Clinical Cancer Research

American Association for Cancer Research

Assessing Tobacco Use by Cancer Patients and Facilitating Cessation: An American Association for Cancer Research Policy Statement

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Executive Summary

When diagnosed with cancer, patients can immediately make a meaningful positive impact on their health by stopping their tobacco use. Scientific evidence clearly shows that tobacco use in patients with cancer leads to poorer outcomes. The specific biological processes driving tobacco consumption's interference in cancer therapy are the subject of continuing research, but the evidence is clear that tobacco use in patients with cancer leads to decreased treatment efficacy and safety, decreased survival, decreased quality of life, increased treatment-related toxicity, and increased risk of cancer recurrence and second primary tumors. Data suggest that tobacco cessation can improve outcomes and survival in patients with cancer, yet full execution of evidence-based cessation interventions is infrequent in oncology settings. Therefore, both improved provision of cessation assistance to all patients with cancer who use tobacco or have recently quit and further study of the deleterious effects of tobacco use and benefits of tobacco cessation on cancer progression and treatment are needed and recommended by the American Association for Cancer Research. Progress on both fronts begins with universal assessment and documentation of tobacco use as a standard of quality cancer care regardless of treatment setting and will be further facilitated through the development of reliable, valid, and standard measures of tobacco use, incorporation of evidence-based procedures into quality and accreditation procedures, and the development of appropriate training, clinical infrastructure, and incentives for delivery of tobacco cessation interventions. *Clin Cancer Res; 19(8); 1941–8. ©2013 AACR.*

Introduction

There is a large, clear, incontrovertible and convincing body of scientific evidence establishing tobacco use as the world's leading cause of premature death. Starting with the landmark publication of the first U.S. Surgeon General's Report on Smoking and Health in 1964, a causal relationship between smoking and lung cancer was established (1). Evidence of the dangers of tobacco consumption continue to accumulate, and now there is sufficient scientific evidence to causally link tobacco use to cancers at 18 different human organ sites (2). In the United States, tobacco causes nearly 30% of all cancer-related deaths and 87% of all lung cancer–related deaths, totaling an estimated 169,000 lives lost in 2009 alone (3). The best strategy for preventing tobacco-related disease and death is never to begin using tobacco products. However, for those already using tobacco, achieving and maintaining complete abstinence is critical, as research has shown that tobacco-related morbidity and mortality risk for smokers is reduced by tobacco cessation at all ages including those more than 80 years old (4, 5). For tobacco users who have developed cancer, patients and their physicians may act as if it is too late for tobacco cessation to provide meaningful benefit. Fortunately, this is not true. Evidence presented in this statement points to the benefits that patients with cancer across the disease spectrum can experience by quitting tobacco use, including fewer treatment complications, improved effectiveness of cancer treatments, improved survival, and reduced risk of future second primary tumors. This same evidence also points to the need to focus research efforts more robustly on studying the specific effects of tobacco use and cessation in patients with cancer. Although this statement provides references to a significant body of evidence surrounding tobacco use in patients with cancer, the references contained herein are meant to be illustrative,

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doi: 10.1158/1078-0432.CCR-13-0666

as an exhaustive review of the literature is beyond the scope of this policy statement.

Evidence Summary

Effects of smoking on cancer outcomes

Several studies show that smoking has an adverse effect on cancer treatment outcomes. Analysis of long-term survival in a cohort of 5,185 patients with cancer showed that smoking at the time of diagnosis significantly decreased overall and disease-specific survival in the overall cohort relative to former or never smokers (6). A meta-analysis of smoking and cessation on patients with early-stage lung cancer confirmed that smoking significantly decreased disease-free survival and overall survival while increasing the risk for developing second primary tumors (7). A recent analysis of 4,200 patients from a prospective National Comprehensive Care Network database found that continued smoking also decreased survival in advanced patients with lung cancer (8). Similar findings are also noted in patients with head and neck cancer. Browman and colleagues (9) found that smoking during radiotherapy or chemoradiotherapy for head and neck cancer significantly reduced survival; however, patients who quit 12 weeks before treatment did not have significantly reduced survival. A recent analysis from a randomized phase III trial of radiotherapy or chemoradiotherapy found that current smoking during treatment significantly decreased disease-specific and overall survival in patients with head and neck cancer, and that smoking substantially worsened the otherwise favorable prognosis of human papillomavirus-driven head and neck cancer (10).

The adverse effects of smoking are not limited to disease sites traditionally associated with tobacco, such as lung or head and neck cancer. Smoking also increases cancer-specific and/or overall mortality in patients with breast, prostate, colorectal, esophageal, cervical, endometrial, bladder, and ovarian cancer and leukemia and lymphoma (6, 11–21). Moreover, smoking by patients with cancer increases their risk of developing new cancers at other sites. For example, patients with Hodgkin disease who smoke have a substantially enhanced risk of developing lung cancer after chemotherapy and/or radiotherapy (22), as do survivors of breast cancer who continue to smoke (23).

Smoking is also associated with increased risk of treatment complications, treatment-related toxicity, decreased quality of life, and decreased adherence to treatment. Smoking increases surgical complications such as infection, pulmonary complications, poor wound healing, anastomosis failure, return to the operating room, and 30-day mortality (24–26). Smoking also increases side effects from nonsurgical therapy. Analysis of 3,489 patients with cervical cancer treated with radiotherapy found that current smoking increased the risk of rectal, bladder, and small bowel complications (27). Notably, in 836 patients with prostate cancer treated with radiotherapy, smoking following treatment was associated with increased risk of diarrhea, abdominal cramps, defecation urgency, and sensation of incomplete emptying, but quitting tobacco use after radiotherapy eliminated these risks (28). Another study found that across cancer sites, continued smoking among patients with advanced cancer was associated with greater pain severity and interference with normal activities due to pain, but among former smokers pain severity was diminished with increasing time since smoking cessation (29). Drug metabolism has also been found to be affected by smoking status, as is the case with erlotinib, a chemotherapy drug used for patients with lung cancer. For instance, one study found that serum drug levels of erlotinib in smokers were significantly lower than those of nonsmokers (30). Smoking is also associated with poorer adherence to cancer-related treatment regimens. In the National Surgical Adjuvant Breast and Bowel Project P-1 breast cancer prevention trial of tamoxifen versus placebo, current smoking was associated with poorer adherence to assigned therapy (31). Thus, patients with cancer who smoke may experience treatment-related toxicity without receiving the full benefit of therapy. At the same time, cessation may reduce the adverse effects of tobacco on treatment toxicity.

Other health consequences of continued smoking among cancer patients

The health consequences of tobacco smoking are not limited to cancer outcomes. Smokers of any age remain at increased risk of all-cause mortality (4), and this association holds regardless of cancer diagnosis. Thus, among patients with cancer, decreased overall survival is also related to significant risks associated with the development and progression of cardiovascular and other non–cancer-related diseases caused by smoking. These consequences are most apparent and important in patients with "potentially highly curable" cancers because non–cancer-related mortality may dominate survival patterns. For example, among 7,425 breast cancer survivors with at least 10 years of survival and 17.7 median years of follow-up, current smoking increased the risk of both myocardial infarction and congestive heart failure (21). Notably, radiotherapy alone had no significant effect on the risk of developing heart disease, but risk from radiotherapy became significant when combined with current smoking. Similarly, in a study of 2,707 patients with testicular cancer with at least 5 years of survival and 17.6 years of median follow-up, smoking at or following diagnosis increased the risk of cardiovascular disease as well as secondary malignancy (32). In an evaluation of tobacco use from 5,366 patients with prostate cancer in the Health Professionals Study who completed structured questionnaires every 2 years, smoking at diagnosis was associated with an increased risk of not only prostate cancer death but also cardiovascular death and death from any cause (15). Importantly, in a cohort of 1,354 patients with prostate cancer treated using brachytherapy, cardiovascular disease was the primary cause of death, whereas prostate cancer was only responsible for 8.7% of deaths (33). In this cohort, current tobacco use significantly increased the risk of death from cardiovascular disease, cancers other than prostate cancer, and death from other causes. In another study, continued smoking after a colorectal cancer diagnosis

increased the risk of developing diabetes, hypercholesterolemia, and ischemic heart disease (34).

Effects of smoking cessation on cancer outcomes

Although in the general population smoking cessation is beneficial at any age (4, 35), to date there is relatively little direct evidence on the effects of smoking cessation upon cancer treatment outcomes. However, 2 reviews suggest that smoking cessation may improve outcomes in patients with lung cancer and bladder cancer (7, 36). Moreover, a recent study found that patients with lung or head and neck cancer who quit tobacco use within 12 months before a cancer diagnosis had improved survival as compared with current smokers (6). A recent analysis of the Radiation Therapy Oncology Group-9003 dataset suggested that, at a median of 32 days after completion of radiotherapy, patients who were not current smokers during radiotherapy had better survival than current smokers during radiotherapy, suggesting that cessation even after diagnosis may improve survival (10). However, as detailed by Land (37) in a recent editorial, evidence of the effects of tobacco and cessation is limited by a reliance on retrospective nonstandardized tobacco use information, lack of formal tobacco use definition, lack of longitudinal follow-up data, assessment of cigarette use only, and inadequate information to assess tobacco cessation and timing around the diagnosis and treatment. Measures that have typically been used are those designed for the general population, and might not distinguish between cessation just before the start of therapy versus cessation after the start, or relapse during or after therapy. These distinctions are necessary to determine the clinical significance of tobacco use during therapy. In addition, data suggest that patients with cancer who are smoking may misrepresent tobacco use (38, 39). The importance of biochemical confirmation is exemplified by Marin and colleagues (25), who found that self-reported assessment of tobacco use did not correlate with poor wound healing, but biochemical confirmation of tobacco use significantly predicted poor surgical outcome in patients with head and neck cancer. Therefore, the adverse effects of smoking observed in the literature may underrepresent the true effects. Improving assessment of tobacco use and cessation support is necessary to improve the understanding of the temporal ordering of events and quantitative effects of tobacco use and cessation on cancer treatment outcomes. Already, several studies suggest that smoking cessation can result in an increased likelihood of reversal of lung premalignancy (40) and a reduction in annual incidence of second primary tobacco related cancers in head and neck cancer survivors (41).

Emerging data suggest that nicotine may have an effect on cancer treatment. Preclinical studies suggest that nicotine may impair the therapeutic effects of chemotherapy and/or radiotherapy *in vitro* and in an animal model (42–44). Nicotine and nicotinic metabolites can activate nicotinic acetylcholine receptors and beta-adrenergic receptors in both cancerous and noncancerous tissue, promoting a more aggressive tumor phenotype that is less responsive to cancer treatment (45). Although nicotine may be one mechanism by which tobacco decreases therapeutic response, removal of nicotine from cigarette smoke does not prevent the tumor-promoting activities of tobacco (46), and nicotine itself does not seem to increase risk for the development of lung cancer (47). These facts illustrate that compounds in tobacco may modulate therapeutic response, leading to failure of cancer treatment, but they do not preclude the use of nicotine replacement for patients with cancer. The authors are unaware of any studies that have evaluated the effects of nicotine replacement on therapeutic response or survival in patients with cancer. In addition, nicotinic receptor-based pharmacotherapies are also proven cessation aids that eliminate the diverse other chemicals in tobacco smoke (48). Future research is necessary to understand fully the impact of cessation pharmacotherapies on cancer patients in active treatment, but currently, the use of U.S. Food and Drug Administration approved pharmacotherapies (varenicline, nicotine replacement therapy, and bupropion) continues to be recommended as an important and effective tool to support long-term tobacco cessation (49).

Other benefits of smoking cessation by cancer patients

The benefits of smoking cessation extend beyond physical health. In general, and even though these relationships may not be causal, smokers report greater stress, poorer mood, and lower health-related and overall quality of life than nonsmokers (50, 51), and quitting smoking seems to improve these dimensions in the long term (50–54). The inverse association between smoking and quality of life has also been found in patients with cancer as well as caregivers for patients with cancer (55–59). Thus, quitting smoking is not only likely to increase the longevity of patients with cancer but may also be associated with improved emotional and physical functioning during their remaining life. Of course, regardless of cancer status, smoking cessation has economic benefits in terms of monetary savings related to tobacco purchases, health, and insurance expenses (60) and secondary expenses such as costs of cleaning smoke residue from home, automobile, and clothes. Although smokers tend to have smaller social networks than nonsmokers (49), a social benefit of quitting includes reduced exposure of family members and other contacts to the harmful effects of one's secondhand smoke (61). Indeed, quitting smoking is an opportunity for patients with cancer to exert control over their health and life during a period when one's sense of control is often deeply challenged (62, 63).

Current State of Tobacco Assessment and Treatment

As of 2010, the majority of current tobacco users, nearly 69%, reported a desire to quit, and more than 52% had made an attempt over the past year (64). Unfortunately, most cessation attempts are made without evidence-based pharmacotherapy or counseling support. Without that support, quit attempts result in successful smoking cessation only 4% to 7% of the time in the general population (49).

Although certain highly motivated groups, such as lung and head and neck cancer survivors, experience short-term tobacco cessation rates as high as 70% immediately following cancer diagnosis (65), long-term relapse of this group can be as high as 50% and typically occurs within 1 to 6 months after cessation (65–67). Another highly motivated group includes individuals who are seeking or have expressed interest in lung cancer screening information; this group assigns a greater risk to smoking and has been found to be more receptive to acceptance of cessation support and to show higher rates of short-term quitting (68, 69).

The U.S. Department of Health and Human Services Public Health Service (PHS) has developed an evidence-based cessation intervention model known as the "5 A's": (i) Ask about tobacco use at every clinic visit, (ii) Advise to quit, (iii) Assess interest in quitting, (iv) Assist by providing counseling and pharmacotherapy, and (v) Arrange follow-up (49). Adherence to these guidelines has been shown to dramatically increase rates of successful quitting as compared with unsupported attempts, with interventions as short as 3 minutes making a difference both in the likelihood to initiate a cessation attempt and the cessation success rate (49). The model is sometimes simplified to a 3-step model: (i) Ask, (ii) Advise, and (iii) Refer, with referral of the tobacco user to a telephone quitline or dedicated cessation support staff equipped to carry out the remaining 3 A's (70). Although referral to a dedicated cessation support staff may be an option, the Ask, Advise, Refer model lacks an evidence base for patients with cancer. Evidence-based recommendations support the active participation of clinicians in tobacco cessation assistance through repeated assessments, counseling, and pharmacologic support when necessary (49).

The PHS tobacco treatment guidelines are endorsed by key oncology professional societies, including the American Association for Cancer Research (AACR; ref. 71), the American Society of Clinical Oncology (72), and the Oncology Nursing Society (73). In addition, aspects of the guidelines have been included in the Joint Commission standards and the Medicare "meaningful use" incentive program that pays hospitals and providers for the use of electronic medical records systems (74). Despite universal acknowledgement of the efficacy of the PHS guidelines and their importance, they have been poorly implemented in both primary care and oncology settings. With 70% of smokers visiting a primary care physician annually, there are high numbers of intervention opportunities; yet less than 40% of smokers depart from their physician visits having been offered evidence-based cessation assistance (49). In the oncology setting, the National Cancer Institute (NCI) Cancer Centers are widely viewed as exemplars of high-quality, evidence-based cancer care. However, only 38% of surveyed centers record smoking as a vital sign, and less than half have dedicated tobacco cessation personnel (75). In contrast, 78% of the same centers have personnel dedicated to nutrition.

A survey of individual oncologists in a wide variety of treatment settings indicated that whereas 61% reported providing smoking cessation services, only a third of the same individuals reported having general training in cancer prevention (76), with other studies suggesting that less than 10% of providers have specific training in smoking cessation (77). In a similar survey of nurses, 73% self-reported providing some degree of cessation interventions, but questions about each of the 5 A's indicated suboptimal adherence to PHS guidelines (66). Across different types of health care providers, "Ask" and "Advise" are the most commonly implemented steps, with evidence indicating much poorer performance on the remaining steps. For example, only a third or fewer smokers are typically provided with pharmacologic support by their providers, which is a level of performance that can be improved through training (66, 78–80). The reasons offered for the poor execution of evidence-based cessation strategies include lack of proper resources, lack of institutional incentives, and low provider awareness and education (81). A recent large survey from 1,500 members of the International Association for the Study of Lung Cancer evaluated practice patterns, perceptions, and barriers to implementing tobacco cessation for cancer patients (82). Although more than 90% of respondents felt that tobacco affects cancer outcomes and that tobacco cessation should be a standard part of cancer care, only 40% discussed medications or provided active cessation support. Respondents suggested that clinicians needed more education, but the dominant barriers to cessation were perceived inability to get patients to stop using tobacco and patient resistance to cessation interventions (82). Systems-level changes on the part of hospitals and health systems are effective in reducing smoking prevalence and smoking-related physician visits (83) and have been identified as a necessary step to successfully mitigate the negative impacts of tobacco (49, 74, 84).

The cancer clinical trials system is designed to test the safety and efficacy of new cancer therapies that are intended to lengthen and improve the lives of patients with cancer, and although most clinical trials are not specifically designed to probe the effects of tobacco use on therapeutic effectiveness, direct and indirect negative effects of tobacco use have the potential to confound the results of clinical research. Most clinical trials are unable to quantify tobacco's specific confounding effects on a given trial's results due to a lack of tobacco use assessment as part of the trial protocol (85). A survey of 155 NCI Cooperative Group trials indicated that as few as 29% of registered trials assessed any form of tobacco use in accrued patients at the point of enrollment and even fewer recorded current smoking status (86). The proportion of trials that collected tobacco use data at patient follow-up was under 5%. In addition to testing new cancer therapies, the cancer clinical trials system also serves as the care delivery system for thousands of patients annually and is typically thought of as an exemplar of high-quality patient care. Clinical trials, therefore, represent another avenue for providing cancer patients who use tobacco products with cessation support if they are not receiving such support elsewhere. The same survey noted above indicated

that none of the 155 studied trials evaluated nicotine dependence or interest on the patient's part in quitting as part of the registered trial protocol (86), which is widely considered standard-of-care treatment for tobacco users (49). These findings indicate that underappreciated opportunities already exist to collect critical data on tobacco, which has been labeled as the "missing drug interaction" (85).

Conclusions

Tobacco use is the single largest preventable cause of cancer, leading to 30% of all cancer-related deaths (3). Continued tobacco use after cancer diagnosis negatively affects treatment efficacy and patient outcomes, and there are multiple important benefits from smoking cessation. These findings emphasize the critical importance of integrating evidence-based tobacco dependence treatment into all oncology health care delivery. Unfortunately, at present there is a paucity of dedicated cessation treatment programs in or associated with oncology settings. As a result, clinical provision of the 5 A's often does not progress beyond "Ask" and "Advise."

Furthermore, despite evidence that tobacco use can affect multiple health outcomes in patients with cancer, clinical trials rarely evaluate tobacco as a confounding factor. Without widespread, rigorous assessment of tobacco use in clinical trials, scientific questions pertaining to different populations of patients (based on demographic and clinical characteristics) and therapeutic modalities will persist. Even when the primary researcher does not evaluate the effect of tobacco use on trial outcomes, robust data collection allows later pooling of data and meta-analysis that may elucidate potential mechanisms of change and specific populations or conditions that are more or less amenable to treatment.

Recommendations

On the basis of the evidence presented in this policy statement, we recommend taking concrete steps to improve the assessment of tobacco use and provision of evidence-based cessation treatment for patients with cancer. Recognizing that institutional change takes time and effort and is constrained by competition for available resources, we provide the following principles to guide near-term policy changes that will enable progress toward the goal of reducing the adverse effects of tobacco on patients with cancer and supporting all patients with cancer in their tobacco cessation efforts.

1. Patients with cancer from all clinical settings, participants in therapeutic cancer clinical trials, and cancer screening patients who use tobacco or have recently quit (past 30 days) should be provided with evidence-based tobacco cessation assistance. Ideally, that assistance capacity should be within or associated with the oncology practice. Even if the assistance is provided through an external service, the cancer patient's oncology service provider should assume responsibility for ensuring that the patient receives appropriate care. That capacity can also be supplemented by telephone cessation quitlines in all 50 states that can be reached via a common toll-free telephone number (800-QUIT-NOW).
2. Tobacco use should be comprehensively and repeatedly documented for all patients so that the confounding effects of tobacco on cancer treatment, disease progression, comorbid events, and survival can be evaluated in all oncology clinical trials, from registration to survival endpoints, and in all clinical cancer settings.

To provide all patients with tobacco cessation assistance and facilitate improved research into the confounding effects of tobacco, the following objectives should be pursued:

a. Universal assessment and documentation of tobacco use by cancer patients in all clinical settings, participants in therapeutic cancer clinical trials, and cancer screening patients;
b. Development of universal standards for measurement of tobacco use and exposure in clinical and research settings;
c. Incorporation of evidence-based tobacco interventions into review criteria used by research and health care quality and accreditation bodies; and
d. Recognition and support of the value of tobacco cessation interventions by health systems, payers, and research funders through provision of appropriate incentives for infrastructure development and intervention delivery.

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Disclosure of Potential Conflicts of Interest

The AACR takes great care to avoid any potential or actual conflicts of interest that may emanate from a personal, professional, or business interest of a member of the Writing Committee. Conflict of interest statements from the Writing Committee were obtained and are on file with the Association. The following financial relationships were disclosed: B.A. Toll received commercial research grants and support in excess of $10,000 from Pfizer for medicine only; T.H. Brandon received commercial research grants and support in excess of $10,000 from Pfizer; R.S. Herbst received consultant fees in excess of $10,000 from Biothera, Diatech, and Quintiles and less than $10,000 from N of 1. No potential conflicts of interest were reported by the other authors.

Acknowledgments

The Tobacco and Cancer Subcommittee of the Science Policy and Government Affairs (SPGA) Committee oversaw the development of this Policy Statement, which was prepared by a Writing Committee. The statement was reviewed by the AACR SPGA Committee and approved by the AACR Board of Directors on March 12, 2013. The Tobacco and Cancer Subcommittee thanks Drs. Neal Benowitz, Sonia Duffy, Michael Fiore, Patricia Ganz, Stephen Hecht, Caryn Lerman, Jamie Ostroff, Elyse Park, and Nancy Rigotti for providing insightful comments on the statement. The Tobacco and Cancer Subcommittee is grateful to Dr. William S. Dalton, Chairperson of the AACR SPGA Committee, Dr. Frank McCormick, AACR President, and Dr. Margaret Foti, AACR CEO, for their guidance and support of the Tobacco and Cancer Subcommittee. Special thanks are extended to Drs. Mark Fleury, Jennifer Hobin, and Pamela Bradley of the AACR for research, organizational support, and editorial assistance.

Received March 8, 2013; accepted March 12, 2013; published OnlineFirst April 9, 2013.

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