CLINICAL INVESTIGATION

Smoking causes adverse outcomes in cancer patients: addressing the evidence base through efficient design

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The recent release of the 2014 Surgeon General's Report (SGR) "*The Health Consequences of Smoking – 50 Years of Progress: A Report of the Surgeon General*" [1] has profound implications for clinical research and standard clinical cancer care. Presented are data from hundreds of studies in cancer patients evaluating the effects of smoking on cancer treatment outcomes using a well-established model of causality that have been used in prior SGRs over the past 50 years. Included among the many new findings from the 2014 SGR are the conclusions, in brief, that smoking [1]:

- Increases adverse outcomes in cancer patients and that quitting smoking improves the prognosis of cancer patients;
- Increases all-cause and cancer-specific mortality;
- Increases the risk of developing second primary cancers;
- Is associated with an increased risk of recurrence, poor treatment response and cancer treatment toxicity.

Whereas these findings may seem fairly obvious to some, there has never been a large evidence review on the effects of smoking in cancer patients. Thus, these conclusions essentially serve as the first large evidence base needed to address tobacco use and cessation in clinical practice and research.

Precluding the results of the 2014 SGR, both the American Association for Cancer Research (AACR) and American Society for Clinical Oncology (ASCO) released recommendations in 2013 for addressing tobacco use by cancer patients [2,3]. In general, recommendations from the AACR stipulated that all cancer patients should be screened for tobacco use at repeated intervals, all eligible patients should be provided tobacco cessation support, and that tobacco should be evaluated as a confounder or effect modifier in clinical research [2]. The updated recommendations from ASCO specifically addressed cancer patients through a commitment by ASCO to educate the oncology community and provide information that clinicians can use to integrate tobacco cessation activities into clinical practice. Guidelines by ASCO that clinicians could use to help address tobacco use by cancer patients have also been developed [4]. Unfortunately, in close proximity to the strong evidence presented in the SGR [1] and advocacy by leading cancer organizations [2–4], data demonstrates that significant work is needed to implement tobacco cessation practices into standard clinical care. Two large surveys conducted by ASCO [5] and the International Association for the Study of Lung Cancer (IASLC) [6] demonstrated that approximately 90% of oncologists believe that tobacco affects cancer outcomes and approximately 90% ask about tobacco use, but fewer than half provide tobacco cessation support.

A recent report from the ASCO Cancer Research Committee discussed the need to develop clinically meaningful outcomes in clinical trials [7]. This much-needed discussion proposed the need to achieve 20–40% reductions in hazard ratios (HRs) in order to achieve a clinically meaningful outcome.

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As detailed in the 2014 SGR, across all disease sites and treatments current smoking increased the risk of overall mortality with a median HR of 1.51 and cancer-related mortality with a median HR of 1.61 [1]. Although more discrete estimates of risk have yet to be determined, these risks are substantial and place smoking as an effect modifier well within the range of consideration for affecting clinically meaningful outcomes. Given the breadth of evidence, clinicians must now ask themselves if ignoring tobacco use or cessation results in a clinically meaningful negative outcome. The same perspective should also be stringently considered by clinical research organizations in the design of clinical trials. Is the cost and effort associated with a clinical trial worth missing a clinically meaningful outcome based upon the omission of a significant effect modifier such as smoking?

An efficient design is likely possible for tobacco assessment and cessation in cancer patients. Although there is a paucity of data, in a mandatory assessment, mandatory referral model where all patients were screened with a standardized tobacco use assessment and automatically referred to a dedicated tobacco cessation program, the overwhelming majority of patients were receptive to tobacco cessation support [8]. However, what is pertinent to efficient clinical practice and research is the observation that of six potential screening questions at initial consult, three questions identified over 98% of patients who needed tobacco cessation support. Moreover, repeated assessments could be performed at 4-week intervals resulting in delayed identification or referral in only 1% of patients. The net result is that assessment using three questions no more frequently than on a monthly basis may provide a highly efficacious platform to identify tobacco use by cancer patients. Given the broad spectrum of adverse effects in cancer patients caused by smoking [1], the accurate assessment of tobacco use should be considered in the potential inclusion/exclusion criteria and data analysis plans as a potential confounder or effect modifier. The argument that additional data collection is cost prohibitive is nullified by the potential loss of clinically meaningful outcomes due to false negatives or false positives associated with tobacco use.

Efficient design should not only consider tobacco assessment during and following a cancer diagnosis, but should also consider addressing tobacco use through a structured tobacco cessation intervention. A recent Editorial provided strong and rational advocacy for tobacco cessation support discussing more versus less intensive methods and favoring high-intensity cessation support [9]. However, the intensity of tobacco cessation support provided to patients may vary based upon research infrastructure, available institutional resources, ability to track tobacco use data, and outcome. For these reasons, centralizing tobacco assessment data and tobacco cessation support may make sense to efficiently capture a common variable such as smoking in clinical research. There are no reports of phone-based versus in-person tobacco cessation to provide services for clinical research, but a recent report of phone versus in-person counseling for genetic counseling demonstrated efficacious yet cost-saving results with phone-based support [10]. Coupling structured assessments with centralized tobacco cessation such as quit lines has proven effective in the primary care setting [11]. With relatively little effort, clinical trialists could design within a clinical trial standardized periodic tobacco assessments with automatic referral patterns for smokers to dedicated centralized phone-based tobacco cessation support, thereby ensuring consistent assessment and treatment delivery. This approach has yet to be tested for tobacco use in clinical research.

Optimizing tobacco assessment is critical for efficient design. For practical purposes, smoking represents the majority of tobacco use by cancer patients and is the only tobacco use habit with significant evidence associated with cancer treatment outcomes [1]. There are currently no standard recommendations by any cancer organization detailing specific questions or methods for assessing tobacco use or smoking in clinical trials [12]. This unfortunate deficit limits the ability to incorporate standardized evidence-based assessments into clinical trials design and further limits the ability to interpret confounding or effect modification from smoking in a standardized format. However, the 2014 SGR again provides evidence that significant effects are noted based upon current smoking, former smoking, ever smoking (current and former smoking combined) and exposure (such as pack year history). The lack of prior structured data in many completed clinical trials and lack of tobacco use assessments in active clinical trials [13] limits the ability to retrospectively assess the effects of tobacco on completed and forthcoming clinical trials. The promise of accurately evaluating and addressing the effects of smoking lies in the design and implementation of future clinical trials.

The adverse effects of smoking can be generally divided into fixed risks or potentially reversible risks. Former smoking appears to increase the risk of many adverse outcomes, suggesting that some effects of smoking may be irreversible. The known effects of smoking on chronic diseases such as heart disease, pulmonary disease, and so on increase mortality risks regardless of a cancer diagnosis. Although many of these risks decrease when a person quits smoking, many risks remain elevated compared with never smokers. However, the adverse effects of current smoking are worse

than former smoking and can be reduced with quitting smoking [1]. This reversible effect modification by smoking can significantly alter cancer treatment outcomes and prevent accurate interpretation of clinical trials. Although there are no standardized recommendations for specific tobacco use questions in clinical trials, researchers should strongly consider capturing at least the following information:

- Current tobacco use: frequency (everyday, some days, not at all) and amount (cigarettes per day);
- Prior tobacco use history: age of starting a regular tobacco use habit, age of quitting a regular tobacco use habit, and average cigarettes per day when a person smoked cigarettes regularly;
- Use of other tobacco products: current and former use;
- In patients who report a former tobacco use history, time since last using tobacco should be captured.

Current smoking, current other tobacco use, and time since last tobacco use should be collected at repeated intervals to assess the potentially reversible effects achieved with smoking cessation. These parameters will provide a rudimentary foundation that can be assessed with relatively few questions and still provide useful details that can be used to assess the effects of tobacco on cancer treatment outcomes. Readers are referred to papers that have used specific questions that can capture this information in cancer patients [8,14]. Importantly, the above questions do not detail a complete tobacco use history nor do they capture enough information to be used for tobacco cessation treatments. However, these questions can be used for data collection purposes and to identify patients who require tobacco cessation treatment either directly or through referral to a dedicated tobacco cessation program.

In conclusion, clinicians and researchers must now consider the overwhelming evidence-base that tobacco use is a likely confounder or effect modifier across cancer as a whole in clinical practice and clinical trials design. This paper is not meant to minimize the importance of tobacco cessation support for cancer patients nor does it advocate that all patients should receive low-intensity tobacco cessation assistance. Whenever possible, clinicians should provide structured and repeated tobacco assessments and cessation support. However, an effective system must be developed to identify tobacco use and provide tobacco cessation support for patients enrolled on clinical trials. Such a system will not only provide direct benefit for patients enrolled, but also has the potential to more accurately identify efficacious treatments for cancer patients regardless of smoking status.

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References

1 US Department of Health and Human Services. *The Health Consequences of Smoking – 50 Years of Progress: A Report of the Surgeon General*. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, GA, USA (2014).

2 Toll BA, Brandon TH, Gritz ER, Warren GW, Herbst RS. AACR subcommittee on tobacco and cancer. Assessing tobacco use by cancer patients and facilitating cessation: an American Association for Cancer Research policy statement. *Clin. Cancer Res.* 19, 1941–1948 (2013).

3 Hanna N, Mulshine J, Wollins DS, Tyne C, Dresler C. Tobacco cessation and control a decade later: American society of clinical oncology policy statement update. *J. Clin. Oncol.* 31, 3147–3157 (2013).

4 American Society of Clinical Oncology; Tobacco Cessation Guide for Oncology Providers (2012). www.asco.org/sites/default/files/tobacco_cessation_guide.pdf

5 Warren GW, Marshall JR, Cummings KM *et al.* Addressing tobacco use in patients with cancer: a survey of American Society of Clinical Oncology members. *J. Oncol. Pract.* 9, 258–262 (2013).

6 Warren GW, Marshall JR, Cummings KM *et al.* IASLC Tobacco control and smoking cessation committee. Practice patterns and perceptions of thoracic oncology providers on tobacco use and cessation in cancer patients. *J. Thorac. Oncol.* 8, 543–548 (2013).

7 Ellis LM, Bernstein DS, Voest EE *et al.* American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. *J. Clin. Oncol.* doi:10.1200/JCO.53.8009 (2014) (Epub ahead of print).

8 Warren GW, Marshall JR, Cummings KM *et al.* Automated tobacco assessment and cessation support for cancer patients. *Cancer* 120, 562–569 (2014).

9 Rabius V, Karam-Hage M, Blalock JA, Cinciripini PM. 'Meaningful use' provides a meaningful opportunity. *Cancer* 120, 464–468 (2014).

10 Schwartz MD, Valdimarsdottir HB, Peshkin BN *et al.* Randomized noninferiority trial of telephone versus in-person genetic counseling for hereditary breast and ovarian cancer. *J. Clin. Oncol.* 32, 618–626 (2014).

11 Rothemich SF1, Woolf SH, Johnson RE *et al.* Promoting primary care smoking-cessation support with quitlines: the QuitLink randomized controlled trial. *Am. J. Prev. Med.* 38, 367–374 (2010).

12 Land SR. Methodologic barriers to addressing critical questions about tobacco and cancer prognosis. *J. Clin. Oncol.* 30, 2030–2032 (2012).

13 Peters EN, Torres E, Toll BA *et al.* Tobacco assessment in actively accruing National Cancer Institute Cooperative Group Program Clinical Trials. *J. Clin. Oncol.* 30, 2869–2875 (2012).

14 Gritz ER, Dresler C, Sarna L. Smoking, the missing drug interaction in clinical trials: ignoring the obvious. *Cancer. Epidemiol. Biomarkers Prev.* 14, 2287–2293 (2005).