Cancer Research

American Association for Cancer Research

Tobacco and Cancer: An American Association for Cancer Research Policy Statement

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Executive Summary

The evidence against tobacco use is clear, incontrovertible, and convincing; so is the need for urgent and immediate action to stem the global tide of tobacco-related death and suffering and to improve public health.

The American Association for Cancer Research makes an unequivocal call to all who are concerned about public health to take the following immediate steps:

- Increase the investment in tobacco-related research, commensurate with the enormous toll that tobacco use takes on human health, to provide the scientific evidence to drive the development of effective policies and treatments necessary to dramatically reduce tobacco use and attendant disease.
- Develop new evidence-based strategies to more effectively prevent the initiation of tobacco use, especially for youth and young adults.
- Promote the further development of evidence-based treatments for tobacco cessation, including individualized therapies, and ensure coverage of and access to evidence-based behavioral and pharmacological treatments.
- Develop evidence-based strategies for more effective public communication to prevent, reduce, and eliminate tobacco use and to guide health policies and clinical practice.
- Develop effective, evidence-based policies to reduce disparities across the tobacco continuum among social groups and developed and developing nations.
- Implement to the fullest extent existing evidence-based, systems-wide tobacco control programs to prevent initiation and foster cessation. Adapt and implement appropriate approaches to reduce the growing burden of tobacco use in the developing world.
- Enhance and coordinate surveillance efforts, both in the United States and globally, to monitor tobacco products, tobacco use, and tobacco-related disease, including tobacco use in oncology clinical trials.
- Establish a comprehensive, science-based regulatory framework to evaluate tobacco products and manufacturers' claims.
- Promote research that addresses the following: the potential harms of current and new tobacco products; the impact of altering the levels of addictive components in tobacco products; the identification of risk and risk-reduction measures for current and former tobacco users; enhanced early detection methods for tobacco-related cancers; and effective treatments against tobacco-related cancers tailored to the unique effects of tobacco on cancer.
- Pursue domestic and international economic policies that support tobacco control.
- Urge the United States to ratify the World Health Organization Framework Convention on Tobacco Control. Foster global scientific efforts to support the Framework.
- Work together with stakeholders worldwide, including federal agencies, to develop and implement effective tobacco control strategies and to deter counter-tobacco control efforts by the tobacco industry.

Only such concerted global actions by scientists, policymakers, and advocates together can prevent the invidious impact of tobacco, the use of which is cutting wide swathes of death and disease around the world.

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Preamble

The large body of scientific evidence establishing tobacco use as the world's leading cause of premature death is clear, incontrovertible, and convincing. Despite this knowledge, global tobacco use is on the rise. Tobacco kills more than five million people every year, and according to the World Health Organization, tobacco's global death toll will increase to more than eight million deaths a year by 2030, 80% of which are likely to be in the developing world (1). To stem the global tide of tobacco use and promote public health, efforts to improve tobacco control, understand mechanisms of nicotine addiction and tobacco-induced disease, and improve the treatment of diseases caused by tobacco must be redoubled. The research community at large must engage collaboratively to advance progress in these areas. The American Association for Cancer Research (AACR) is dedicated to preventing and curing cancer through research, education, communication, and collaboration, and is committed to joining the global community in combating this preventable epidemic with the ultimate goal of a tobacco-free world.

Tobacco consumed in any form, but particularly when smoked, is carcinogenic. The landmark publication of the first U.S. Surgeon General's Report on Smoking and Health in 1964 identified the causal relationship of smoking to lung cancer in men (2). Tobacco smoke contains more than 5,000 chemical constituents, including more than 60 established carcinogens and numerous toxicants (3). Studies have demonstrated a strong relationship between tobacco smoke, carcinogen-DNA adduct formation, smoke exposure, and cancer risk (4). Now, there is sufficient scientific evidence to causally link tobacco use to cancers at 18 different organ sites (5–9). In the United States, tobacco causes nearly 30% of all cancer deaths and 87% of all lung cancer deaths, totaling an estimated 169,000 lives lost in 2009 alone (10). Tobacco use causes many other diseases and detrimental health conditions, including cardiovascular and respiratory disease, killing an estimated 443,000 people annually in the United States (11). Although the AACR is cancer-focused, it recognizes that the adverse effects of tobacco on health must be addressed concomitantly for many diseases.

In addition to its toll on human health, tobacco use extracts great economic costs. In the United States, the total annual economic burden of cigarette smoking, including direct health care expenditures and productivity losses, was approximately $193 billion in 2004 (11). Recent estimates suggest that the global economy is losing more than $500 billion to tobacco use in a single year (12).

An added concern is that the burden of tobacco is not uniformly suffered across population groups. Despite the fact that the number of adult smokers in the United States has declined appreciably, from 42.4% in 1965 to 20.6% in 2008 (13, 14), the persistently large burden of tobacco use is distributed unequally across different classes, races, ethnicities, and geographies (15). The disparities are related to a number of complex factors, ranging from environment, social class, and smoking behavior to genetics and biology. These disparities are apparent throughout the entire tobacco continuum: tobacco initiation; tobacco use and number of cigarettes smoked per day; efficacy of and access to cessation treatment and success in quitting; and health consequences such as cancer (16). With such clear detrimental effects on health and society, it is astonishing that 1.3 billion people worldwide still use tobacco and that this number is growing (12).

Moreover, smoking in some countries, such as the United States, starts at an early age. Every year in the United States, more than 350,000 children under the age of 18 become regular, daily smokers (17). Worldwide, it is estimated that almost 100,000 youths begin tobacco use on any given day, and about one-fourth of them are 10 years old or younger (18).

Most people who use tobacco regularly do so because they are addicted to nicotine, the major addictive component in tobacco. Although the majority of users express a desire to reduce their use or stop entirely, overcoming the addiction is difficult and may require both pharmacologic and behavioral treatments, as well as policy changes. Worldwide tobacco control efforts must contend with the highly addictive nature of tobacco compounded by extremely aggressive tobacco industry marketing.

The substantial public health burden and suffering related to tobacco use is a global problem, with a diverse set of circumstances, types of tobacco, and tobacco use. Today, there are unprecedented opportunities for tobacco control in the United States and globally. The U.S. Food and Drug Administration (FDA) recently received regulatory authority over tobacco products under the Family Smoking Prevention and Tobacco Control Act of 2009 (FSPTCA), signed into law by President Obama in June 2009. Through policy decisions based on sound scientific evidence, the FDA has the opportunity to reduce tobacco use and protect public health. Globally, the World Health Organization (WHO)-led Framework Convention on Tobacco Control (FCTC) is the first health treaty of its kind that addresses the devastating consequences of tobacco use around the world. The FCTC, ratified by 168 countries as of the end of 2009, aims to tackle both the supply and demand sides of tobacco use through evidence-based strategies (19).

While evidence-based approaches to tobacco control exist and should be implemented to the fullest extent, there are also new and pressing needs for a broad research agenda that will provide the evidence base for new policies, new strategies for prevention of initiation, and better treatments for cessation. It is well documented that the tobacco industry has frequently subverted scientific progress and public health using a myriad of tactics to increase tobacco use (20). These

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past actions must be considered as we move forward to advance tobacco control.

Even the most successful efforts in tobacco control, however, will not prevent the onslaught of illness and death that will result from current tobacco use. The delay in onset of disease caused by tobacco means that what is done—or not done—today will directly and dramatically impact public health for decades to come. To fully combat the tobacco problem, significant advances must be made in preventing and treating tobacco-related diseases. Research will continue to shed light on the biology of addiction and the molecular mechanisms by which tobacco causes cancer. Such knowledge will better inform the development of individualized strategies to prevent, detect, and treat the numerous tobacco-caused cancers, with the ultimate goal of saving lives that otherwise would be lost to tobacco.

Principles

The AACR believes there is a clear imperative to eliminate the burden of tobacco use and attendant disease by advancing science and communicating scientific breakthroughs to the public, funders, and regulators. AACR members and the research community at large should address the tobacco problem through transdisciplinary approaches, looking across the entire tobacco use and harm continuum, from preventing initiation and facilitating cessation to elucidating biological mechanisms to improve prevention, early detection, diagnosis, and the treatment of diseases caused by tobacco use.

Research provides new opportunities to dramatically reduce tobacco use and attendant disease, as the scientific evidence will guide the development of the most effective public policies, clinical practices, and novel therapies. The AACR strongly urges a substantial increase in the investment in tobacco-related research, commensurate with the enormous toll tobacco use takes on human health.

Given that there is no known safe form of tobacco, the AACR will work diligently with the global community, including other professional organizations, funders, and regulators, toward the goal of a world free of tobacco. The AACR strongly encourages the widespread implementation of evidence-based practices known to be effective in tobacco control, both nationally and internationally, and further encourages the conduct of new research to drive even greater advances in tobacco control. The AACR fully supports the WHO FCTC and urges its immediate ratification by the United States.

The AACR Task Force on Tobacco and Cancer has identified policy and research initiatives that it feels are critical to overcoming the tobacco problem from the unique perspective of the AACR, a scientific organization with member researchers from all over the world addressing the full spectrum of the tobacco problem. These recommendations are presented below for the following thematic areas: tobacco product regulation, tobacco use and exposure, and tobacco-related cancers.

Evidence-Based Regulation of Tobacco Products

Tobacco use, nicotine addiction, and the numerous adverse effects of tobacco use present a complex, multi-faceted public health problem that must be addressed through comprehensive and systems-wide tobacco control efforts in a regulatory environment. There is no simple or single way to do this, and methods may vary worldwide. Many effective approaches to reducing tobacco use have been developed and need broader implementation; however, given the persistently large number of tobacco users, there is a grave need for additional, novel approaches. Research, ranging from laboratory and population studies to clinical trials, is needed to inform the regulatory process and implement the best policies, and then to justify them as needed to the public, legislators, and the courts.

As tobacco control efforts have increased, the tobacco industry has continued to prosper by increasing markets in developing countries and continually introducing new tobacco products and tobacco-like products. While cigarettes account for the largest share of tobacco products in the world, myriad other forms exist that are inhaled, sniffed, sucked, or chewed. These other forms of tobacco consumption—such as smokeless tobacco (e.g., snus, snuff, or chewing tobacco); waterpipe tobacco smoking (also called hookah); or clove-flavored kreteks—while not yet making up a significant portion of the worldwide market, can serve as a gateway to lifelong addiction (12). Tobacco companies are developing and marketing new products with implied and/or explicit health claims, such as reducing carcinogen exposure or harm, or facilitating cessation, as a way to perpetuate tobacco use; however, these claims are unsubstantiated and effects on human health, nicotine dependence, and cessation efforts are unknown.

While the historical lack of regulation of tobacco products in the United States has slowed success of tobacco control efforts, the recently enacted FSPTCA holds the possibility of dramatically reducing tobacco use by granting the FDA regulatory authority over tobacco products. The FDA now has the authority to require changes to tobacco products that the agency finds to be appropriate for the protection of the public health. For example, the FDA has the authority to require a reduction of the addictive agents in tobacco to levels that are not addictive to anyone; this would both stop the progression from experimentation to addiction and foster complete cessation. The law also bans the terms "light," "low," and "mild" because the implications that these products are less hazardous are unsubstantiated, erroneous, or both. The law also makes any manufacturer's claim of reduced harm or reduced risk of tobacco-related disease subject to FDA regulation; the scientific evaluation of the claim must consider impact on both the individual and the population.

The FSPTCA also grants the FDA authority to mandate tobacco product standards and ingredients in order to reduce toxicant exposures. Thus, the FDA has authority to require the elimination

of all additives that promote tobacco use that are flavorants, that augment the effects of nicotine, or that affect a smoker's perception. The United States ban on cigarettes containing artificial or natural flavors, herbs, or spices as characterizing flavors went into effect in September 2009 as a first step toward reducing the number of children who start to smoke (21). Menthol, a cigarette additive marketed for its physiological effects as an anti-irritant and a cooling agent, was explicitly excluded from the ban by the legislation. Examination of tobacco industry documents has revealed that tobacco companies have specifically marketed menthol cigarettes to youth, young adults, women, and African Americans (22). Surveys have shown that menthol cigarette use is more common among newer, younger smokers, and thus menthol cigarettes may serve as a starter product similar to other flavored cigarettes (23). Mentholized cigarettes are also used by a large majority of African-American smokers. There is evidence that menthol helps to sustain tobacco use, in part by making tobacco smoke more palatable, which may contribute to the higher dependence levels and greater health burden found among African-American smokers compared with the general population (24, 25). A significant body of scientific findings from decades of research on menthol should help to inform a policy on banning menthol (26).

The FDA and regulatory authorities worldwide must be forward thinking and fully integrated into the research and public health infrastructures. As a matter of law, regulators, including the FDA, must make some policy decisions based on incomplete scientific evidence; the AACR believes it is appropriate for regulators to base such policies on the strength of evidence available (e.g., biological plausibility, animal studies, limited clinical trials with biomarkers). In expectation that those with an interest in sustaining tobacco use will strive to undermine the intent of the FSPTCA, the AACR strongly urges the research and advocacy communities to support the FDA in its efforts because new research and public education will be critical.

In light of the substantial evidence base, the AACR strongly encourages the following actions related to tobacco product policies:

1. Pursue domestic and international economic policies that support tobacco control, including the establishment and enforcement of trade, taxation, and pricing regulations; reduction or elimination of tobacco industry government subsidies; and support of tobacco farm conversion to alternative crops.

2. Allocate government revenues from tobacco product taxes or tobacco industry sources (e.g., penalties resulting from regulatory or legal action) to tobacco research and control.

3. Exercise all available regulatory authorities, based on sound science, to rapidly and dramatically reduce the morbidity and mortality from tobacco use.

4. Increase communication and collaboration among all federal agencies contributing to tobacco control to facilitate and coordinate research infrastructures and the dissemination of research findings into practice and policy.

5. Require manufacturers to provide sufficient scientific evidence to support health claims or significant changes in product design. Establish a comprehensive framework for the evaluation of all tobacco products and manufacturer health claims before introduction and/or marketing, and require post-market research. The framework should include all relevant validated approaches for evaluation, including laboratory studies, clinical trials, and epidemiological studies with biomarkers, and surveillance. The evaluation of manufacturer claims will need to be assessed through human studies of sufficient size, scope, and duration. This framework should provide a means to evaluate the impact on both toxicity and consumer perception and use in order to assess individual and population health effects.

6. Develop and implement a national surveillance system to track all tobacco products, knowledge, perceptions, behavior, and consumption with the goal of creating an early warning system to identify harmful new tobacco products and populations that use them through collaboration among relevant federal agencies, including the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), the Department of Agriculture, and the Bureau of Alcohol, Tobacco, and Firearms. Such a system should include a national cohort of tobacco users and non-tobacco users, with special focus on populations at greatest risk or that are underserved, to assess the impact of tobacco industry marketing, FDA regulations, and other efforts to reduce tobacco use.

7. Require that the Center for Drug Evaluation and Research and the Center for Tobacco Products at the FDA coordinate efforts to assure that regulation and labeling of tobacco products be more stringent than that of cessation treatments in proportion to the relative harm of these two classes of products.

8. Require stringent and effective warning labels, including graphics, for tobacco products. Warning labels should be selected based on scientific evidence and should be specific in terms of content and causative diseases.

9. Require that all tobacco product labels include messages to encourage cessation, including the national toll-free quit line number (1-800-QUIT-NOW), and provide resources to the CDC to meet increased demand for services that may result (e.g., an improved and expanded quitline infrastructure).

10. Issue a regulation to deem all tobacco products, including cigars, pipe tobacco, and waterpipe tobacco, subject to the FSPTCA. Specifically, prohibit these products from having candy, fruit, and spice flavors as characterizing flavors; apply all package labeling requirements to these products; and apply youth access, advertising, and promotion restrictions to these products.

11. Ban menthol from cigarettes, as was done for other flavorings.

12. Require the removal and prevent the new inclusion of additives that facilitate tobacco use by affecting a tobacco user's perception, use, addiction, abuse liability, and/or sensation.

13. Ban the sale of gum, candy, or other food products that are designed and packaged to mimic tobacco products. Such products constitute tobacco marketing that appeals to children (27).

The AACR particularly encourages the following research agenda related to regulation of tobacco products:

1. Develop and evaluate effective, evidence-based communication methods in experimental and field research; translate research findings into improved communication strategies to educate the public about the need for the above policies.

2. Prioritize and support research that fills in current knowledge gaps in order to facilitate FDA implementation of a comprehensive framework for the evaluation of all tobacco products, as described above (recommended action #5).

3. Promote research to increase our understanding of genetic and metabolic factors related to mechanisms of nicotine addiction and mechanisms of carcinogenesis that arise from use of tobacco products and their constituents.

4. Evaluate methods used to assess the impact of tobacco use on health, including clinical trial methods, panels of biomarkers for exposure and harm, and measures to assess smoking behavior, consumer perception, and abuse liability.

5. Develop better laboratory methods to assess the delivery of toxins and toxicologic effects (including improved uses of the smoking machine) of all tobacco products, including those purported to be potential reduced exposure products (referred to as PREPs), in order to evaluate product performance standards and manufacturer health claims.

6. Assess the strategy of reducing nicotine and other addicting constituents in tobacco products as a means to reduce or eliminate addiction potential. Further research is needed to determine the target levels for nicotine content and delivery, the method and timeline for implementation, and the potential behavioral and social sequelae.

7. Foster experimental and field research on youth and adult perceptions of tobacco products, packaging, and tobacco product effects to guide the design and evaluation of effective messages to counter tobacco industry product advertising, marketing tactics, and other methods intended to sustain tobacco use.

Tobacco Use and Exposure

Globally, there are an estimated 1.3 billion current smokers (12). In 2008, an estimated 70.9 million Americans aged 12 or older were current users of tobacco. Among these individuals, 59.8 million were current cigarette smokers, 13.1 million smoked cigars, 8.7 million used smokeless tobacco, and 1.9 million smoked pipes (28).

Over the past four decades, public health efforts have led to enormous reduction in tobacco use in the United States. Nevertheless, an estimated one in five adults still smoke cigarettes on a regular basis (14). Smoking rates remain higher among Alaskan natives, American Indians, those living below the federal poverty line, and those with less than high school education (14). Smoking rates are also higher among persons with psychiatric diagnoses and substance abuse conditions (29). Globally, the situation is worsening. In developing countries, nearly 50% of men smoke, and although the percentage of women smokers (9%) is lower than in developed countries (22%), smoking rates appear to be increasing in this population (12).

Significant progress in both prevention and cessation is critical to dramatically reduce the prevalence of tobacco use. In the United States, the FSPTCA will provide new tools to arm the tobacco control community, such as increased restrictions on marketing and sales to youth, improved tobacco product warning labels, reduction of product components that attract youth, and prohibition of misleading, unsubstantiated health claims. The need for rigorous scientific evidence to support new FDA regulations is essential for the effective implementation of these tools.

The AACR believes it is critical that more urgent efforts are made to identify effective ways of preventing initiation and fostering cessation of tobacco use through further investment in research and through public education.

Preventing Initiation of Tobacco Use

The ideal strategy to combat tobacco use is to prevent its initiation. Every day in the United States nearly 4,000 youths aged 12 to 17 years smoke their first cigarette, and about

1,000 become daily cigarette smokers (30). Prevention of initiation requires both education and policy efforts to discourage people—especially youth—from experimenting with tobacco. Due to the incredibly addictive nature of tobacco, experimentation or casual smoking can quickly lead to dependence. It is critical to implement comprehensive tobacco control programs—including communication, educational, clinical, regulatory, enforcement, social, and economic strategies—where efficacy is known and to conduct research to improve the effectiveness of other approaches. For example, national media campaigns have proven successful in preventing initiation and even promoting cessation (20). Other strategies, such as increasing the unit price of tobacco and implementing smoking bans, have been found to be effective in preventing tobacco uptake among youth (31). Mobilizing communities to draw attention to tobacco use among youth, combined with effective enforcement strategies, including preventing retail sales to minors and education of retailers, has also been successful in stemming initiation and use (31).

In addition to cigarette smoking, other forms of tobacco consumption, including use of smokeless tobacco products or smoking of cigars, pipes, and waterpipes, also warrant increased attention and vigilant surveillance because these products can serve as a gateway to lifelong addiction (12). In particular, there needs to be careful vigilance to identify any adverse impact on the initiation of modified tobacco products, sometimes referred to as PREPs, as well as other forms of nicotine-delivery products that resemble tobacco products.

The AACR urges all stakeholders to make far-reaching global efforts to discourage people, particularly children and young adults, from initiating tobacco use. In light of the substantial evidence related to tobacco use initiation, the AACR strongly encourages the following actions:

1. Establish and sustain evidence-based, comprehensive statewide tobacco control programs, such as those defined by CDC's Best Practices for Comprehensive Tobacco Control Programs; provide the level of annual investment recommended by CDC (32).

2. Enact trade, pricing, and taxation policies that increase the price of tobacco—the single most effective intervention to reduce initiation—at the federal, state, and local level.

3. Invest in national and local media campaigns worldwide that discourage young people from initiating tobacco use. Such media campaigns should be based on scientific evidence of efficacy.

4. Implement effective enforcement strategies to prevent access to tobacco among youth.

5. Ensure adequate surveillance methods for specific tobacco products and other nicotine-delivery devices resembling tobacco products. Surveillance data should be analyzed rapidly to identify and counter any adverse impact of new products on preventing tobacco initiation. National surveillance efforts should be coordinated with global efforts.

6. Reduce exposure of youth to smoking in media, including motion pictures, through regulatory changes where possible.

The AACR strongly advocates for increased federal investment in research and particularly encourages the following research agenda related to tobacco use initiation:

1. Develop and evaluate effective communication methods in experimental and field research, and translate the results of these studies for public education about the need for the above policies.

2. Assess the impact of effective strategies for primary prevention of tobacco initiation in controlled trials as well as observational research.

3. Evaluate the control of nicotine levels and delivery from cigarettes as a means to prevent the transition from experimentation to dependence.

4. Evaluate the effects of warning labels, product packaging, and advertising on initiation in controlled trials and field research studies.

5. Promote research on modified tobacco products and other forms of nicotine-delivery products that contain tobacco or resemble tobacco products to determine their effects on efforts to prevent initiation of tobacco use.

6. Foster research to understand how tobacco industry marketing targets specific populations in order to develop effective means of tailoring counter-messages.

7. Foster research to understand differential use of tobacco among different population groups in order to develop effective means of prevention with the goal of eliminating tobacco-related disparities.

8. Identify the effects and interactions of genetic, behavioral, and socio-environmental risk factors for initiation and continued use among different population groups, and apply this knowledge to develop targeted prevention research programs.

9. Foster research and educational efforts to change social norms surrounding tobacco use.

10. Develop and evaluate methods to prevent initiation using new social media technologies.

Treating Tobacco Addiction and Fostering Cessation

Currently, roughly 70% of U.S. smokers want to quit, but only 40% of smokers try to quit in a calendar year (33, 34).

Most of these attempts to quit are both unaided and unsuccessful. More than 95% of those who try to quit on their own relapse, and most do so within a week because tobacco is extremely addictive (35, 36). There is extensive empirical evidence that nicotine is the primary addictive component of tobacco products; however, other components, such as acetaldehyde, are also known to contribute to tobacco's addictive properties (36). Chronic exposure to nicotine produces changes in brain function that make quitting difficult for many smokers (36). Evidence clearly shows that counseling coupled with treatment increases cessation, and this association is reflected in the updated clinical practice guidelines on cessation (35). Opportunities to reap the benefits of such evidence-based treatments are often lost, however, because recommendations are not always followed. Moreover, many clinicians lack knowledge about how to identify smokers quickly and easily, which treatments are effective, how such treatments can be delivered, and the relative effectiveness of different treatments (35).

New treatment approaches to achieve cessation of tobacco use are urgently needed because, despite some progress in the development of treatments for tobacco dependence, available medications and behavioral approaches are successful for only a fraction of users (37). Even when following the comprehensive evidence-based tobacco treatment guidelines in state-of-the-art cessation programs, abstinence rates fall well below 50% (35). Relapse prevention is also extremely important because tobacco dependence is a chronic, relapsing disease, often taking multiple quit attempts to become successful in the long term.

Among cancer patients, the problem is even more striking because continued smoking after diagnosis has an adverse impact on clinical outcome (38). Rates of current smoking at diagnosis among patients with lung or head and neck tumors are 40% to 60% (39). Initial high quit rates of cancer patients decline over time, and patients with cancers less strongly associated with smoking have lower long-term quit rates. Overall, up to 30% to 50% of patients smoking at diagnosis do not quit, or they experience a relapse after initial quit attempts (39). Relapse even occurs among cancer patients who quit smoking for one year or more (40). However, relapse is often substantially delayed in cancer patients compared with healthy individuals, providing a unique opportunity to implement relapse prevention (41).

In light of the substantial evidence base surrounding tobacco cessation, the AACR strongly encourages the following actions:

1. Implement a large-scale initiative to increase the development of medications to treat tobacco dependence and tailoring of therapies, taking into account genetic, behavioral, and socio-environmental factors and medication accessibility, through coordination among the FDA, other federal agencies (including NIH, Agency for Healthcare Research and Quality, and Centers for Medicare and Medicaid Services), and the private sector. Fast track review and approval of tobacco cessation products by the FDA should be implemented.

2. Integrate tobacco use assessment and intervention into the training and practice of primary medical, pharmacy, and dental care providers; specialists in oncology, cardiology, pulmonology, obstetrics, and pediatrics; and other relevant health care providers.

3. Broaden dissemination and use of evidence-based tobacco treatment guidelines, such as the 2008 Public Health Service Guideline, *Treating Tobacco Use and Dependence* (35). This effort would include the dissemination of empirically supported behavioral interventions, which are underutilized despite evidence that they improve cessation rates when used in conjunction with pharmacotherapy.

4. Increase public awareness and behavioral change through evidence-based public education regarding the health, economic, and social costs of tobacco use; the benefits of cessation; and the pharmacologic and behavioral approaches to cessation.

5. Ensure adequate surveillance methods for specific tobacco products and other nicotine-delivery devices that resemble tobacco products. Surveillance data should be analyzed rapidly to identify and counter adverse impacts of such products on quitting and re-uptake by former smokers. National surveillance efforts should be coordinated with global efforts.

6. Require the Centers for Medicare and Medicaid Services to provide coverage for both behavioral and pharmacologic smoking cessation treatment for all covered patients. Strive for comprehensive cessation coverage by all health plans.

7. Encourage cancer centers to offer comprehensive cessation services for their patients and family members.

Current research funding available for treating tobacco use and dependence is small relative to 1) the high prevalence of tobacco users who would like to quit; 2) the high failure rate of quit attempts using current approaches, indicating a need for more research; and 3) the enormous potential impact on public health if tobacco users succeed in quitting. Given the large impact that increased success in cessation will have on the public's health, the AACR strongly advocates for increased federal investment in research and particularly encourages the following research agenda related to cessation:

1. Develop and implement effective communication methods to educate the public about the need for the above policies.

2. Promote research on the social, behavioral, economic, and societal determinants of tobacco addiction, cessation, and relapse.
3. Reinvest in the development, validation, and dissemination of behavioral treatments for tobacco

dependence. Progress on behavioral interventions has stalled over the past two decades, as researchers have focused on pharmacotherapies. However, cessation efficacy is likely to be achieved through both strong behavioral and pharmacologic treatments, combined or individually.

4. Promote basic, preclinical, and applied research on the genetic, neurophysiologic, and neuropathologic mechanisms of nicotine addiction, including genetic factors, gene-environment interactions, and susceptible populations; invest in the development of novel agents to counteract this addiction and the translational application of these discoveries in human trials.

5. Develop and evaluate novel evidence-based approaches to tobacco dependence treatment and targeted therapeutic approaches based on tobacco users' biological, social, and cultural backgrounds; invest in research in the viability, development, and testing of personalized cessation treatments based on genetic associations with nicotine addiction.

6. Examine racial, ethnic, and socioeconomic disparities in the efficacy of cessation approaches, and the underlying biological and social mechanisms that account for such differences.

7. Evaluate the effects of warning labels, product packaging, and advertising on cessation.

8. Promote research on modified tobacco products and other forms of nicotine-delivery products that contain tobacco or resemble tobacco products to determine their effects on tobacco cessation methods and long-term abstinence.

9. Determine the impact of public policies, such as clean indoor and outdoor air laws, on cessation.

10. Promote research on the control of nicotine levels and delivery with the intent of reducing or eliminating the addictiveness of tobacco products.

11. Develop and evaluate cessation methods using new social media technologies and mass media campaigns, and disseminate effective methods broadly to promote cessation.

Reducing Exposure to Secondhand Tobacco Smoke

Secondhand smoke, also referred to as environmental tobacco smoke, causes disease and premature death in nonsmoking adults and children. Recent estimates suggest that secondhand smoke causes about 600,000 deaths annually worldwide (42). In 2006, the U.S. Surgeon General concluded that there is no safe level of exposure to secondhand tobacco smoke and that the only way to fully protect nonsmokers from secondhand smoke exposure is to completely eliminate smoking in indoor spaces (43). Secondhand smoke is composed of sidestream smoke given off by the burning end of a tobacco product as well as exhaled mainstream smoke from the smoker. Sidestream smoke contains more than 50 cancer-causing chemicals, some of which occur in proportionately higher levels than mainstream smoke. Secondhand smoke is known to cause lung cancer in nonsmokers, resulting in an estimated 3,400 deaths annually in the United States (11). Evidence also suggests a link between exposure to secondhand smoke and cancers of the larynx and pharynx (9).

Exposure is a particular concern for children and those adults unable to avoid the exposure due to occupation or housing. In recent years, many state and local governments have passed laws to reduce exposure to secondhand smoke, prohibiting smoking in public facilities and requiring private workplaces to be smoke–free. As of January 2, 2010, 26 states and the District of Columbia have passed laws that prohibit smoking in almost all public places and workplaces, including restaurants and bars (44). Recent evidence indicates that smoking bans are effective in reducing the prevalence of some tobacco-associated disease (45). Smoking restrictions not only protect nonsmokers but also facilitate smoking cessation and relapse prevention.

In light of the substantial evidence base surrounding exposure to secondhand smoke, the AACR strongly encourages the following actions:

1. Implement smoke-free environments for both indoor and outdoor public spaces where secondhand smoke will affect vulnerable populations.

2. Educate the public on the invidious impact of environmental exposure through mass media and other evidence-based public educational strategies.

The AACR strongly advocates for increased federal investment in research and particularly encourages the following research agenda related to exposure to secondhand smoke:

1. Foster research on the health impacts of exposure to tobacco smoke or other airborne contaminants from tobacco products and other nicotine-delivery devices.

2. Assess the impact of public policy and educational initiatives on environmental exposure.

3. Assess the impact on fetal health of smoking or other tobacco use during pregnancy.

4. Determine the toxic effects of tobacco residue in fabrics, upholstery, and air—the so-called thirdhand smoke.

Tobacco-Related Cancers: Mechanisms, Prevention, Screening and Early Detection, Treatment, and Survivorship

Tobacco use is the single largest cause of cancer worldwide, and smoking alone accounts for at least 30% of all cancer deaths in the United States (11). The causal association of

tobacco use with lung cancer—the most common cancer in the world—was first described in the 1950s and brought to public attention by the U.S. Surgeon General in 1964 (2). In the United States, smoking causes approximately 87% of deaths from lung cancer, which is the leading cause of cancer death in both men and women (10). Although most people are aware that cigarette smoking causes lung cancer, few are aware that tobacco use also causes cancer at no less than 17 other organ sites. In the past half century, evidence from epidemiologic studies has demonstrated the causal link between tobacco smoking and cancer of the oral cavity, oropharynx, nasopharynx, hypopharynx, esophagus (adenocarcinoma and squamous-cell carcinoma), stomach, colorectum, liver, pancreas, nasal cavity and paranasal sinuses, larynx, lung, uterine cervix, ovary (mucinous), urinary bladder, kidney (body and pelvis), ureter, and bone marrow (myeloid leukemia) (ref. 9). Secondhand smoke also causes lung cancer, and parental smoking is causally linked to hepatoblastoma, a rare embryonic cancer of the liver (9). Use of smokeless tobacco causes cancer of the oral cavity, esophagus, and pancreas (9). This list of tobacco-caused cancers continues to grow as new scientific evidence is generated.

The carcinogenic nature of tobacco smoking, oral use of tobacco, and secondhand tobacco smoke has been extensively studied. Tobacco mainstream smoke contains more than 5,000 identified chemicals, at least 60 of which are known to be carcinogenic, in addition to numerous toxicants (3). The new authority granted to the FDA under the FSPTCA will require extensive disclosure by the tobacco industry, including product ingredients and any studies on the effects of the ingredients, such as toxicology. This information will provide valuable new information to the scientific community and will help to determine which ingredients contribute to tobacco harm and addiction.

Research has elucidated many biological mechanisms by which tobacco use and smoke exposure lead to cancer. For example, tobacco carcinogens are metabolically activated in humans to forms that bind to DNA and create DNA adducts, which then cause mutations in genes such as the important growth-regulatory genes *ras* and *p53* (46). Smoking also induces epigenetic effects that contribute to carcinogenesis (47). Genetically determined host capacity can influence these outcomes and the risk for tobacco addiction (48). A deeper understanding of the molecular pathways underlying tobacco carcinogenesis, using new technologies and systems biology approaches (e.g., genomics, epigenomics, transcriptomics, proteomics, and metabolomics), is critical to developing effective therapies to prevent and treat tobacco-related cancers.

The most important step in preventing cancer is to not smoke or to stop smoking. Quitting tobacco use at any age reduces cancer risk, as compared with continued smoking; however, former smokers continue to suffer an increased cancer risk compared with never smokers (49). As more than one half of all newly diagnosed lung cancers are in former smokers, an understanding of the cancer risk in former smokers is critical and will become even more important if cessation rates improve as a result of new therapies and enhanced tobacco control efforts. In addition to facilitating cessation as a means of preventing disease in tobacco users, the identification of chemopreventive agents that prevent cancer in high-risk populations would help to alleviate the tobacco-associated disease burden. Research that elucidates the mechanisms of tobacco carcinogenesis will guide the development of chemopreventive agents, as well as other approaches to prevention of tobacco-induced cancer, such as the identification of highly susceptible individuals.

Prevention of tobacco-related cancers will also be aided by the identification of genetic or other factors that significantly increase an individual's susceptibility to the disease-causing effects of tobacco products or exposure to those products. Validated risk assessment methods to predict who will get cancer need to be developed. These will include validated biomarkers of exposure, effect, harm, and susceptibility. Identification of higher-risk individuals would allow targeted novel cessation strategies and tailored early detection, as well as an option to take added precaution with chemopreventative treatments.

Efforts are underway to identify improved methods to screen current and former tobacco users for tobacco-related cancers to discover and treat disease at the earliest stage possible. In general, cancers detected at earlier stages are more successfully treated, as measured by the 5-year survival rate. For example, non-small cell lung cancer detected in an early, localized stage has a 52.6% average 5-year survival rate, compared with less than 3.5% when detected after metastasis (50). Given the massive number of current and former tobacco users, screening technologies will need to be low cost, high volume, and have high sensitivity and specificity. Large-scale clinical trials now underway, such as the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial and the National Lung Screening Trial, will determine whether certain cancer screening tests reduce deaths from cancer (51, 52).

Advances in research have revealed that cancer is not one disease but, rather, more than 200 different diseases. The ability to identify the genetic and epigenetic alterations of a tumor, especially those caused by tobacco toxin exposure, provides insight into the underlying biological mechanisms that have gone awry, leading to cancer. This information can guide the rational development of therapies that are targeted to a particular type of cancer.

Modern approaches to cancer therapy take into account that cancer in one particular organ site could be one of many different molecular subtypes. Identifying a cancer by its molecular composition allows treatment to be tailored more appropriately to the individual, as occurs, for example, in people with lung cancer and epidermal growth factor receptor (EGFR) mutations (53). A related challenge is the identification of the underlying differences between individual patients, such as in their metabolic and cellular responses to therapies. A personalized medicine approach that incorporates assessments of tumor and host has the potential to improve the efficacy of treatment and reduce toxic side effects.

The AACR strongly advocates for an increase in federal investment in research on tobacco-related cancers that is

commensurate with the enormous burden of tobacco on human health. The AACR particularly encourages the following research agenda related to mechanisms of cancer induction, cancer prevention, diagnosis, treatment, and survivorship:

1. Promote research, including the development of better laboratory methods to assess the toxicologic effects of tobacco products, to understand the mechanisms of tobacco carcinogenesis in order to guide rational development of more effective approaches and therapies to prevent and treat tobacco-related cancers.

2. Improve cancer risk assessment through genetic profiles and biomarkers of tobacco exposure, effect, harms, and susceptibility in order to identify those individuals who are particularly susceptible to tobacco-induced cancers; develop risk models for individual smokers and former smokers, and the general population, as well as for users of other types of tobacco.

3. Develop cancer prevention strategies for current and former tobacco users through lifestyle and chemoprevention.

4. Develop methods for the early detection of lung and other smoking-related cancers, which may combine multiple modalities, such as imaging and biomarkers.

5. Develop novel pharmacotherapies for tobacco-related cancers that are better targeted to individual types of cancers, as well as to the molecular changes induced by tobacco exposure.

6. Promote research on nicotine enzymology and metabolism to better understand individual susceptibility to addiction and other adverse effects of nicotine.

7. Determine the effects of long-term nicotine exposure on cancer risk, cancer treatment, cancer progression, and survival.

8. Determine the underlying biological and environmental factors and comorbidities that affect tobacco-related health disparities on carcinogen metabolism and effect, cancer risk, early detection, cancer treatments, and survival.

9. Assess tobacco use, cessation attempts, and sustained abstinence in all oncology clinical trials, from registration to survival endpoints, in order to determine adverse affects of tobacco on cancer treatment, disease progression, comorbid events, and survival.

10. Assess the impact of continued tobacco use on cancer treatment, cancer progression, and survival.

11. Establish a national surveillance system to fully comprehend the impact of tobacco use on cancer and health.

12. Establish a communication infrastructure to disseminate research advances on the biology of cancer and to convey the tremendous potential for research to improve public health.

Conclusions

Tobacco use in any form is one of the strongest threats to public health around the globe, with the burden disproportionately borne by the poor, minorities, and the underserved, and by those in developing countries. Tobacco use causes 18 different cancers, as well as heart disease, stroke, and other serious health problems. Millions of lives are lost every year because of tobacco use. The morbidity and mortality related to tobacco use also extracts a heavy economic toll through medical costs and loss in productivity. Thus, reducing tobacco use and advancing the prevention, early detection, and treatment of tobacco-related disease would have a profound impact on public health. Research has identified a number of strategies that have led to important progress, yet this success remains small compared with the complex and multifaceted problems caused by tobacco use. New methods, technologies, communications, and the global call for governmental regulation hold the promise for increased strides in reducing tobacco use and disease. With the recent enactment of the Family Smoking Prevention and Tobacco Control Act in the United States and the growing number of countries ratifying and implementing the WHO Framework Convention on Tobacco Control, there is an unprecedented opening to promote vigorous efforts to (1) enforce existing laws and evidence-based policies with greater vigor; (2) invest in more research to understand initiation, addiction, and biological, clinical, and public health impacts of tobacco use in order to inform effective control measures; and (3) promote evidence-based policies to stem tobacco use around the world through research, education, and communication in collaboration with all significant stakeholders involved in tobacco control and public health.

Although advances must be made on many fronts simultaneously to achieve significant progress, the AACR particularly calls for the increased investment in tobacco-related research, the establishment of a science-based regulatory framework for evaluating the harms of tobacco products, the enhancement of warning labels on tobacco products with effective, evidence-based messaging, and the expansion of coverage of and access to evidence-based cessation treatments. A robust research agenda is of the utmost importance and the AACR feels that special attention should be given to research that will guide the development of new prevention programs, novel approaches to reducing the addictiveness of tobacco products (i.e., by reducing nicotine levels), and improved treatments to counter addiction and promote cessation. The AACR also strongly urges a massive research effort to understand the molecular mechanisms of tobacco carcinogenesis to provide the biological basis for improved toxicologic assessments of tobacco products; methods to predict cancer risk in individual current and former tobacco users, and for the population; novel methods for the early detection of cancer; and rational development of therapies to prevent and treat tobacco-related cancers. The AACR strongly supports the development of evidence-based tobacco control strategies and policies to reduce and eliminate tobacco-related disparities among social groups and nations. The AACR is fully committed to working

in concert with the global community to achieve a world free from tobacco-related death and suffering.

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