Tobacco Assessment in Actively Accruing National Cancer Institute Cooperative Group Program Clinical Trials

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ABSTRACT

Purpose

Substantial evidence suggests that tobacco use has adverse effects on cancer treatment outcomes; however, routine assessment of tobacco use has not been fully incorporated into standard clinical oncology practice. The purpose of this study was to evaluate tobacco use assessment in patients enrolled onto actively accruing cancer clinical trials.

Methods

Protocols and forms for 155 actively accruing trials in the National Cancer Institute's (NCI's) Clinical Trials Cooperative Group Program were evaluated for tobacco use assessment at enrollment and follow-up by using a structured coding instrument.

Results

Of the 155 clinical trials reviewed, 45 (29%) assessed any form of tobacco use at enrollment, but only 34 (21.9%) assessed current cigarette use. Only seven trials (4.5%) assessed any form of tobacco use during follow-up. Secondhand smoke exposure was captured in 2.6% of trials at enrollment and 0.6% during follow-up. None of the trials assessed nicotine dependence or interest in quitting at any point during enrollment or treatment. Tobacco status assessment was higher in lung/head and neck trials as well as phase III trials, but there was no difference according to year of starting accrual or cooperative group.

Conclusion

Most actively accruing cooperative group clinical trials do not assess tobacco use, and there is no observable trend in improvement over the past 8 years. Failure to incorporate standardized tobacco assessments into NCI-funded Cooperative Group Clinical Trials will limit the ability to provide evidence-based cessation support and will limit the ability to accurately understand the precise effect of tobacco use on cancer treatment outcomes.

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INTRODUCTION

Tobacco is a well-established risk factor for multiple types of cancer and is responsible for 30% of all cancer-related deaths in the United States.¹⁻³ Increasing evidence demonstrates that tobacco use has adverse effects on the course of cancer and treatment outcomes, including increased complications from surgery, increased treatment-related toxicity, increased risk of recurrence and second primary tumors, and decreased survival.⁴⁻³⁵ Tobacco may also affect treatment delivery through alterations in drug metabolism and activation of tumor-promoting molecular pathways leading to a more aggressive tumor phenotype.³⁶⁻⁴⁴

Because of the growing evidence for the adverse effects of tobacco in patients with cancer, oncologists have increasingly been encouraged to use empirically based guidelines to integrate tobacco cessation into their clinical practice.⁴⁵⁻⁵⁰ In addition, recommendations for the systematic collection of tobacco use in cancer clinical trials have been proposed.⁵¹ According to these recommendations, clinical trials should incorporate standardized items to assess tobacco use, including smoking history, current smoking status and amount, nicotine dependence, readiness to stop smoking, other tobacco use, and exposure to secondhand smoke. Tobacco status should be collected at cancer diagnosis, at treatment intake, and throughout treatment and follow-up.⁵¹

Despite these recommendations, data suggest that routine assessment of tobacco status has not yet been fully incorporated into cancer clinical protocols. In an examination of clinical trials in one US state for non-tobacco-related cancer malignancies enrolling 8,506 patients, only three of 46 trials assessed tobacco status at treatment intake, and none assessed tobacco status through follow-up.⁵²

A significant limitation of most trials correlating tobacco use with cancer outcomes is their retrospective nature and lack of structured assessments.^{5,51,52} The optimal mechanism for evaluating the effect of tobacco on cancer outcomes is to prospectively measure tobacco use at patient enrollment and follow-up in clinical trials. Accurate data are also necessary to provide effective cessation support to patients at risk for continued tobacco use. The purpose of this study was to evaluate tobacco use assessments for patients enrolled in actively accruing National Cancer Institute (NCI) Cooperative Group Program Clinical Trials.

METHODS

The data source of this study included actively accruing trials in the NCI Clinical Trials Cooperative Group Program. Included in this study were trials in which protocols and forms were accessible online from individual cooperative groups or the NCI Clinical Trials Support Unit. A total of 155 actively accruing trials among 10 cooperative groups were identified as of June 3, 2011.

A coding instrument was developed to assess trials' descriptive characteristics and tobacco assessment at intake and through follow-up. Nine of the 155 trials were pilot-rated by two raters (E.N.P. and E.T.) using a draft coding instrument with a 93.7% rate of agreement. On the basis of pilot ratings and subsequent discussions to resolve discrepancies in coding, the coding instrument was revised and finalized. The nine pilot studies were rated a second time with the final version of the coding instrument. Of the remaining 146 trials, 65 were independently evaluated by both raters (E.N.P. and E.T.). Agreements occurred on 97.4% of items, suggesting a high rate of concordance. Discrepancies were resolved by discussion between E.N.P., B.A.T., and G.W.W. Because of the high concordance, the remaining 81 studies were evaluated by one rater (E.N.P. or E.T.). The final coding instrument is found in the Data Supplement. Each rater evaluated trials by using a paper or electronic version of the coding instrument. Raters submitted their completed evaluations to a data manager at the Yale University School of Medicine who scanned the evaluations and downloaded data into Predictive Analytics Software (PASW) Statistics 18 (IBM, Chicago, IL).

Descriptive statistics analyzed trial characteristics and assessment of tobacco status. A multivariate logistic regression model evaluated differences in frequency of tobacco assessment at enrollment based on trial characteristics (cooperative group, phase of trial, disease site, and year that patient accrual started). Cooperative group was coded as an ordinal variable according to the percentage of trials in each group that assessed tobacco use at enrollment (0, cooperative group with smallest percentage of trials that assessed tobacco use; 9, cooperative group with largest percentage of trials that assessed tobacco use). Phase of trial was coded as phase III trial versus non-phase III trial. Disease site was coded as lung/head and neck versus non-lung/head and neck disease site.

RESULTS

Trial Characteristics

As of October 6, 2011, 144 of the 155 trials were still actively recruiting patients, according to ClinicalTrials.gov. Of the 11 trials that were no longer categorized as actively recruiting patients, two were ongoing, one was active but had stopped recruiting since June 3, 2011, five had been suspended, and three were not yet recruiting.

Three of the suspended trials on ClinicalTrials.gov had also been categorized as suspended on the respective cooperative group Web sites; however, two trials categorized as suspended on ClinicalTrials.gov were listed as open to recruitment on the cooperative group Web sites. The three trials categorized as not yet recruiting on ClinicalTrials.gov were listed as open to recruitment on the cooperative group Web sites. Five had no forms available for downloading, but because tobacco use was not mentioned in the protocol text, these studies were coded as not assessing tobacco use. One trial in Ewing sarcoma allowed enrollment of pediatric patients as well as adult patients, but no other pediatric trials were included. For completeness, all 155 trials that were actively recruiting as of June 3, 2011, were included for analysis.

Table 1 describes trial characteristics. The start year of patient accrual ranges from 2003 to 2011 (mean, July 2008; standard deviation, 1.8 years). The cumulative target accrual for the trials is 106,985 patients (mean, 690 patients; median, 300 patients). Trials of patients

Table 1. Cooperative Group Trial Characteristics

Characteristic	No. of Trials	Percent of Total Studies	No. of Patients	Percent of Total Patient Sample
Cooperative Group				
A	43	27.7	21,747	20.3
B	35	22.6	33,475	31.3
C	30	19.4	12,971	12.1
D	15	9.7	8,687	8.1
E	9	5.8	5,387	5.0
F	9	5.8	3,243	3.0
G	7	4.5	9,800	9.2
H	4	2.6	10,230	9.6
I	2	1.3	815	0.8
J	1	0.6	630	0.6
Disease site				
Hematologic	33	21.3	6,478	6.1
Lung	24	15.5	11,628	10.9
Breast	23	14.8	33,770	31.6
Genitourinary	20	12.9	13,041	12.2
Gynecologic	13	8.4	6,127	5.7
Upper GI	12	7.7	3,006	2.8
Lower GI	10	6.5	17,234	16.1
CNS	7	4.5	2,458	2.3
Other	5	3.2	9,282	8.7
Head and neck	4	2.6	1,409	1.3
Bone, sarcoma	2	1.3	1,480	1.4
Cutaneous	2	1.3	1,072	1.0
Primary type of trial				
Phase I	1	0.6	45	0.0
Phase II	61	39.4	7,561	7.1
Phase III	80	51.6	79,225	74.1
Phase I/II	5	3.2	529	0.5
Phase II/III	1	0.6	189	0.2
Biomarker	3	1.9	706	0.7
Prevention	2	1.3	10,970	10.3
Observation	1	0.6	7,200	6.7
Other	1	0.6	560	0.5
Total	155		106,985	

NOTE. "Other" under "Disease site" reflects a trial for patients with bone metastases. "Other" under "Primary type of trial" reflects a trial to prevent lymphedema in patients treated for breast cancer.

with hematologic cancers represent the largest percentage of trials, although patients with breast cancer represent the largest percentage of total patients. The majority of trials are phase III trials representing 74.1% of the total patient sample. The range of trials per cooperative group was one to 43 (median, 9 trials).

Discussion of Tobacco in Protocol Texts

A keyword search of the protocols found that 45 of the 155 trials (29%) representing 46.0% of total patients mention the words “tobacco,” “cigarette,” or “smoking” in the protocol text. Five (3.2%) of the protocols mention tobacco as a cause of cancer, and 21 protocols (13.5%) report that tobacco status would/could influence the interpretation of treatment outcomes.

Tobacco Assessment at Study Enrollment

Table 2 describes the details of tobacco assessment. Of the 155 trials, 45 (29.0%) assess any tobacco use (ie, any former or current cigarette, pipe, cigar, smokeless tobacco, or unspecified “tobacco” use), representing 35.2% of total patients. Thirty-two of the 34 trials that specifically assess cigarette use gather details of cigarette use (ie, age or date stopped or started smoking or number of cigarettes smoked). Regarding non-cigarette tobacco use (eg, pipe,

Fig 1. Assessment of tobacco use at enrollment according to disease site. Bars represent trials that assess any form of tobacco use (ie, former or current cigarette, pipe, cigar, smokeless tobacco, or unspecified tobacco use) at enrollment. Tobacco-related sites were defined according to the 2010 Surgeon General's Report: lung, head/neck, pleura, salivary gland, esophagus, pancreas/bile duct, kidney, ureter, urinary tract, bladder, cervix, and acute myeloid leukemia. For lung/head and neck trials, n = 28; for tobacco-related sites, n = 54; for tobacco-related sites excluding lung/head and neck, n = 26; for non-tobacco-related sites, n = 101.

cigar, or smokeless tobacco), current use was assessed in 5.8% of trials, and former use was assessed in 5.2% of trials. Ten trials (6.5%) assess both former and current tobacco status, and one additional trial (7.1%) assesses only former tobacco status; however, these trials do not specify type of tobacco use. Four of the 155 trials (2.6%) assess past or current secondhand smoke exposure, representing 1.6% of the total patient sample. Three trials (1.9%) assess current cessation methods, but these trials assess pharmacotherapy methods only with no assessment of counseling or behavioral modification. No trials assess nicotine dependence or interest in quitting tobacco use, and no trial explicitly reports that tobacco cessation treatments are provided. Appendix Table A1 (online only) provides more details on tobacco assessment at study enrollment.

Figure 1 highlights tobacco assessment at enrollment across cancer disease sites. Both the percentage of trials within a disease site and the percentage of patients within a disease site are included to reduce the representative effect of excluding tobacco assessments in smaller trials. Lung/head and neck cancer trials evaluate tobacco use in the majority of trials (71.4%) and of patients (91.6%). Trials of cancer at “tobacco-related sites” as defined by the 2010 Surgeon General's Report⁵³ also evaluate tobacco use in the majority of trials (57.4%) and patients (74.9%); however, when excluding lung/head and neck cancer trials from the categorization of tobacco-related sites, prevalence of tobacco use assessment decreased to 42.3% of trials and 48.2% of patients. Only one quarter of patients with non-tobacco-related malignancies are evaluated for any tobacco use at enrollment.

Tobacco Assessment During Follow-Up

The extent of tobacco assessment through follow-up is also shown in Table 2. Seven trials (4.5%) representing 8.3% of total patients assess for any type of tobacco use at follow-up. Most of the seven trials specifically assess current cigarette status, with a minority addressing pipe, cigar, or smokeless tobacco use. All seven trials assess the amount of current tobacco use. Only one trial assesses secondhand smoke exposure. None of the trials assess nicotine dependence, current cessation methods, or interest in quitting, and none of the trials report that tobacco cessation treatments are provided.

Table 2. Tobacco Assessment Characteristics

Characteristic	No. of Trials	Percent of Total Studies	No. of Patients	Percent of Total Patient Sample
Any tobacco assessment at enrollment	45	29.0	37,665	35.2
Assessment of current tobacco use at enrollment				
Cigarette use	34	21.9	30,114	28.1
No. of cigarettes per day	32	20.6	22,254	20.8
Pipe, cigar, or smokeless tobacco use	9	5.8	6,854	6.4
Pipe, cigar, or smokeless tobacco amount (eg, No. of pipes smoked)	5	3.2	5,665	5.3
Unspecified tobacco use	10	6.5	7,455	7.0
Unspecified tobacco amount	0	0.0	0	0.0
Assessment of former tobacco use at enrollment				
Cigarette use	33	21.3	29,864	27.9
Age or date cigarette use started or stopped	23	14.8	17,466	16.3
Number of cigarettes per day	29	18.7	20,330	19.0
Pipe, cigar, or smokeless tobacco use	8	5.2	6,554	6.1
Age or date pipe, cigar, or smokeless tobacco use started or stopped	4	2.6	4,085	3.8
Pipe, cigar, or smokeless tobacco amount (eg, No. of pipes smoked)	4	2.6	5,165	4.8
Unspecified tobacco use	11	7.1	7,551	7.1
Age or date unspecified tobacco use started or stopped	4	2.6	2,981	2.8
Unspecified tobacco amount	0	0.0	0	0.0
Any tobacco assessment at follow-up	7	4.5	8,880	8.3
Cigarette use	6	3.9	5,620	5.3
Pipe, cigar, or smokeless tobacco use	3	1.9	1,750	1.6
Unspecified tobacco use	1	0.6	3,260	3.0

Table 3. Multivariate Association of Trial Characteristics With Tobacco Use Assessment at Enrollment

Trial Characteristic	Percent of Trials That Assessed Tobacco Use	Unadjusted OR	95% CI	Wald Statistic	df	P
Cooperative group				9.16	9	.42
Trial phase						
Phase III	35.8	4.01*	1.52 to 10.61	7.85	1	< .01
Non-phase III (Ref)	21.6					
Disease site				22.91	1	< .01
Lung/head and neck	71.4	14.26*	4.80 to 42.36			
Non-lung/head and neck (Ref)	19.7					
Year patient accrual started		0.95	0.76 to 1.20	0.14	1	.71

NOTE. Results of a logistic regression model, with tobacco use assessment at enrollment as the outcome variable (1, assessed tobacco use; 0, did not assess tobacco use). Cooperative group was analyzed as an ordinal variable, according to percent of trials in each cooperative group that assessed tobacco use at enrollment. Year that patient accrual started was analyzed as a continuous variable.

Abbreviation: OR, odds ratio; Ref, reference.

* $P < .05$.

Contribution of Trial Characteristics to Tobacco Assessment

Table 3 shows the unadjusted odds of trial characteristics predicting tobacco use assessment at enrollment. Phase III trials were four times more likely than non-phase III trials to assess tobacco use. Trials with a disease site of lung or head/neck were 14 times more likely than other trials to assess tobacco use at enrollment. There was no observable effect of accrual year ($P = .71$) or cooperative group ($P = .42$) on tobacco use assessment; however, interpreting the effect of cooperative group is limited by the relatively large number of cooperative groups ($n = 10$ cooperative groups) in the sample of 155 trials and inherent imbalances (such as proportions of disease site) among cooperative groups.

DISCUSSION

Less than one third of actively accruing Cooperative Group clinical trials assess tobacco history, and fewer collect detailed information about current tobacco use during treatment, suggesting that even among trials guided by rigorous, evidence-based science, patients' tobacco use status is largely ignored. Efforts to assess or provide tobacco cessation is minimal or absent. Data suggest that the incidence of tobacco use assessment has not changed over the past several years, demonstrating that there is still little effort to investigate the effect of tobacco on cancer outcomes in national clinical oncology trials that represent the future of cancer treatment.

The objective of clinical trials is to advance the understanding of cancer to ultimately improve cancer treatment outcomes. Many investigators might argue that the effects of tobacco and smoking cessation are important in well-established tobacco-related disease sites such as lung or head/neck cancer,⁴⁻⁶ and trials of lung and head/neck cancer in this analysis were significantly more likely than trials of other disease sites to assess tobacco use. However, substantial evidence demonstrates that assessing tobacco use is an important component of clinical trials design in a broad spectrum of disease sites. Former and current tobacco use is associated with a younger age at presentation and a more advanced tumor stage and comorbidity at diagnosis.⁷⁻⁹ Tobacco use decreases the effectiveness of surgery,¹⁰⁻¹⁶ is a risk factor for poor compliance with cancer

treatment,¹⁷⁻¹⁹ and increases the risk of treatment toxicity and complications.²⁰⁻²² Tobacco use increases the risk of developing second primary cancers,²³⁻²⁵ decreases quality of life,²⁶ increases the risk for developing comorbid conditions after a cancer diagnosis,²⁸ and decreases cancer-related and non-cancer-related survival.^{26,29-31} In more indolent disease sites, such as prostate cancer, the increased non-cancer-related mortality risks associated with tobacco use may dominate overall survival outcomes.^{9,10,32} Unfortunately, there is little data assessing the effect of tobacco cessation on cancer outcomes, but available data show that tobacco cessation may improve primary or secondary outcomes in clinical trials.^{5,33-35} Cumulatively, these data support inclusion of tobacco use assessment in most cancer clinical trial designs to accurately interpret outcomes.

The most significant limitation in current studies is the lack of standardized prospective tobacco assessment that includes detailed former and current tobacco use. As noted by other authors,^{5,9,33} the marked deficit of accurate tobacco use assessment and reliance on retrospective reviews of medical records in most studies makes it difficult to accurately gauge the impact of tobacco use on cancer treatment outcomes. Interpreting tobacco use data from medical records is complicated by a lack of standardized tobacco assessments, lack of defined response criteria, and subjective interpretation of the treating physician/practitioner. Tobacco use during cancer treatment can change dramatically: some patients with cancer who smoke may quit and maintain long-term tobacco cessation, although many will relapse within a few weeks or months.⁵⁴⁻⁵⁶ Collectively, these data support the need to include structured, prospective, evidence-based tobacco assessments at the time of diagnosis or study enrollment and at periodic follow-up intervals.

Several biologic mechanisms support the effects of tobacco use on cancer treatment response, toxicity, and ultimate survival.^{4,6,11-13,16,22,23,35,36-44,53,57-63} The only method for evaluating the potential effects of tobacco use on cancer treatment is to incorporate structured and repeated tobacco assessments into clinical trials design. Evidence-based recommendations to collect detailed information on smoking behavior and exposure have been suggested,⁵¹ and major oncology groups, including the American Association for Cancer Research⁴⁵ and the American Society of

Clinical Oncology,⁴⁷ have issued policy statements regarding the importance of tobacco control. However, these recommendations are largely being ignored. Details on tobacco consumption patterns are important because they can alert treatment providers to the intensity of tobacco cessation treatment that would best serve patients (eg, dose of nicotine replacement therapy) and to factors that may undermine cessation success (eg, other smokers in the household). Unfortunately, at this time, there are no consensus recommendations from national or international organizations for tobacco assessments in clinical trials. Including structured assessments of former and current tobacco use at diagnosis, during follow-up, and assessment of cessation efforts as advocated by Gritz et al⁵¹ would capture necessary data to explain the relationship between tobacco and cancer treatment outcomes. By using Clinical Practice Guidelines, these data would also provide sufficient information to implement tobacco cessation interventions in appropriate patients with cancer.⁵⁰

Importantly, assessment of tobacco use in patients with cancer may be easier than in the general population because patients with cancer often follow a rigorous medical schedule for 6 to 18 months during and following treatment. This schedule promotes opportunities to address tobacco use through repeated assessments and cessation counseling for appropriate patients. Guidelines can be easily incorporated into most clinical trial designs without altering primary or secondary trial objectives, clinical evaluations, stratification, drug administration, or outcomes analysis. Using well-established, evidence-based methods to collect tobacco exposure data reduces concerns of routinely assessing tobacco status because of inadequate resources, methods of collection, or data storage, as well as concerns about potentially invalid reporting of tobacco status by patients.⁵⁰ Accurate assessments can be completed in a few minutes and can be enhanced with inexpensive methods such as biochemical confirmation.⁶⁴ Data from patients with cervical cancer have demonstrated that self-reported tobacco use correlates highly with biochemically confirmed tobacco use,²⁶ although biochemical confirmation in patients with head and neck cancer has identified 39% of self-reported recent quitters as active smokers.⁶ A recent prospective analysis of weekly self-reported tobacco use compared with serum cotinine in patients with head and neck cancer during 7 weeks of radiotherapy demonstrated that repeated self-reported assessments increased the accuracy of identifying true tobacco use by 14.9%, but biochemical confirmation was necessary to confirm active tobacco use in 29.4% of patients who denied tobacco use.⁶⁵ There are no studies that have clarified the optimal utility of biochemical confirmation in patients with cancer, but future studies can identify specific patient subgroups in which biochemical confirmation may be useful in identifying non-reported tobacco use.

These results are limited by possible bias due to selection of trials for analysis. Analyses did not include all active trials in the NCI Clinical Trials Cooperative Group Program and were performed only in trials for which full protocols were available online. The inability to access total trials initiated by a cooperative group per year according to disease site, phase, and tobacco use assessment further limits the ability to comprehensively evaluate the effect of these factors on the inclusion of tobacco use assessments in trials design. This sample cohort may not be an accurate representation of the NCI Clinical Trials Cooperative Group Program: trials not included could have a higher (or lower) rate of tobacco use assessments. However, it is important to note that analyses indicate that only 29% of trials assessed any form of tobacco use. Moreover, minimal details of tobacco use were even less commonly collected: only 21.9% of trials assessed current cigarette use

at enrollment, and 4.5% of trials evaluated tobacco use at follow-up. No trial assessed nicotine dependence or interest in cessation. As a result, even though not all cooperative group trials were available for analysis, the limited attention to tobacco use in the 155 trials in this analysis suggests that tobacco use receives little attention within NCI-sponsored Cooperative Group clinical trials. It is also noteworthy that this study represents a small percentage of the total patients who are expected to be diagnosed with cancer this year and may not reflect clinical practice patterns. However, this study is the most complete evaluation to date of tobacco assessment in large, nationally supported clinical trials.

Tobacco assessments in clinical trials could be substantially enhanced through standardized, efficient, evidence-based assessments at study enrollment and during follow-up. These assessments could be provided through NCI or another universal resource that Cooperative Group trials are required to include in all federally funded research. A standardized assessment would reduce variability across clinical trials due to subjective experience or opinion of patients or investigators and would facilitate assembly of a common data reporting structure that could be useful for comparisons across clinical trials. Incorporating structured assessments into clinical trial design will affirm NCI's commitment to lead efforts in curtailing tobacco use in patients with cancer,⁶⁶ thereby potentially improving both cancer-related and non-cancer-related health outcomes.

In conclusion, even among well-designed, federally funded current clinical trials from a wide range of cancer types, a minority of patients are assessed for tobacco status. Oncology research and patients enrolled in research trials may benefit from comprehensive assessment of tobacco status and subsequent increased knowledge about the effects of tobacco on treatment outcome. Implementing structured tobacco assessments into clinical trials design will improve the understanding of the effects of tobacco use on treatment outcomes and may directly improve health outcomes in patients with cancer enrolled onto clinical trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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