Review Article

Mitigating the adverse health effects and costs associated with smoking after a cancer diagnosis

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Abstract: Smoking after a cancer diagnosis causes adverse outcomes and is associated with substantial additional treatment cost. Mitigation of the adverse effects of smoking require active commitment from health systems, providers, and patients. Three areas of mitigation are discussed: (I) smoking cessation after a cancer diagnosis to improve cancer treatment outcomes; (II) identifying optimal cancer treatment strategies for patients who smoke at the time of diagnosis; and (III) how health systems can prioritize the effect modification caused by smoking. As innovation continues for healthcare delivery, priority should be placed on interventions that reduce the effect modification and associated costs caused by continued smoking after a cancer diagnosis.

Keywords: Smoking; tobacco; cessation; cancer; health policy; cost; health insurance; value; patient centered care

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Introduction

The past decade has seen significant progress in addressing tobacco use in cancer patients, and there is now significant evidence and support to justify resources that help cancer patients quit using tobacco, even after a cancer diagnosis. Whereas smoking has been definitively linked to the development of cancer and several other medical conditions (1), less attention had been given to whether continued smoking could affect therapeutic outcomes for patients treated for one or more medical conditions caused by smoking. In 2014, the landmark Surgeon General's Report: The Health Consequences of Smoking [2014 SGR (1)] was the first to take on how smoking affected cancer treatment outcomes. Collating the substantial work from over 400 published studies representing over 500,000 patients across virtually all cancer disease sites and treatments, the 2014 SGR categorically concluded that smoking by cancer patients and survivors causes adverse outcomes including an increased overall mortality, increased cancer specific mortality, and increased risk for developing a second primary cancer. Also included were strong associations with increased toxicity from cancer treatment. This work has since provided an irrefutable foundation for the clinical importance of smoking in the context of cancer management.

Perhaps the most significant reason why the 2014 SGR was so important relates to the fundamental question about whether addressing behavioral health is worthwhile in the management of cancer. Prior to the 2014 SGR, there was relatively little consensus around whether there was any cohesive effect of smoking across cancer. One could posit in the mind of clinicians, researchers, and administrators, "why address a patient behavior if it did not make a difference on therapeutic outcome?" A recent analysis of the incremental cost of treating cancer failure due to continued smoking after a cancer diagnosis demonstrated a $10,678 average cost per smoking patient in the United States, or potentially $3.4 billion annually across national estimates for cancer (2). The modeling provided a method of estimating costs across a broad spectrum of smoking prevalence, risk for failure due to smoking, and estimated cure rates. This allowed for estimating cost under a variety of conditions, and generally supported that the cost effects of smoking were more

pronounced for highly curable cancers than for cancers with poor cure rates. The nuance of this study is that it estimated cost specifically around cancer treatment failure, and did not include cost due to treatment for progression of other non-cancer health conditions caused by continued smoking. As a result, these costs were estimated to be conservative.

With broad risks for adverse health effects caused by continued smoking, and substantial associated costs, there are three key questions that arise in the context of smoking and cancer treatment. First, can smoking cessation prevent or reverse the adverse health and costs effects of smoking? Second, are there more effective therapeutic approaches for cancer patients who smoke at the time of diagnosis? Third, how will the health system deal with the health and cost effects of smoking in cancer care? Importantly, each of these topics requires considerable discussion across a broad set of variables that extend beyond the scope of a single manuscript. However, these are important and practical discussions that are often overlooked when considering how to address smoking after a cancer diagnosis. This manuscript will discuss these questions that are on the forefront of addressing tobacco use in cancer care.

Can smoking cessation after a cancer diagnosis improve health and cost outcomes?

Several studies have shown that smoking cessation after a cancer diagnosis can improve or prevent the adverse effects of smoking on cancer treatment outcomes. Quitting smoking after diagnosis reduced overall mortality in 321 lung cancer patients treated with surgery [HR 0.34, 95% CI: 0.16–0.71, (3)] and a similar effect was noted in a separate study of 284 limited stage lung cancer patients [HR 0.55, 95% CI: 0.38–0.79, (4)]. Quitting smoking has also been shown to improve overall survival in lung cancer patients treated with stereotactic body radiotherapy (SBRT) (5). Smoking cessation using a phone-based tobacco treatment program reduced overall mortality by 44% in lung cancer patients who quit smoking (6). The benefits of smoking cessation on overall survival have been shown across multiple other disease sites (7-9). However, the effects of cessation after a cancer diagnosis have not been fully elucidated. In three studies of breast (10), head/neck (11), and colorectal cancer (12), both smoking and quitting smoking after a cancer diagnosis were associated with increased risk of overall mortality as compared with never smoking, with no significant difference between continued smoking and smoking cessation.

The beneficial effects of smoking cessation on cancer specific mortality and recurrence have also been reported in several studies. Smoking cessation reduced recurrence and metastasis by 46% in surgically treated lung cancer patients (3) with a similar 41% reduction in small cell lung cancer (4). In other disease sites, decreased local failure has been noted in head/neck cancer patients who quit smoking (8,9,13). In a large cohort of breast cancer patients, whereas continued smoking increased the risk of breast cancer mortality by 72%, there was no increased risk for patients who quit smoking (10). Other studies have demonstrated the benefits of smoking cessation on other cancer treatment outcomes such as quality of life (14).

There are several limitations related to whether smoking cessation improves cancer treatment outcomes. There have traditionally been no standardized methods to report tobacco use or smoking cessation for cancer care (15). An abstract presented in 2014 reporting on studies from the 2014 SGR demonstrated substantial heterogeneity across tobacco use reporting in published studies (16). A recent effort by the National Cancer Institute (NCI) and the American Association for Cancer Research (AACR) developed cognitively tested items to better define tobacco use (17,18). However, it is extremely difficult to ascertain answers to the following broad questions in the context of improving cancer treatment outcomes: What is the optimal timeframe? Do patients need to quit smoking entirely or can patients reduce for smoking to a low level without quitting? If patients relapse after quitting or reducing, what effect does that have on outcome? These types of questions are further confounded when combined with smoking cessation strategies. What are the optimal smoking cessation approaches when combined with cancer care? Are in-person strategies better than phone-based strategies? How many interventions are needed and will patients participate in regular smoking cessation interventions after they have already been burdened with repeated cancer treatment visits? What patients benefit most from one approach *vs.* a different approach? Perhaps most importantly, what approaches can be implemented and sustained within the resources of a cancer treatment center?

In practical terms, the complexity of cancer care is dynamic. As an effect modifier for recurrence, toxicity, and mortality, smoking has the potential to exert effects across a complex set of patient experiences. Across these experiences, patients may very well become fatigued and not want to bother with smoking cessation. Practitioners may feel overwhelmed by clinical responsibilities, or feel poorly

equipped to deal with smoking. Analysis of reported barriers to smoking cessation from oncology providers suggest that a lack of time, education, and resources are significant for predicting assistance with quitting (19). Utilization of health records to promote smoking cessation for cancer survivors across 28 cancer centers demonstrated that less than 10% had optimal program goals or guidelines in place (20). A unique approach to defining smoking cessation in the context of cancer treatment has been framed by Djalalov *et al.* (21), who modeled smoking cessation for cancer patients in the context of best practice outcomes, baseline cessation, relapse rates, mortality risks, cancer treatment costs, and program costs. This very unique approach considered many of the practical aspects related to evaluating cost effectiveness, concluding that a best-practice smoking cessation program would be cost-effective. It is unclear how centers will be able to implement change for smoking cessation. Recent national efforts sponsored by the NCI to develop dedicated smoking cessation programs across 42 NCI Designated Cancer Centers has the potential to better refine how dedicated programs can be implemented (22). The Canadian Partnership Against Cancer (CPAC) has initiated development of smoking cessation programs across all 13 provinces in Canada (23). These efforts represent substantial national investments to help curb the adverse effects of smoking on cancer treatment, but it remains to be seen what approaches can be sustained and how these approaches can inflect meaningful change in patient behavior or cancer treatment outcomes. However, given the high incremental cost associated with continued smoking by cancer patients (2), health systems will need to balance provision of smoking cessation against the cost of inaction. It is proposed that identifying the optimal strategies to achieve smoking cessation after a cancer diagnosis should be a clinical and financial priority for health systems and patients.

Are there more effective therapeutic approaches for cancer patients who smoke at the time of diagnosis?

The fundamental question of what the optimal treatment approach for cancer patients who smoke at the time of diagnosis has not been answered. Cancer care is centered around refining therapeutic approaches to improve cancer treatment efficacy hopefully in combination with decreasing toxicity from cancer treatment. There are significant discussions around the goals of cancer care according to stage of disease and treatment, with increasing awareness that quality of life can be as important or more important than prolonging life (24,25). The fascinating conundrum around smoking and cancer care is that whereas smoking can affect a broad spectrum of cancer treatment outcomes (1), there has been relatively little effort to improve therapeutic outcomes beyond simply considering smoking cessation. In defining the optimal clinical treatment approach for cancer patients who smoke, it is critical to note that smoking and having a smoking related cancer is associated with significant stigma (26). Smoking at the time of a cancer diagnosis should be viewed as a severe addiction that can serve as a profound effect modifier for cancer treatment (1). Efforts to mitigate the health and cost effects of smoking after a cancer diagnosis should be focused on therapeutic efficacy and outcomes. Health systems, providers, patients, and researchers may need to work to overcome any stigmatization associated with smoking that would prevent this focus of optimizing therapeutic outcomes.

To exemplify the theoretical question of defining existing alternative treatment approaches for patients who smoke, the example of treatment for esophageal cancer is presented. Esophageal cancer is a particularly difficult cancer to manage in part because treatment may require a total esophagectomy and significant permanent changes in quality of life. Chemotherapy in combination with radiotherapy prior to surgery has been shown to improve survival (27), and this remains the standard of care for many patients. Alternatively, definitive chemoradiotherapy is a viable treatment option that may avoid an esophagectomy with recurrences treated using salvage surgery (28). A fundamental clinical question could be whether surgery could be avoided in patients where chemoradiotherapy has eradicated all viable tumor. Analysis of 540 esophageal or gastric cardia patients treated with surgery in Sweden demonstrated that current smoking had no effect on mortality in patients treated with surgery (29). These effects are mirrored in a study on overall survival by Shitara *et al.* who present data on 363 patients with esophageal squamous cell carcinoma (30). Though not focused specifically on current smoking, data demonstrated that a heavy smoking history (20+ PY) significantly increased overall mortality in patients treated with chemoradiotherapy (HR 2.43, 95% CI: 1.38–4.27) with no significant effect in patients treated with surgery (HR 0.88, 95% CI: 0.41–1.85). These data would point toward the suggestion that smoking has a lesser effect in esophageal cancer patients who receive surgery. If

smoking were further investigated as a critical determinant that could guide treatment for patients with esophageal cancer, then the significant comorbidity associated with surgery could be better tailored to specific patient situations. There is insufficient evidence to make any recommendation for changing management of esophageal cancer stratified according to smoking status, but the concept of choosing the optimal treatment for patients even according to smoking status should be considered.

To date, there has not been a thorough analysis of existing cancer treatments to decide whether there is a superior cancer treatment approach for patients who smoke at the time of diagnosis. Smoking does appear to have an effect on the metabolism of cancer drugs (31). Biologically, cigarette smoke and constituents such as nicotine and nitrosamines have been shown to affect therapeutic response to chemotherapy and radiotherapy in cancer cells (32-34). Collectively, these data implicate cytotoxic therapeutics, such as chemotherapy and radiotherapy, as potentially inferior in the context of cancer treatment as compared with a surgical approach when multiple treatment options are available. In contrast, data are increasingly suggesting that newly developed immunotherapy approaches, such as program death ligand-1 (PD-L1) based therapies, may be more effective in patients with a smoking history (35,36). Recent biologic data further supports connections between smoking and PD-L1 modulation (37). However, the efficacy of PD-L1 based therapies as related to smoking is still largely defined according to ever-smoking status, with less clarity around the effects of current smoking. Perhaps immunotherapy based approaches will eventually be shown to be superior approaches for patients who smoke at the time of a cancer diagnosis, but this remains largely untested at this time.

Research is desperately needed to ascertain if the adverse effects of smoking can be overcome with an existing or forthcoming cancer treatment. Addressing tobacco use in clinical practice and research has been advocated by large cancer organizations (14). Structured methods to address tobacco have been developed including standardized, annotated, and cognitively tested methods of assessing tobacco at diagnosis and follow-up (17,18). It should be relatively straightforward to collect information about smoking on patients in ongoing clinical trials. However, a study from 2012 suggested that 71% of active oncology trials did not assess tobacco (38) and a pooled analysis project to analyze the effects on smoking was terminated due to lack of usable data on tobacco (39). This unfortunate result is a clear demonstration of a lost opportunity to better define the optimal treatment strategy for patients who smoke at the time of diagnosis. Smoking affects the primary and secondary objectives of virtually all clinical trial designs including overall survival, cancer specific survival, toxicity from cancer treatment, and risk of second primary cancer (1). Ignoring smoking as a part of clinical research not only limits the ability to better define optimal treatment strategies for cancer patients who smoke, but also limits the interpretation of clinical trial outcomes.

How can health systems, clinicians, and patients deal with smoking at the time of diagnosis?

Unfortunately, there are few published discussions on this topic. Smoking after a cancer diagnosis is an effect modifier for cancer treatment outcomes (1) with significant additional incremental cost due to cancer treatment failure (2). These data justify the need to develop individual as well as system wide solutions to the adverse health effects caused by smoking. The biggest question generated by the recent analysis of the added cancer treatment costs due to smoking could be "how do we plan to pay for this?" This comment may seem insensitive in the context of selecting appropriate cancer care, but it is extremely applicable to the current healthcare system. How should resources be allocated to maximize value for cancer patients individually and across health systems? Considerations for the development of smoking cessation approaches and identifying cancer treatments that may be more effective in patients who smoke at the time of diagnosis are approaches that could improve therapeutic outcomes. However, resources and prioritization is needed for these efforts to be successful. Buy-in for a solution is required by all participants in the health system (40).

Patients should be able to easily understand the adverse clinical effects caused by smoking. Continued smoking after a cancer diagnosis increases the risk of death, increases the risk of failing cancer treatment, and increases the risk for toxicity from cancer treatment (1). This information can be easily presented to patients using patient brochures or could be delivered by videos, commercials, online, or using mobile technology. Continued smoking increases the risk of having to spend more on healthcare (2). This too could be easy to communicate, but eliciting change during the stress of a new cancer diagnosis could be difficult (41,42). Patients are fundamentally limited to the ability to make the decision to quit smoking and hope that this will result

in a more efficacious cancer treatment. Effective tobacco controls strategies in the United States over the past decades have resulted in making cigarette consumption more expensive, and quitting smoking will directly save patients money simply because they will no longer need to spend money on cigarettes (43,44). Any cost savings to be related to preventing additional health interventions would further reduce costs to patients. Patients will be unable to affect the design or delivery of cancer treatment, and will further be unable to govern health systems ability to pay for treatment. Patients will remain largely at the mercy of the health system with respect to out-of-pocket expenses. Collectively, a firm decision to quit smoking and progress toward quitting are the practical solutions patients can take to help mitigate these effects and costs.

Clinicians and providers have a broad variety of choices and responsibilities surrounding smoking by cancer patients. The full scope of options is beyond the scope of this manuscript, but several manuscripts have discussed the role of clinicians in promoting or providing assistance with smoking cessation for cancer patients (14,32,41,42,45,46). The clinician will be the direct conduit for communicating the effects of smoking and assisting patients in making value-based decisions. "Value" is increasingly recognized as the target of cancer care (47), and making clinical decisions based upon available evidence-base is certainly justified. However, others have brought to light the importance of patient-centered decision making to define value (48) that perhaps has not been captured in prior evidence-base. A patient may value continued smoking if they are not adequately informed about the adverse consequences. Clinicians are tasked with the responsibility of directly informing patients about the adverse effects of tobacco, and are further tasked with assisting patients smoking cessation as the only current potential method to reduce the adverse effects of smoking. Additionally, smoking cessation in the context of cancer care will not be 'one-size-fits-all.' The resources available to clinicians for smoking cessation are highly pertinent and lead to critical individualized decisions within a cancer clinic (14,32,49). Who will ask patients about tobacco use? Will clinicians provide cessation support or will patients be referred to a dedicated treatment program? Will patients receive medications, counseling, or both? Will documentation of smoking status and cessation be documented in the electronic health record? Will support be provided in person, by phone, or through another means? Each clinical setting or institution will likely have different clinical treatment pathways and resources to consider.

One critical aspect to consider in the context of clinicians is clinical revenue. Will treatment for smoking require billing? Though a side-by-side comparison of reimbursement for cancer care *vs.* smoking cessation has not been performed, the cost of cancer treatment and associated reimbursement far exceeds reimbursement for smoking cessation. In a study evaluating some parameters of cost-effectiveness for smoking cessation in cancer care using a Canadian based approach (21), fees for smoking cessation nurses and administration were estimated at approximately $150. Suppose a clinician provides cessation support and is unable to bill as much within a given timeframe as compared with billing for cancer treatment services. How will that lost clinical revenue affect the clinician, clinic, and medical institution where the clinic is located? The very high revenue stream produced by cancer treatment as compared with the low revenue stream produced by smoking cessation serves as a significant financial disincentive. A clinician who rightfully provides cessation support in an effort to improve health outcomes would likely be financially penalized. The solution to this dilemma has not been solved. This argument is meant to be thought provoking, and the ethical issues of comparing clinical service are far beyond the scope of this manuscript. However, readers must realize that this is a very practical, real-world situation that requires a thoughtful solution.

Health systems, including medical institutions, insurers, and government agencies, must consider broad issues related to clinical efficacy and cost. It is impossible to discuss the full spectrum of variables that could relate to mitigating the health and cost effects of smoking. Considerable effort has been made to promote smoking cessation in cancer care (14,17,20,22,23,32,40-42,45). There has been little discussion on determining the optimal cancer treatment strategy for cancer patients who smoke at the time of diagnosis, detailed earlier in this manuscript. Health systems that have access to enormous data sets on patient health, health behaviors, treatment, and efficacy have the unique opportunity to capitalize on methods to identify the mose effective treatment strategies. In the era of big data, analytics, and personalized medicine (50), smoking should be viewed as an effect modifier and interrogated to develop better treatment approaches rather than as a stigmatized health behavior (26).

The implications of decreased therapeutic efficacy and increased cost provide a unique opportunity to insurers. Dey and Bach describe the 6 functions of health insurance

in a recently published forum, including: providing financial protection to individuals, providing access for small fees, negotiating health services, increasing the quality of clinicians and hospitals, encouraging healthy behaviors, and wealth transfer (51). Should insurers add to premiums paid by patients who report smoking? Should insurers provide access to better resources for smoking cessation? After a cancer diagnosis, should insurers reach out to patients to proactively engage patients, identify tobacco use, and aggressively assist patients with transitioning off tobacco use? The latter seems most appealing to this author, but it remains to be seen if and how the adverse health and cost effects will be considered by payors. There are numerous alternative and potentially competing interests. In a profoundly forthright book, Elizabeth Rosenthal describes the business of medicine, including interesting relationship between health costs and reimbursement (52). The 80/20 rule is a requirement for insurers to spend 80% of premiums on health care costs and quality improvement and 20% on administrative, overhead, and marketing (53). In a capitalized system where insurers are expected to generate revenue growth, the only method to grow the 20% for profit margin is to also grow the 80%. Whereas this may seem insensitive, a variable such as smoking that can have broad effect modification in cancer care does require thoughtful consideration as to how to mitigate costs. Though not a part of the health system from a treatment perspective, the tobacco industry is responsible for the cause of these problems (54), and perhaps be considered as being responsible for part of the solution. Collectively, health systems have the opportunity to have the largest impact on mitigating the adverse health and cost effects of tobacco by dedicating resources toward preventing continued use and committing resources toward identifying optimal treatment strategies.

Conclusions

Smoking after a cancer diagnosis can have profound health effects leading to increased costs and morbidity for our patients. Addressing tobacco after a cancer diagnosis requires focused resources to mitigate effects. Thoughtful consideration of the magnitude of adverse effect caused by continued smoking on cancer is required, as is consideration on the burdens across other chronic medical conditions. A clear commitment from patients, providers, and health systems is needed to make progress to improve outcomes.

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Footnote

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