EDITORIAL

Improving cancer clinical trial design and clinical practice: the case for tobacco use in cancer patients

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Substantial data support the causative nature of tobacco on the development of several cancers [1]. Unfortunately, most cancer studies do not include tobacco use as a variable to consider in the interpretation of outcomes. Increasing evidence demonstrates that tobacco use during cancer treatment is associated with poor outcomes including decreased treatment response, increased treatment-related toxicity, increased noncancer comorbidity, increased risk of second primary cancer, decreased quality of life and increased mortality from cancer- and noncancer-related causes [2–7]. The effects of smoking affect both tobacco-related cancers (e.g., head/neck and lung cancer), as well as traditionally non-tobacco-related cancers (e.g., prostate cancer). In fact, data suggest that in cancers with long expected survival, such as prostate cancer, smoking may be a dominant risk factor for overall mortality due to increased risk of cardiovascular disease and death from other tobacco-related disease [8]. A history of 'ever smoking' decreases survival in several disease sites [2], but 'current smoking' at diagnosis is associated with increased overall and disease-specific mortality compared with those who have never smoked, former smokers (patients who quit ≥12 months prior to diagnosis) and recent quitters (patients who quit during the 12 months prior to diagnosis) [2]. These data suggest that a smoking history is not a fixed variable that affects outcome, but rather suggest that the effects of smoking may be reversible. There are limited studies on the effects of smoking cessation after diagnosis on cancer outcomes; however, available studies indicate that smoking cessation may reverse some of the effects of smoking on cancer outcomes [9–11].

To precisely understand the effects of tobacco on cancer patient outcomes, accurate assessments of current and former tobacco use are necessary. Unfortunately, the overwhelming majority of published literature that reports on the effects of smoking on cancer relies upon nonstandardized tobacco assessments and/or reviews of clinician-based assessments obtained in the medical record [9]. Recommendations for the systematic collection of tobacco use in cancer clinical trials have been proposed and include smoking history, current smoking status and amount, nicotine dependence, readiness to stop smoking, other tobacco use and exposure to secondhand smoke [12]. Cancer patients often report high tobacco quit rates at cancer diagnosis or the beginning of cancer treatment but later show high relapse rates [13]. Due to these unique trends in tobacco use among cancer patients, tobacco status should be collected at cancer diagnosis and treatment intake, as well as throughout treatment and follow up. Failure to assess tobacco use at all patient encounters may miss clinically meaningful changes in tobacco-use status that can dramatically influence cancer treatment response and outcomes. Thus, prospective assessment of tobacco use at multiple time points throughout cancer clinical trials can substantially enhance understanding of the precise impact of tobacco use on cancer treatment outcomes.

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Within both cancer clinical trials and practice, assessing patients' patterns of tobacco use and assessing other factors that may complicate tobacco cessation (e.g., nicotine dependence or psychological distress), is crucial for matching patients to appropriate tobacco cessation services and tailoring tobacco interventions to the unique needs of each patient [14].

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Despite the compelling rationale and strong evidence base to support the inclusion of tobacco-use assessment and cessation into cancer clinical trials and practice, routine assessment of tobacco status has not yet been fully incorporated. A recent analysis of 155 actively accruing cooperative group cancer clinical trials in the National Cancer Institute Clinical Trials Cooperative Group program, demonstrated that only 29% assess any form of tobacco use at enrollment, only 21.9% assess current cigarette use, and only 4.5% assess any form of tobacco use during follow up [15]. Notably, there is no standard method of assessing tobacco use in clinical trial design. As a result, there will be significant limitations in the ability to assess the effects of tobacco on cancer treatment outcomes reported in forthcoming clinical research. With regards to clinical trial design, this limitation extends to a potential 'confounding' or 'effect modification' that can significantly alter the interpretation of a clinical trial. Most clinical trials incorporate disease recurrence, survival, treatment toxicity, quality of life and development of comorbid disease as a part of either primary or secondary outcomes analysis. As noted above, smoking can affect all of these variables in cancer patients, thereby conferring a high risk of altering the interpretation of the primary and secondary outcomes of a clinical trial.

Prospective and repeated assessment of tobacco-use status should be implemented in both cancer clinical trial design and practice. Prospective assessment is needed in order to minimize recall biases [16], and because recall may be less accurate for some tobacco-use variables, such as cigarettes per day [17]. Repeated assessment is needed since smoking patterns in cancer patients tend to show variability over time [13] and since baseline assessments may not be reflective of behavior during cancer treatment [18]. Consistently inquiring as to tobacco-use status at all patient encounters may detect clinically meaningful changes that can dramatically influence cancer treatment response.

There are no standard well-defined recommendations by any national or international organization for tobacco-use assessment in cancer patients. We propose the following items to be considered in cancer clinical trial design and practice:

■ Assessment of tobacco-use status should follow evidence-based recommendations for structured assessment items as put forth by the Clinical Practice Guideline [19];

■ Assessment of prior tobacco use and current tobacco use and amount must be included. These parameters will allow for the analysis of prior tobacco use (years of exposure, amount of exposure and time since quitting) as related to cancer treatment outcomes;

■ Assessment of ongoing tobacco use during and following treatment must be included. This will allow for the analysis of dynamic smoking behaviors on cancer treatment outcomes (i.e., the effect of smoking cessation on reversing treatment outcomes) and will alert treatment providers to changes in tobacco-use status that may warrant referral to tobacco cessation treatment.

Practically speaking, there are several variables to consider in the implementation of tobacco assessments into clinical trial design including:

■ Minimizing additional data collection burden on clinical trialists by using standardized assessments that can be used across a spectrum of clinical settings;

■ Standardizing an approach to implementing tobacco assessments at follow up. There are no studies on the optimal integration of tobacco-use assessments at follow up in cancer patients. Assessing tobacco use every day may not be practical, but assessing tobacco use every 3 months during treatment may allow for considerable variations in tobacco use during a critical time in treatment. Cancer patients may be a unique group due to the inherent nature of aggressive treatment and well-defined follow up for 1–2 years after treatment. Consideration could be given to the practical nature of standard cancer treatment and implementation of tobacco assessments at common intervals (such as weekly or monthly during treatment, and monthly to quarterly during follow up);

■ Centralizing tobacco-related data from several trials into a single resource. There may be an advantage to pooling tobacco data from several clinical trials to assess the effects of tobacco use or cessation on outcomes, toxicity or comorbidity. Pooling data should increase statistical power without substantially increasing the cost of conducting trials by requiring additional patients on a given trial.

Notably, the same assessment parameters should be readily incorporated into clinical practice. Ethically, smoking cessation should be considered for all cancer patients due to the improved health benefits on non-cancer-related disease, as well as the potential benefits on cancer treatment. However, whereas there is considerable information on the benefits of smoking cessation for reducing pulmonary disease, cardiovascular disease, and risk of developing cancer, there is unfortunately far less information on the potential benefits of smoking cessation for improving the efficacy of cancer treatment. The ethical and practical considerations of smoking cessation are beyond the scope of this editorial, but both authors support smoking cessation as a standard of care for all cancer patients.

In conclusion, substantial justification exists for the inclusion of tobacco-use assessments in clinical trials due to the high potential for confounding or effect modification by tobacco on primary or secondary trial outcomes.

There are no specific guidelines for implementation of tobacco-use assessments among cancer patients; however, consideration should be given to accurate assessments administered in a clinically efficient manner. Improving tobacco assessments in cancer patients will significantly increase the ability to identify relationships between smoking and cancer outcomes. Importantly, tobacco assessments will also be useful in identifying optimal treatment strategies for smoking and nonsmoking cancer patients.

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