

Tobacco Use in the Oncology Setting: Advancing Clinical Practice and Research

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Abstract

Although tobacco is a well-established causal agent for many human cancers, less emphasis has been placed on translating this evidence by evaluating the effects of continued tobacco use after a cancer diagnosis. A broad assessment of the effects of continued tobacco use demonstrates that tobacco increases cancer treatment toxicity, recurrence, second primary tumors, and mortality in patients with cancer. Few studies report the potential benefits of cessation after a cancer diagnosis, but data suggest improved treatment outcomes in patients with cancer who quit smoking. Improving tobacco cessation treatment efficacy and access to cessation support has been sparsely researched in the oncology setting compared with the general population; however, patients with cancer are receptive to standard evidence-based tobacco cessation guidelines. Several studies demonstrate moderate tobacco cessation success in patients with cancer using the general principles of evidence-based tobacco cessation support. Several systems-level issues and research efforts are needed to standardize tobacco use definitions, increase access to tobacco cessation support, improve tobacco cessation efficacy, understand the time-dependent effects of tobacco and cessation on cancer biology, and realize the potential benefits of tobacco cessation for patients with cancer. *Cancer Epidemiol Biomarkers Prev*; 23(1); 3–9. ©2014 AACR.

Introduction

Over the past 50 years, tobacco use has been increasingly identified as a causal agent for multiple health conditions and a variety of human cancers (1). Several reports have discussed the need to incorporate standardized tobacco assessments and cessation support into clinical cancer care (2–6), but proportionately little research and clinical emphasis has been placed on the adverse effects of continued tobacco use after a cancer diagnosis. However, emerging literature documenting the adverse effects of continued smoking has now led to the next critical steps in translating these findings to practice. This article will provide a broad overview of the following in the oncology setting: (i) summary of the adverse effects of continued tobacco use and the benefits of cessation; (ii)

systems issues, including provider behavior, availability of tobacco cessation treatment for oncology patients, and tobacco assessment in clinical trials and clinical practice; and (iii) tobacco cessation treatment, including best practices. This article will further discuss important areas of needed research.

Adverse Effects of Continued Tobacco Use and the Benefits of Cessation

Several lines of evidence support the conclusion that continued tobacco use by patients with cancer decreases the effectiveness of cancer treatment and increases cancer treatment toxicity. A full review of the effects of smoking on patients with cancer is beyond the scope of this article, but the purpose of this discussion is to introduce evidence elucidating several observed effects of smoking on outcomes in patients with cancer. For the purpose of this discussion, the effects of smoking will be emphasized because the overwhelming majority of patients consume cigarette smoke as a primary form of tobacco use and there is almost no literature reporting the use of alternative forms of tobacco on outcomes for patients with cancer. The reader should also consider that the overwhelming majority of studies that report on associations between tobacco use and outcome in patients with cancer unfortunately utilize nonstandardized tobacco assessments, highly variable definitions of tobacco use, and most collect tobacco use information from retrospective medical chart reviews. As a result, the effects of smoking reported in the literature likely underestimate the true effects of smoking on cancer outcomes.

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Evidence demonstrates that a history of ever smoking is associated with an increased risk of overall mortality (7–11) and that the effects of current smoking may be greater than a history of former smoking (12–16). Studies have shown that current smoking increases mortality in patients with tobacco-related diseases (17–19) as well as traditionally nontobacco-related diseases (14, 20–23). The adverse effects of smoking on mortality have been noted in both early-stage patients with cancer (18, 24) as well as advanced-stage patients (25, 26). Notably, smoking increases the risk of both cancer- and noncancer-related mortality. Clinicians may view the effects of smoking as pertinent to tobacco-related diseases, such as head/neck or lung cancer; however, smoking may be extremely important to consider for mortality risks in disease sites, such as prostate cancer. For example, a study of patients with prostate cancer demonstrates that most died from causes other than prostate cancer and smoking substantially increased the risk of mortality from non-prostate cancer causes (27). In summary, the adverse effects of smoking on mortality seem to be important to consider regardless of disease site or stage.

Smoking has been shown to increase toxicity associated with cancer treatment. In a recent large assessment of more than 20,000 gastrointestinal, pulmonary, and urologic patients with cancer, current smoking increased the risk of surgical site infection, pulmonary complications, and 30-day mortality after surgery (13). Several other studies demonstrate that current smoking increases surgical toxicity in several disease sites (28–30). Current smoking increases acute and long-term toxicity associated with chemotherapy and/or radiotherapy (31–34) and the effects of smoking may be higher with increased cigarette use (33). Importantly, studies have shown that approximately 30% of cancer patients, who are smokers, may misrepresent true tobacco use (35, 36). Marin and colleagues demonstrated that a serum cotinine concentration greater than 10 ng/mL was associated with a 2-fold risk of wound complications in patients with head and neck cancer undergoing flap reconstruction, compared with a lower cotinine concentration; however, self-reported smoking status was not significantly related to the relative risk of wound complications (37). Consequently, smoking may have a more pronounced effect than is reflected in the literature based upon self-reported assessments alone.

The effects of smoking have not been clearly defined in patients with cancer and may have some interaction based upon dose, patient variables, and treatment. A higher risk for mortality has been observed in patients with cancer, who are heavier smokers (38–41). The risks of smoking may be modified by obesity (42) or alcohol (43). Data suggest that current smoking may increase mortality in men in disease sites, such as leukemia, lung, and head/neck cancer, with a lesser or nonsignificant effect in women (16). However, most studies have not evaluated the effect of current smoking in men versus women. As noted above, smoking increases the risk of adverse events regardless of cancer treatment modality. Smoking may

also interact with cytotoxic cancer therapy to increase the risk of recurrence or second primary cancer. Whereas several studies demonstrate that smoking increases the risk of developing a second primary cancer (18, 44–46), heavier smokers after a cancer diagnosis may have a higher risk (47). Furthermore, smoking combined with radiotherapy or chemotherapy may act in synergy to enhance risk for developing a second primary cancer (48–50). Several questions remain about the detailed effects of smoking on outcomes for patients with cancer as related to cancer biology, gender, treatment modality, clinical characteristics, and other health behaviors.

Perhaps most relevant to the treatment of patients with cancer is a discussion supporting the role of smoking cessation in improving cancer treatment outcomes. Data support the conclusion that recent tobacco cessation before a cancer diagnosis improves survival (16, 51). Data also demonstrate that cessation for as little as 2 to 3 weeks may improve surgical complications or associated mortality in patients with cancer treated with surgery (30, 52). Smoking cessation after diagnosis is associated with a decreased risk of hospitalization and toxicity (53). Patients with lung cancer who quit smoking at or following diagnosis had a decreased risk of overall mortality (54) and improved performance status (55). Breast cancer patients who quit smoking by the most recent follow-up after cancer had a reduced risk of developing a second primary contralateral breast cancer (56). Smoking cessation decreased the risk of abdominal toxicity following radiotherapy for prostate cancer (31). In one study of patients with head and neck cancer, who smoked during treatment, radiotherapy delivered in the morning was associated with decreased mucositis compared with treatment in the afternoon, suggesting that some of the effects of smoking may be acutely reversible (due to patients not smoking overnight; ref. 57). Unfortunately, there are very few studies that report the effects of tobacco cessation following a cancer diagnosis and much work is needed to clarify the benefits of cessation as related to cancer treatment outcomes.

Systems Level Issues

Though several studies demonstrate that tobacco use is associated with poor therapeutic outcomes, data suggest that many oncology providers do not provide regular assistance to cancer patients to stop smoking. A survey of 601 urologists demonstrates that 56% never discuss cessation, 73% never prescribe medications, and 68% never recommend cessation support for bladder patients with cancer (58). A randomized trial of usual care versus physician led cessation for patients with cancer demonstrated that 56% recommend quitting, but only 35% discuss health benefits of quitting, 5% help to set a quit date, 17% provide materials to help quit, and 19% provide a nicotine prescription to quit (59). In 2 recent large surveys of more than 1,500 members of the International Association for the Study of Lung Cancer (60) and nearly 1,200 members of the American Society for Clinical Oncology

(ASCO; ref. 61), approximately 90% of oncologists believe tobacco use affects cancer outcome and that cessation support should be provided to patients with cancer, but only approximately 40% provide assistance to help patients quit smoking. These findings of poor tobacco cessation support have also been observed in several surveys of patients with cancer (62–64). Moreover, a recent analysis of active National Cancer Institute-funded cooperative group clinical trials demonstrates that only 29% have any form of tobacco assessment and none provide tobacco cessation support (65). As a result, patients with cancer are not receiving necessary cessation support and most clinical trials, which represent cutting-edge oncology research, will not provide critical insight into the potential effects of tobacco on cancer treatment outcomes. These discouraging trends demonstrate that much systems-level work is needed to improve tobacco assessment and access to tobacco cessation support for patients with cancer.

Recent recommendations by the American Association for Cancer Research (66) and ASCO (67) have emphasized the need to promote tobacco assessment and cessation for patients with cancer. Included in these recommendations are standardized tobacco use assessments, evaluating tobacco use at diagnosis, during treatment, and at follow-up, and routine tobacco cessation support for patients with cancer. With increasing access and utilization of electronic medical records and evidence-based medicine, increasing access to tobacco cessation support for patients with cancer through standardized automated systems has become more feasible. A recent study suggests that a mandatory assessment and cessation program for patients with cancer can provide service to a high proportion of patients with cancer and that nearly all patients are receptive to cessation support (68). However, systems-level support will require active participation by clinicians as well as healthcare organizations, including health insurers, healthcare institutions, departments, and healthcare providers from multiple disciplines. At the same time, delivering a consistent level of tobacco cessation support may manifest a clinical benefit to all patients with cancer regardless of tumor site, stage, or treatment.

Tobacco Cessation Treatment

In-depth reviews of smoking cessation research in oncology populations have revealed surprisingly few significant treatment effects compared with usual care or minimal advice condition (5, 69). The studies have been affected by a variety of adverse methodological factors, including barriers to recruitment, retention, sample diversity, insufficient power to detect statistical differences, and reliance upon self-reported cessation. Considering the reasons for the lack of significant outcome effects that might go beyond methodological issues, several observations emerge. The "natural" cessation rate of patients following cancer diagnosis varies most strongly with disease site (smoking-related tumors are associated with higher quit rates). Such patients have shown high rates of

interest in quitting (70) compared with the general population. Observational studies have reported cessation rates between 50% and 65% in surgically treated patients at 1-year follow-up among early-stage non-small cell lung cancer patients (71, 72). Although we may lament that 35% of these patients may continue to smoke at 1 year, such quit rates are extraordinarily high compared with the general population, and even to intensive interventions featuring state-of-the-art behavioral and pharmacologic therapy with continued smoking rates as high as 70% (73). Thus, elevated motivation, the "teachable moment," whatever advice is delivered by oncology providers, and the powerful impact of surgery, radiation, and chemotherapy may all contribute to higher long-term cessation rates than in a healthy population. Relapse often occurs at intervals of 1 to 6 months as well as past 1 year, which is delayed in time compared with healthy adults (74, 75), but this is well within the time frame of traditional cancer care and follow-up, during which oncology providers can continue to maintain active cessation support.

Many reports have identified multiple characteristics of patients with cancer who smoke and the change process related to tobacco consumption among this population. In patients with head/neck and thoracic cancer, those who were younger, had an earlier stage cancer, or were living with another smoker were more interested in smoking cessation treatment, and patients preferred individualized treatment (62). Patients enrolled in a cessation program have a high prevalence of depressive symptoms, low self-confidence about quitting, low perceived risk of health problems, and low perceived benefits from smoking cessation; however, patients characterized by a shorter time since diagnosis, lower tobacco use and nicotine dependence, higher perceived risk of smoking, and higher perceived benefit of quitting were more motivated to quit (76). Other studies have shown that higher rates of smoking cessation were associated with higher levels of counterconditioning and reinforcement management, lower levels of self-reevaluation, female sex, higher baseline health, lower nicotine dependence, surgical treatment (as opposed to radiotherapy), being non-Caucasian, and being in an "action" stage of change (71, 77, 78). However, lesser readiness to quit, higher nicotine dependence, higher cravings, lower education, younger age of initiation, higher level of pain, and smoking cessation less than 6 months before surgery have been associated with higher rates of relapse (75, 79, 80).

The earliest randomized trial of an oncology-focused smoking cessation intervention was conducted on patients with newly diagnosed first primary squamous cell carcinomas of the head and neck (75, 77). In many ways, it was a model project that presaged many of the key issues that have arisen in the treatment of tobacco dependence among patients with cancer. The intervention condition consisted of an individualized treatment plan featuring personalized, provider-delivered advice to stop smoking at diagnosis along with a quit date contract, 3 specialized booklets covering issues of cessation, relapse

prevention and social support by family/friends, and booster sessions through 6-month follow-up. The usual care condition (minimal advice) was standardized across providers. All advice was delivered by a head and neck surgeon or dentist (maxillofacial prosthodontist) with periodic provider training sessions to maintain fidelity of the intervention. Using self-reported and biochemically confirmed assessments, the continuous abstinence rate was 70% at 12 months for all patients completing the trial. Notably, recent quitters were included in the study, but sustaining a successful quit attempt is vitally important for patients with cancer. Many of these patients were considered difficult to treat because many had comorbid alcohol use, were from a lower socioeconomic status (SES), and enrolled at a time in which most patients smoked up to the time of diagnosis and were less exposed to the public health messages and antitobacco regulations that are more prevalent today. In this model that included the oncology healthcare provider, most patients were very responsive to advice and treatment; notably, more recent studies confirm that patients with cancer may be highly receptive to cessation treatment when presented with similar principles (68).

Implementing Best Practices

The USPHS Clinical Practice Guideline for the Treatment of Tobacco Dependence (81) provides best practice standards for treating tobacco dependence, based on meta-analysis and consensus determinations. To date, the literature has not demonstrated that any program format or content is superior for the treatment of patients with cancer. Thus, although research is ongoing on various intervention timing and formats, pharmacologic agents, relapse prevention, and a variety of tailoring strategies, the programs currently operating at several leading cancer centers (MD Anderson, Memorial Sloan Kettering, Roswell Park, Yale, etc.) are our best strategies in this era. What we suffer from is a dearth of cessation support programs, access, funding, reimbursement, and prioritization. It was observed at the 2009 Conference on Treating Tobacco Dependence at Cancer Centers that of 58 centers surveyed, only 59% offered some form of tobacco use treatment and that less than 50% had dedicated cessation support personnel (82). Motivation and commitment from oncology leadership, with accompanying resource allocation and personnel was notably lacking at that time. With the current growing acknowledgment of the critical adverse impact on cancer treatment outcomes and survival, it is imperative to raise the priority of and access to tobacco dependence treatment. Though major cancer organizations are raising awareness of this issue (66,

67, 83), much work is needed to implement recommended changes into routine cancer care.

Future Research

This article brings into perspective the potential impact that tobacco use has on cancer treatment outcomes and provides a brief review of tobacco use and cessation for patients with cancer. However, substantial work is needed to better understand how to promote effective tobacco cessation for patients with cancer and how effective cessation may alter cancer treatment outcomes. Structural elements are needed, such as standardized definitions of tobacco use, structured tobacco assessments at diagnosis through follow-up, dedicated cessation resources that can provide evidence-based cessation support, and consideration of elements such as biochemical confirmation. Significant work is needed to bring cancer biologists together with tobacco experts and clinical oncologists to specifically define the effects of tobacco on cancer biology, treatment-related toxicity, and therapeutic response. Advances are needed in understanding the time-dependent nature of tobacco cessation as related to potential improvements in cancer treatment outcomes. Finally, much work is needed to increase access to tobacco cessation support, identify mechanisms to integrate cessation into efficient clinical cancer treatment programs, and develop methods to improve tobacco cessation efficacy in patients with cancer. With dedicated access to well-designed tobacco cessation interventions, future research efforts may dramatically improve cancer treatment outcomes for a broad spectrum of patients with cancer across disease sites, stage, and treatment modality.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: E.R. Gritz, G.W. Warren, B.A. Toll
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Writing, review, and/or revision of the manuscript: E.R. Gritz, G.W. Warren, B.A. Toll
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E.R. Gritz

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