are caused by UV radiation from sun exposure and indoor tanning. In addition, although SCC and BCC are not commonly fatal, over 4 million US men and women receive treatment for these cancers each year.

Recommendations for reducing exposure to UV radiation from organizations, including the ACS and the CDC, are summarized in The Surgeon General’s Call to Action to Prevent Skin Cancer. Recommendations for individuals include seeking shade during midday, using sunscreen appropriately, and wearing a hat with a wide brim, sunglasses that block UV radiation, and clothing that covers the arms and legs. Avoiding indoor tanning is also recommended. The CPSTF recommends several community-level approaches to skin cancer prevention in The Guide to Community Preventive Services. These include educational interventions in schools; providing shade at schools, recreational sites, and occupational settings; and conducting multicomponent, community-wide interventions.

Medical Ionizing Radiation

Ionizing radiation is any particle (eg, α, β, or neutrons) or electromagnetic wave (ie, γ-ray or x-ray) that penetrates material (including human tissues) and carries sufficient energy to remove electrons from (ionize) atoms. All types of ionizing radiation are classified as carcinogenic by the IARC. In the general population, natural sources of ionizing radiation includes radon (which is discussed in the next section), cosmic radiation, and other sources. The discovery of x-rays and radioactivity in the late 19th century led to man-made radiation. It is estimated that, in 2006, 48% of ionizing radiation exposure to the general population was from medical sources, including from diagnostic
and therapeutic exposures; whereas, in the 1980s, medical exposure accounted for only 15%. The large increase in medical ionizing radiation exposure has been attributed to significant increases in the number of CT procedures (ie, from 18.3 million in 1993 to 68.7 million in 2007).

The effective dose of ionizing radiation exposure is an estimated measure of the biologic effects (eg, cancer and genetic alterations) that takes into account the type of radiation and the nature of the organ or tissue being radiated, and is expressed as Sieverts (Sv). The average annual effective dose received by individuals because of natural ionizing radiation exposure is approximately 2.4 mSv (typical range, 1-10 mSv). The dose received by individuals from medical sources of radiation varies considerably by procedure and target tissue. For example, the average (range in literature) dose is 0.01 mSv (range, 0.007-0.09 mSv) from a panoramic dental x-ray, 0.02 mSv (range, 0.05-0.24 mSv) from a chest x-ray, 0.4 mSv (range, 0.1-0.6 mSv) from mammography, 8 mSv (range, 2.0-18.0 mSv) from a barium enema, 2 mSv (range, 0.9-4.0 mSv) from a head CT, 7 mSv (range, 4.0-18.0 mSv) from a chest CT, 16 mSv (range, 5.0-32.0 mSv) from a coronary angiography CT, and 45 mSv (range unknown) from a Positron emission tomography CT. Damage to cells exposed to low doses of ionizing radiation often either is repaired through normal cell processes or leads to cell death. However, ionizing radiation exposure can lead to DNA damage that is not repaired and thus contributes to the etiology of some types of cancer.

Most evidence on the cancer risks associated with ionizing radiation exposure comes from historic studies of individuals who were exposed to the atomic bomb in Hiroshima or from occupationally exposed individuals. Despite the tremendous benefits of ionizing radiation for diagnosing and treating cancer and other health conditions, the risks associated with medical radiation exposure are of concern because of increasing exposure in the general population. Medical radiation is an established cause of many types of cancer, and CT appears to pose the greatest risk. The lifetime risk of cancer associated with a single CT coronary angiography at age 40 years is approximately 1 in 270 for women and 1 in 600 for men; however, this risk is lower for a single head CT (ie, 1 in 8100 women and 1 in 11,080 men of the same age), and, for both procedures, the risk decreases among older persons.

In addition to CT, there has been concern about the possible effects of repeated screening mammography on cancer risk. As a result, a simulation-modeling analysis commissioned by the Agency for Health care Research and Quality to support the work of the US Preventive Services Task Force and by the National Cancer Institute estimated the excess risk of radiation-induced breast cancer incidence and breast cancer mortality from mammography screening under a wide range of conditions. In that study, it was estimated that annual mammographic screening from ages 40 to 74 years using new, lower dose equipment has the potential to induce 125 breast cancers per 100,000 women (95% confidence interval, 88-178 breast cancers per 100,000 women) and lead to 16 breast cancer deaths per 100,000 (95% confidence interval, 11-23 breast cancer deaths per 100,000). However, this risk was approximately 2.3-fold greater for women who had large breasts compared with those who had small or average-sized breasts (ie, 266 vs 113 cases per 100,000 women). Furthermore, both annual and biennial screening starting at age 50 years was associated with a lower risk compared with starting screening at age 40 years. It is critical to consider that the harm of mammography is relative to the estimated number of breast cancer deaths averted; in that study, it ranged from 678 breast cancer deaths averted per 100,000 women screened biennially from ages 50 to 74 years to 968 breast cancer deaths averted per 100,000 women screened annually from ages 40 to 74 years.

The dose of radiation that an individual patient receives can vary significantly because of differences in equipment, technologist skill, application of dose-reduction strategies, and patient size, age, and sex. Newer equipment is automated to minimize the dose delivered based on the shape and size of an individual being scanned. Over the past decade, numerous interest groups have initiated efforts to improve and disseminate radiation reduction strategies and educate physicians, device manufacturers, their training staff, and others about radiation doses associated with specific tests. In 2010, a collaborative initiative (ie, “Image Wisely”) was launched by the American College of Radiology, the Radiological Society of North America, the American Association of Physicists in Medicine, and the American Society of Radiologic Technologist to reduce radiation exposure among adults as a result of medical imaging. More specifically, it encourages imaging providers to: 1) optimize imaging examinations to use only the radiation necessary to produce diagnostic quality images, 2) convey the principles of the initiative to the imaging team to ensure that the facility optimizes its use of radiation when imaging patients, 3) communicate optimal patient imaging strategies to referring physicians and be available for consultation, and 4) routinely review imaging protocols to ensure the use of the least amount of radiation necessary to acquire a diagnostic quality image. Recognizing the greater risk associated with pediatric medical radiation exposure, a similar initiative called “Image Gently” was launched earlier (in 2008) that focuses on changing radiologic practice by raising awareness of the opportunities to lower radiation exposure.
doses in the imaging of children, including scanning only when necessary, only the indicated area, and only once (multiple scans are often not needed). In 2010, the President’s Cancer Panel called for improvements in equipment and operator skill, as well as the elimination of unnecessary testing, to minimize radiation exposure without affecting diagnostic quality. Notably, the licensing of imaging and radiation therapy technologists is regulated by states, most (but not all) of which have some type of requirement. Efforts are needed to expand these requirements to the entire US population.

Radon

Radon is an ionizing, radioactive gas formed naturally from the decay of uranium in rocks and soil. Radon is present at low levels in outdoor air but can move up from the soil through building foundations and accumulate to higher levels in indoor air. Indoor air levels in the United States average about 1.3 picocuries per liter (pCi/L) but vary substantially, depending on factors including soil geography and construction characteristics. The US Environmental Protection Agency (EPA) recommends mitigation for homes with indoor air at or above an “action level” of 4.0 pCi/L. The EPA estimates that about 6% of homes in the United States have radon levels at or above the 4.0 pCi/L action level.

Case-control studies of residential exposure to radon in which α-track detectors were used to directly measure radon levels in participants’ homes, generally over 2 to 12 months, demonstrate that the risk of lung cancer increases with increasing radon levels. The magnitude of this increase in risk is consistent with extrapolation of the risk associated with higher levels of radon exposure in uranium miners. Combined analyses of 7 North American case-control studies that included 7148 patients with lung cancer, 13 European case-control studies that included 3662 patients with lung cancer, and 2 Chinese case-control studies that included 1050 patients, yielded relatively consistent results, with an overall estimated 10% increase in the risk of lung cancer per 100 Becquerel/m³ (2.7 pCi/L) increase in indoor air levels. It should be noted that these studies likely underestimate true risk because of imperfect measurement of long-term radon exposure.

α-particles emitted by inhaled radon and its radiation decay products are thought to cause lung cancer by damaging DNA in the cells of the respiratory epithelium. Associations between radon exposure and other cancers, notably leukemia, have been reported in some epidemiologic studies, but these associations are less consistent than those with lung cancer and are not established as causal.

According to a risk assessment by the EPA, radon exposure caused 13% (21,000) of all lung cancer deaths in the United States in 1995, making radon the second leading cause of lung cancer behind smoking. This estimate, although based on lung cancer deaths in 1995, remains applicable because, despite a decline in lung cancer mortality rates, the absolute number of lung cancer deaths each year in the contemporary United States is similar to that in 1995. According to a risk assessment by the National Research Council, approximately 3% to 4% of all lung cancer deaths in the United States could be prevented by mitigating all homes with radon levels at or above the EPA action level of 4.0 pCi/L. It should be noted that the WHO recommends residential radon reduction at a somewhat lower level (2.7 pCi/L).

In the general population, radon exposure from indoor air can be reduced substantially by testing existing residences and mitigating those found to have high levels. Home testing for radon can be done with a relatively quick, low-cost test kit and is recommended by the EPA for all homes below the third floor. Effective mitigation techniques include installing systems that pipe radon gas from underneath homes and vent it into outdoor air, and new construction can be built to be “radon-resistant.” In 2014, the American Lung Association, together with 11 other nonprofit, government, and industry organizations, collaboratively developed the National Radon Action Plan. This plan calls for a range of actions to reduce radon-induced lung cancer, including changes to state and local building codes, financial incentives for radon testing and mitigation, and promotion of radon awareness to the medical, public health, and childcare communities.

Conclusion

A US comprehensive cancer control plan designed to support the implementation of evidence-based interventions, including cancer prevention interventions like those described herein, has great potential to substantially reduce both the number of individuals diagnosed with and dying from cancer and the costs associated with cancer each year. Furthermore, a national plan would support the expansion of ongoing initiatives at the state and local levels. Numerous population-level and individual-level strategies have proven to be effective at reducing exposure or susceptibility to established cancer risk factors, and some (e.g., reductions in smoking and increases in HBV vaccination) have been proven to reduce cancer incidence and mortality rates. The highest priority in a national cancer control plan must be expansion of tobacco control—the intervention with the largest potential health benefits. Although some cancer
prevention interventions can be implemented fairly quickly, such as increasing HPV vaccination rates, others, including promoting access to healthier living environments and addressing the social determinants of health, will require concerted and sustained efforts. Finally, it is the responsibility of government and industry as well as the public health, medical, and scientific communities to work together to invest in and implement a comprehensive cancer control plan. Failure to do so will slow progress in our national efforts to reduce the burden of cancer.

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