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REVIEW

Reporting of tobacco use and tobacco-related analyses in cancer cooperative group clinical trials: a systematic scoping review☆

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Background: Continued smoking after a diagnosis of cancer negatively impacts cancer outcomes, but the impact of tobacco on newer treatments options is not well established. Collecting and evaluating tobacco use in clinical trials may advance understanding of the consequences of tobacco use on treatment modalities, but little is known about the frequency of reporting and analysis of tobacco use in cancer cooperative clinical trial groups.

Patients and methods: A comprehensive literature search was conducted to identify cancer cooperative group clinical trials published from January 2017-October 2019. Eligible studies evaluated either systemic and/or radiation therapies, included $\geq$100 adult patients, and reported on at least one of: overall survival, disease/progression-free survival, response rates, toxicities/adverse events, or quality-of-life.

Results: A total of 91 studies representing 90 trials met inclusion criteria with trial start dates ranging from 1995 to 2015 with 14% involving lung and 5% head and neck cancer patients. A total of 19 studies reported baseline tobacco use; 2 reported collecting follow-up tobacco use. Seven studies reported analysis of the impact of baseline tobacco use on clinical outcomes. There was significant heterogeneity in the reporting of baseline tobacco use: 7 reported never/ever status, 10 reported never/ex-smoker/current smoker status, and 4 reported measuring smoking intensity. None reported verifying smoking status or second-hand smoke exposure. Trials of lung and head and neck cancers were more likely to report baseline tobacco use than other disease sites (83% versus 6%, $P < 0.001$).

Conclusions: Few cancer cooperative group clinical trials report and analyze trial participants' tobacco use. Significant heterogeneity exists in reporting tobacco use. Routine standardized collection and reporting of tobacco use at baseline and follow-up in clinical trials should be implemented to enable investigators to evaluate the impact of tobacco use on new cancer therapies.

Key words: tobacco use, clinical trials, cancer cooperative groups

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INTRODUCTION

Continued smoking after a diagnosis of cancer is associated with poorer cancer outcomes across a variety of tumor sites including both tobacco- and non-tobacco-related cancers.[1,2] Specifically, continued smoking worsens surgical outcomes by increasing complication rates and worsening wound healing.[3,4] Among patients receiving radiation therapy, smoking can reduce treatment efficacy and increase toxicities.[5-7] When patients are treated with systemic therapies, smoking can impact treatment efficacy and alter drug metabolism.[8-10] Smoking can also worsen quality of life and increase the risk of recurrence and second primary malignancies.[11-14] Cancer patients who continue to smoke are

also at increased risk for non-cancer related illnesses, including cardiovascular and respiratory diseases.[15]

With improvements in the early detection of cancer and better treatment options for many cancers, the survival prospects for patients are improving. A better understanding of how tobacco use impacts treatment outcomes is important given both the growing population of cancer survivors and new treatment options available. In clinical trials evaluating new agents or combination therapies, there may be unexpected consequences of tobacco use.[16] Prior formal and informal studies identified that most oncology clinical trials do not routinely collect data on smoking history unless the tumor site is known to be associated with tobacco.[16-18] Despite the lack of a clear association between tobacco use and the development of some cancers, there remains the potential for tobacco to have a negative impact on treatment outcomes. If smoking status is documented in clinical trials, it is often only at the first visit and not routinely at follow-up visits.[16] This makes the evaluation of the impact of smoking tobacco on trial outcomes challenging, as some patients may quit during follow-up while others continue to smoke. Tobacco can alter the metabolism of systemic therapies, which can make the evaluation of treatment efficacy difficult if smoking status has not been assessed over time.[9,16,19,20] Importantly, tobacco use could impact many trial outcomes including survival, quality of life, toxicities, and recurrence.[2] In particular, as tobacco use can have a negative prognostic effect, not accounting for smoking status in clinical trials may hinder the interpretation of treatment outcomes, as some trials may only have demonstrated small differences detected between treatment arms. Therefore, the capture of smoking status should be a routine part of clinical trial data collection so that its impact on outcomes can be assessed.

Peters et al[17] previously conducted a review of the National Cancer Institute (NCI) Cooperative Group Program clinical trials in the United States and identified that only 29% of trials assessed any form of tobacco use at enrollment and 22% assessed current cigarette usage at enrollment, with even fewer (5%) collecting tobacco use during the follow-up period. Most trials collecting tobacco use information were either phase III trials or trials in lung or head and neck cancer. This study focused on information collected from study protocols; however, rather than what was reported to readers in the study publication. This could further limit how much information is available to the medical community on the impact of smoking during the conduct of trials. Furthermore, the study primarily focused on trials conducted in the United States that were actively accruing patients in June 2011. Information about trials conducted by groups outside of the United States, and over a longer time period may provide a better global perspective on the extent of tobacco assessment in clinical trials.

We carried out a scoping review to better understand the reporting and analysis patterns of smoking history among cancer cooperative group clinical trials. We specifically focused on cooperative groups as these trials are undertaken by academic centers and are not directed primarily by pharmaceutical manufacturers.[21] Our overall objective was to determine the frequency and format of reporting on tobacco use both at baseline and follow-up, second-hand smoke exposure, and how frequently this information was analyzed and presented in cancer cooperative group clinical trial publications.

MATERIALS AND METHODS

Search query

We conducted a systematic scoping review guided by the methodological framework articulated by Arksey and O'Malley.[22] For this review, an extensive literature search was carried out for relevant studies published in English between January 2017 and October 2019 in Medline, EPub Ahead of Print and In-Process & Other Non-Indexed Citations, Embase, and Cochrane Central Register of Controlled Trials, all using the OvidSP platform. Where available, both controlled vocabulary terms and text words were utilized in the search. Where applicable, the search was limited to adults, and the following study designs: clinical trials, controlled clinical trials, randomized controlled trials, and multicenter studies. The SIGN Randomized Controlled Trials Filter and additional terms were used to ensure robustness for this topic. See Appendix S1 for the list of all search terms and search strategy used, available at https://doi.org/10.1016/j.esmoop.2022.100605.

Study inclusion and exclusion criteria

Article eligibility was first reviewed independently by two reviewers from a group of four (LE, JB, AN, SM) who screened both titles and abstracts. In cases where there was disagreement regarding eligibility, the senior author (MG) provided a third review. After title and abstract screening, full-text screens were conducted independently by two reviewers (LE and JB) and cases of disagreement in either eligibility or reason for exclusion was decided upon by the senior author (MG).

Eligible articles were original peer-reviewed studies involving cancer cooperative group clinical trials, which evaluated systemic therapy and/or radiation therapy. Eligible studies included clinical trials of any phase and disease site that involved $\geq$100 adult cancer patients and mentioned at least one cancer cooperative group in the title, abstract, full text, or supplementary files. In addition, eligible trials had to report at least one of the following primary or secondary endpoints: overall survival, progression-free/disease-free survival, time to progression, time to recurrence, response rate (including overall response rate, complete response, partial response), adverse events/toxicities, and/or quality of life. We included studies that were interim analyses or long-term follow-up studies if at least one of the primary or secondary endpoints were included. For the purposes of this study, we included cancer cooperative groups from all regions of the world.

Studies evaluating or comparing surgical interventions, diagnostic tests, supportive care measures only (e.g. adjunctive medications, physical activity) were excluded from the analysis. We also excluded any secondary analysis

of previously published trials (e.g. subgroup analysis, single-arm analysis, genetic analysis). Finally, review papers on trials or publications that only described the clinical trials protocol were excluded.

Data extraction and organization

The following data were extracted from each publication: title, authors, disease site, countries involved, sample size and/or actual number of patients included in analysis, patient inclusion/exclusion criteria, treatment/intervention details, trial outcomes reported in the manuscript, whether collection of baseline tobacco use information was reported in the methods or tables and how it was reported, documentation of smoking intensity and how it was quantified, reporting on the collection of follow-up smoking information, reporting of second-hand smoke exposure, how smoking status was assessed (self-report or biochemical verification). How associations between tobacco use and outcome data were recorded in manuscripts (e.g. hazard ratios along with their respective confidence intervals) was also captured.

Statistical analysis

All statistical analyses were carried out using SAS 9.4 (SAS, Cary, NC). Descriptive statistics were applied to help summarize characteristics of all included studies and compare between studies reporting and not reporting tobacco use information. As only a small number of studies collected tobacco use information, subsequent meta-analyses were not carried out. Logistic regression models were conducted to evaluate factors associated with the reporting of tobacco use in cancer cooperative group clinical trials.

RESULTS

Summary of included and excluded studies

A total of 24 975 studies were initially identified (Figure 1). Of these, 10 132 were duplicate reports/studies and were excluded and an additional 14 347 studies were excluded based on screening of the title and abstract. Among the remaining 496 manuscripts undergoing full-text review, 259 did not mention or involve a cancer cooperative group, 52 had a sample size $<$100 patients, 41 did not have an appropriate study design for inclusion (e.g. cohort studies, not a clinical trial), 19 did not evaluate an appropriate intervention for inclusion (e.g. surgical intervention, diagnostic test evaluation, physical activity, supportive care medications), and 13 were secondary analyses of previously published trials. Twenty-one further studies were excluded because they only described the study protocol, evaluated a non-adult patient population, did not evaluate the correct outcome, or did not have the right study design. A total of 91 studies representing 90 trials met the inclusion criteria and were included in the final analyses.[23-112] Our search

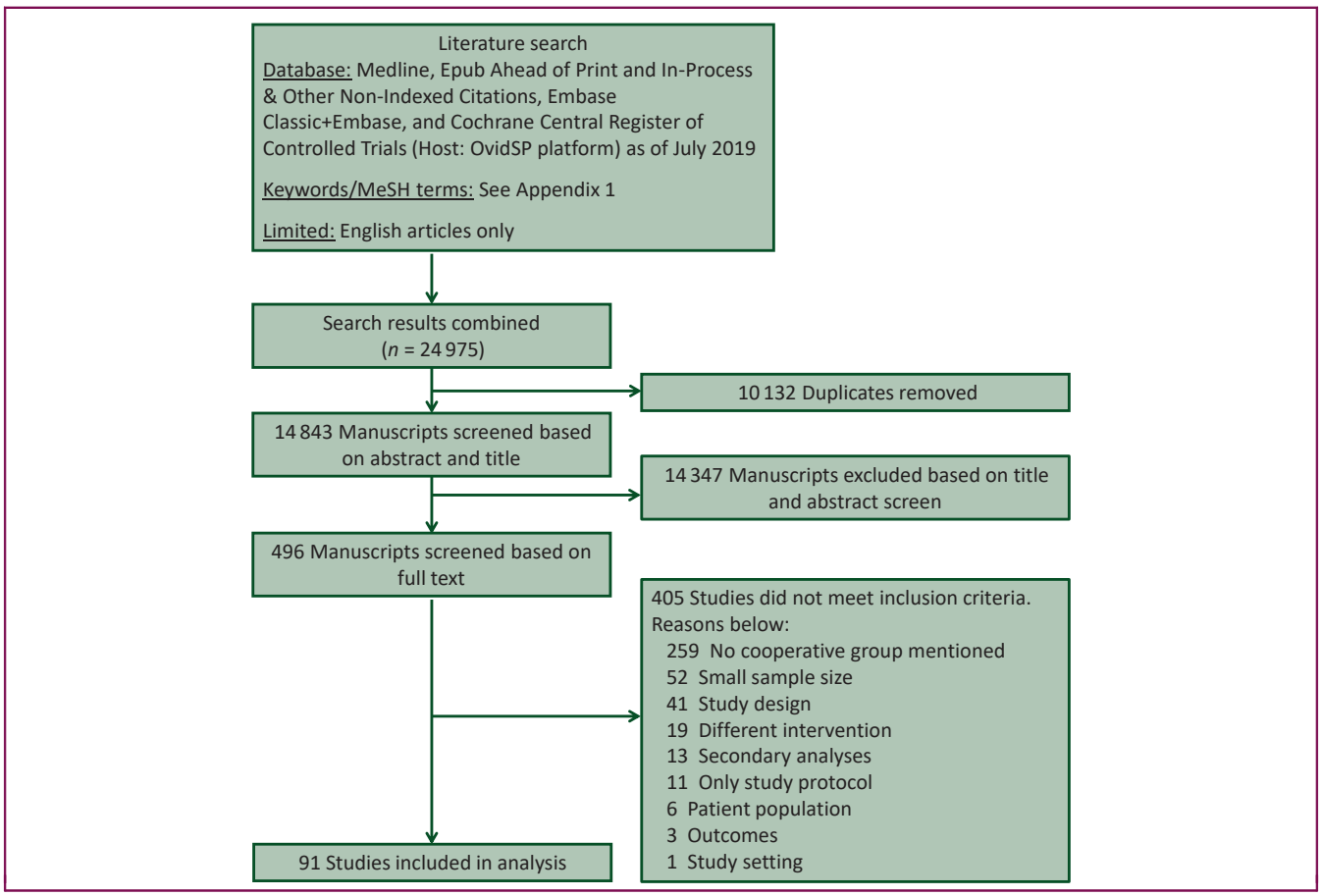

Figure 1. Flow chart summarizing the literature search and selection process for inclusion of studies into the systematic scoping review.

Table 1. Study design characteristics of included studies in the systematic scoping review

Variable	Subgroup	Number of studies (%)
Sample size analyzed	Median (range)	406 (100-4994)
Type of trial	Phase I	0 (0)
	Phase II	22 (24)
	Phase II/III	2 (2)
	Phase III	67 (74)
	Phase IV	0 (0)
Location of study	North and Central America	42 (46)
	South America	1 (1)
	Europe	43 (47)
	Asia	16 (18)
	Africa	1 (1)
	Australia/Oceania	5 (5)
Year of initial trial recruitment	Pre-2005	17 (19)
	2005-2010	48 (53)
	2011 And beyond	26 (29)
Year of publication	2017	39 (43)
	2018	24 (26)
	2019	28 (31)
Intent of trial	Curative	46 (51)
	Palliative	30 (33)
	Hematological	15 (16)
Duration of trial	Median (range), in years	4 (0.75-17)
Modality under study	Radiation therapy	32 (35)
	Systemic therapy	78 (86)
Disease sites involved	Breast	14 (15)
	Central nervous system	5 (5)
	Gastrointestinal	15 (16)
	Genitourinary	6 (7)
	Gynecologic	10 (11)
	Head and neck	5 (5)
	Hematological	15 (16)
	Lung	13 (14)
	Melanoma/skin derived	1 (1)
	Sarcoma	3 (3)
	Other (mesothelioma, neuroendocrine)	2 (2)
	Non-site specific	2 (2)
Type of outcomes	Overall survival (OS)	73 (80)
	Progression/disease-free survival (DFS/PFS)	73 (80)
	Toxicity/adverse events	78 (86)
	Quality of life	36 (40)

found two trials that each had two manuscripts and another manuscript, in which the primary results of two similar trials were presented together.

Most of the included studies were phase II or phase III clinical trials and had a sample size of <500 patients. Other characteristics of the included studies are shown in Table 1. Although all of the included studies were published after the Surgeon General's 2014 Report, the majority of the trials were started in 2005-2010 before the report. Most studies involved systemic therapy (78%) while about one-third involved radiation therapy.

Reporting and analysis of tobacco use in clinical trials

Among the 91 studies included, only 19 studies reported collecting tobacco use in the publication, and only two of these reported collecting any tobacco use information over the course of the trial. A summary of how tobacco use was

Table 2. Tobacco use assessment and reporting characteristics among included studies (n = 19) in the systematic scoping review

Variable	Subgroup	Number of studies (%)
Format for baseline smoking status	Ever/never[a]	7 (37)
	Current/ex-smoker/never	10 (53)
	Unknown	2 (11)
Smoking intensity collected at baseline	Pack-years	4 (21)
	Not captured	15 (79)
Smoking information presented in tables	Presented in main tables	17 (89)
	Not presented	2 (11)
Verification of smoking status	Yes	0 (0)
	No	19 (100)
Follow-up smoking status collected	Yes	2 (11)
	No	17 (89)
Smoking status used in analysis	Yes	7 (37)
	Analyzed, but not presented	3 (16)
	No	9 (47)
Second-hand smoke exposure reported	Yes	0 (0)
	No	19 (100)

[a]Includes studies reporting pack-years only.

assessed in these 19 studies is shown in Table 2 with details on each of these studies shown in Table 3. A detailed summary of all 91 studies included in this review is available by disease site in Supplementary Tables S1-S8, available at https://doi.org/10.1016/j.esmoop.2022.100605. A total of 7 studies reported smoking status as ever smoker versus never smoker status, whereas 10 studies reported smoking status as current smoker versus ex-smoker versus never smoker. We included those studies reporting smoking status only in pack-years, as lifetime smoking status (ever/never smoker) can be inferred based on pack-years. Upon review of the methodology section of these manuscripts, none formally defined smoking status or clarified the difference between current versus ex-smoker status. Only four studies reported collecting information on smoking intensity and all of them used pack-years as the measure of intensity with two reporting it as a continuous measure and two dichotomizing it at the 10 pack-year level. In the two studies that collected information on smoking status over the course of the trial, it was unclear how the information was collected and at what time intervals it was collected.

None of the manuscripts reviewed reported on how smoking status was verified. Only one study reported collecting information on nicotine dependence but did not describe what tool was used to evaluate this. Ten studies carried out analyses on the relation between tobacco use and treatment outcomes, with only seven presenting it in the results section of the manuscript; the majority of these analyses showed no significant differences in outcomes based on smoking status. None of the studies reported collecting any information on second-hand smoke exposure.

Factors associated with the reporting of tobacco use

Table 4 summarizes the univariate and multivariate logistic regression analysis of factors associated with reporting on

Table 3. Summary of cancer cooperative group clinical trials that report collecting tobacco use information

Site	Author Initiation Year	Treatment	Cooperative group	Phase	Countries Sample size	Formal for baseline smoking status	Follow-up info	Impact of smoking on outcomes
Lung	Atagi et al[23] 2003	CRT with carboplatin versus RT in elderly lung cancer patients	JCOG	III	Japan 200	Ever versus never	None	Smokers had improved OS with CRT versus RT Never smokers showed no difference between CRT and RT Smoking did not impact grade 2+ heart or lung toxicities
Lung	Baggstrom et al[24] 2008	Sutent versus placebo after four cycles of first-line platinum-based doublet chemotherapy +/- bevacizumab in advanced NSCLC	CALGB	III	USA 210	Never smoker, ex-smoker, current smoker	None	Smoking status did not impact OS or PFS between arms
Lung	Ball et al[25] 2009	SABR versus standard RT for early lung cancer	TROG ATLG	III	Australia New Zealand 101	Never smoker, ex-smoker, current smoker Pack-years	None	Not evaluated
Lung	Bradbury et al[26] 2012	Docetaxel or pemetrexed +/- pelareorep as second line in advanced NSCLC	CCTG	II	Canada 166	Never smoker, ex-smoker, current smoker	None	Not evaluated
HNC	Chera et al[27] 2014	De-intensified CRT with 60 Gy (with weekly cisplatin if applicable) in early HNC	NCI	II	USA 114	Never, ≤10 pack-years, >10 pack-years	None	Pack-years not significantly associated with time to recurrence
Mesothelioma	Eberst et al[28] 2008	Cisplatin + pemetrexed +/- bevacizumab in advanced mesothelioma	FCIG	III	France 448	Ever versus never	None	Not evaluated
Lung	Faivre-Finn et al[29] 2008	CRT with cisplatin + etoposide comparing 45Gy/30Fr versus 66Gy/33 Fr in limited SCLC	CRUK	III	Belgium, Canada, France, Poland, Netherlands, Slovenia, Spain, UK 547	Never smoker, ex-smoker, current smoker	None	Not evaluated
Breast	Ganz et al[30] 2000	Doxorubicin and cyclophosphamide followed by paclitaxel +/- trastuzumab in early breast cancer	NSABP NRG	III	USA 441	Yes versus No*	Yes versus No*	Smoking did not impact DASI score at follow-up. *Smoking collected during baseline PRO assessment in late follow-up
HNC	Gillison et al[31] 2011	CRT with cetuximab versus cisplatin in early HNC	RTOG	III	USA, Canada 987	0, 0-10, >10 pack-years	None	Patients with >10 pack-years had better 5-year OS with cisplatin compared with cetuximab Patients with ≤10 pack-years did not show a significant difference in 5-year OS
Lung	Herbst et al[32] 2009	Carboplatin and paclitaxel with or without bevacizumab +/- cetuximab in advanced NSCLC	SWOG	III	USA, Mexico 1313	Never smoker, ex-smoker, current smoker	None	Not evaluated
Lung	Isla et al[33] 2011	Cisplatin with either oral vinorelbine versus oral etoposide in CRT in stage III NSCLC	SLCG	II	Spain 140	Never smoker, ex-smoker, current smoker	None	Possibly included in model selection, but not selected.
Lung	Karampeazis et al[34] 2006	Docetaxel plus gemcitabine versus single agent gemcitabine among elderly advanced NSCLC patients	HORG	III	Greece 116	Never smoker, ex-smoker, current smoker	None	Not evaluated

Continued

Table 3. Continued

Site	Author Initiation Year	Treatment	Cooperative group	Phase	Countries Sample size	Formal for baseline smoking status	Follow-up info	Impact of smoking on outcomes
Pancreas	Neoptolemos et al[35] 2008	Adjuvant gemcitabine + capecitabine versus gemcitabine in resected pancreatic cancer	ESPAC	III	England, Wales, Scotland, France, Germany, Sweden 732	Never smoker, ex-smoker, current smoker	None	Included in model selection, but not selected. Subgroup analysis showed smoking status did not impact difference between treatment arms
Lung	Ramalingam et al[36] 2010	Bevacizumab versus pemetrexed versus both after non-progression with carboplatin, paclitaxel and bevacizumab in advanced NSCLC	ECOG-ACRIN	III	USA 1516	Never smoker, ex-smoker, current smoker	None	Smoking entered in multivariable modelling but not included in final model
HNC	Tao et al[37] 2008	CRT with cetuximab +/- carboplatin and 5-FU in locally advanced HNC	GORTEC	III	France, Belgium, Switzerland 406	Collected but not displayed in tables	None	Not evaluated
Cervix	Tewari et al[38] 2009	2 × 2 Trial evaluating cisplatin + paclitaxel versus topotecan and +/- Avastin in advanced cervical cancer	GOG, SOCG	III	USA, Canada, Spain 452	Yes, but no details	Yes but no details provided	Prevalence of active smoking, tobacco or nicotine dependence as an outcome will be reported in future studies. These variables were not included in the current manuscript
Lung	Wakelee et al[39] 2007	Adjuvant cisplatin doublet +/- bevacizumab in early NSCLC	ECOG-ACRIN CCTG ICORG	III	USA, Canada, Ireland, Peru, South Africa 1501	Ever versus never	None	Smoking status did not impact OS or DFS between chemotherapy + bevacizumab versus chemo alone
Lung	West et al[40] 2007	Combined results for two trials evaluating erlotinib and Avastin in advanced NSCLC: 1. Bronchoalveolar cancer 2. Never smokers	SWOG	II	USA 79/85	Never smoker, ex-smoker, current smoker (only in 1 of the 2 trials)	None	Not evaluated
HNC	Xiao et al[41] 2002	Accelerated-fractionation versus standard-fractionation radiation therapy in stage III and IV HNC	NRG Oncology RTOG	III	USA Canada 743	Pack-years	None	Not evaluated

5-FU, 5-fluorouracil; ATLG, Australasian Lung Cancer Trials Group; CALGB, Cancer Alliance Leukemia Group B; CCTG, Canadian Cancer Trials Group; CRT, chemoradiotherapy; CRUK, Cancer Research UK; DASI, Duke Activity Status Index; DFS, disease-free survival; ECOG-ACRIN, Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN); ESPAC, European Study Group for Pancreatic Cancer; FCIG, French Cooperative Thoracic Intergroup; GOG, Gynecologic Oncology Group; GORTEC, Groupe Oncologie Radiothérapy Tête et Cou; HNC, head and neck cancer; HORG, Hellenic Oncology Research Group; ICORG, Ireland Cooperative Oncology Research Group; JCOG, Japan Clinical Oncology Group; NCI, National Cancer Institute; NSABP, National Surgical Adjuvant Breast and Bowel Project; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SABR, stereotactic ablative body radiotherapy; SLCG, Spanish Lung Cancer Group; SOCG, Spanish Ovarian Cancer Group; SWOG, Southwest Oncology Group; TROG, Trans Tasman Radiation Oncology Group.

tobacco use in cancer cooperative group clinical trials. There was a non-significant trend in trials involving North or Central America being more likely to report tobacco use compared with other regions of the world [29% versus 14%, odds ratio (OR) = 2.40 (0.85-6.81), $P = 0.10$]. Clinical trials involving either lung or head and neck cancers were more likely to report tobacco use [83% versus 5%, OR = 86.25 (17.45-426.21], $P < 0.001$). Multivariate regression analysis identified that disease site was the only significant factor associated with the reporting of tobacco use. Other trial characteristics including sample size, year of publication, stage of disease, types of treatments under evaluation, and trial start year and phase were not found to be significantly associated with reporting on tobacco use ($P > 0.05$).

DISCUSSION

Continuing to smoke after a diagnosis of cancer is an important clinical concern.[2] Despite evidence to support the negative prognostic effects of smoking on cancer outcomes, less is known about how tobacco can impact treatment outcomes and adverse events. Clinical trials including those run by cancer cooperative groups may provide an opportunity to evaluate the impact of smoking on treatment-related outcomes. In our scoping review, we identified that <30% of cancer cooperative group clinical trials reported collecting any information on smoking status. Only two trials reported that information on smoking status was collected after the initial visit. There was also significant heterogeneity in the reporting of baseline smoking

Table 4. Summary of univariate and multivariate regression analysis results evaluating factors associated with reporting tobacco use in cancer cooperative group clinical trials

Variable	Comparison	Percentage of studies reporting tobacco use within each subgroup	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Year of publication	2016-2017 versus 2019	26% Versus 21%	1.26 (0.40-4.01)	0.69		
	2018 versus 2019	13% Versus 21%	0.52 (0.12-2.37)	0.40		
Trial start year	2005-2010 versus pre-2005	15% Versus 25%	1.56 (0.38-6.38)	0.54		
	2011 Beyond versus pre-2005	18% Versus 25%	0.85 (0.17-4.37)	0.84		
Sample size	Per patient increase	—	1.00 (0.99-1.00)	0.57		
Region of world involved	North/Central America versus not	29% Versus 14%	2.40 (0.85-6.81)	0.10		
	South America versus not	100% Versus —	—	—[a]		
	Europe versus not	19% Versus 23%	0.77 (0.28-2.14)	0.61		
	Africa versus not	100% Versus —	—	—[a]		
	Asia versus not	6% Versus 24%	0.21 (0.03-1.71)	0.15		
	Australia versus not	20% Versus 21%	0.94 (0.10-8.98)	0.96		
Disease site	Lung/head and neck versus other	83% Versus 6%	86.25 (17.45-426.21)	<0.001	86.25 (17.45-426.21)	<0.001
Stage of disease	Hematology versus early	0% Versus 28%	—	—[a]		
	Late versus early	20% Versus 28%	0.64 (0.21-1.91)	0.42		
Trial phase	II versus III	18% Versus 22%	0.77 (0.23-2.63)	0.68		
Involving radiation therapy	Yes versus no	25% Versus 19%	1.45 (0.52-4.09)	0.48		
Involving systemic therapy	Yes versus no	22% Versus 15%	1.53 (0.31-7.59)	0.60		

aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.
[a]Indicates comparisons that were not carried out due to one subgroup not having any trials within it (indicated by —).

information, a lack of verification of smoking status, and importantly, only 10 trials reported any analyses of smoking status in relation to clinical outcomes. These results suggest a missed opportunity to learn about the potential impact of tobacco use on treatment outcomes. Undertaking standardized assessments of tobacco use should be a priority during the conduct of future clinical trials.

To date, there have been few studies evaluating the frequency of assessing tobacco use in cancer clinical trials. A prior review identified that only 30% of active trials accruing in 2011 in the NCI's Clinical Trials Cooperative Group program collected tobacco use information and <5% collected follow-up tobacco information. The majority of these trials were lung and head and neck cancer trials.[17] Similarly, a review of the Alliance Lung Cancer Treatment Trial protocols identified that only 10 of 32 trials collected any information on smoking status, and only 6 of these trials had data that were usable for secondary analysis of the impact of tobacco on clinical outcomes.[18] Apart from the studies included in these reviews, we were unable to identify any further cooperative group studies even amongst trials after the Surgeon General's 2014 Report.[2] Furthermore, most studies have only reported on what smoking status data were collected in the trial protocols and not on analyses of the impact of tobacco use on clinical outcomes. This is a missed opportunity to evaluate how tobacco may impact both prognostic and treatment-related outcomes, especially in the non-tobacco-related cancers. Furthermore, the lack of reporting of tobacco use and analysis in publications can also limit public awareness of the potential impact of tobacco on trial outcomes.

A number of factors may impede the routine collection and reporting of tobacco use in clinical trials. The first may be the perception that tobacco has little impact on clinical outcomes in trials.[18] Previous studies and the 2014 Surgeon General's Report demonstrate, however, that tobacco can have a powerful impact on the outcomes for many cancer types and this should be considered when evaluating clinical trial results.[2] Other factors include the time and resource demands that would be required with the inclusion of smoking status in trial design, and perceptions that tobacco cessation may not be a viable option for many patients, despite evidence that patients not infrequently quit smoking after a cancer diagnosis and that smoking status can have negative impact on treatment outcomes.[18,113]

Standardized routine assessment, collection, and reporting of tobacco use in cancer clinical trials is potentially feasible. Prior studies by our group have identified that almost all cancer patients feel that assessment of tobacco use is important, were comfortable being assessed, and agreed to being assessed at the first visit with about half reporting it should be assessed at every visit.[114] Similarly, many clinicians also feel that assessment and management of tobacco use in cancer patients is important.[115] Brief standardized tools to routinely assess tobacco use and intensity including the NCI Cancer Patient Tobacco Use Questionnaire (c-TUQ) are readily available and can help to improve the consistency of tobacco use assessments and have been recommended by the NCI-American Association for Cancer Research (AACR) Tobacco Use Assessment Task Force for cancer research.[1,116,117] Standardized reporting of tobacco use in demographic tables and subgroup forest plots for main trial outcomes, especially for non-tobacco-related cancers, can be done similar to what has been reported in prior large trials in lung cancer.[118,119] Such reporting would allow readers to appreciate the potential impact of tobacco on outcomes, particularly in disease sites not typically associated with tobacco use.

Although implementing standardized collection of tobacco use information is feasible, there are additional

potential barriers and considerations. First, patients may misreport their tobacco use to their care providers and biochemical testing may be required to verify smoking status. This was not carried out in most of the cancer cooperative group clinical trials included in our review.[16,120,121] Biochemical testing may be challenging to implement in trials.[122] Self-reported smoking status, however, is considered to be fairly accurate in many epidemiological studies.[123] Despite implementing standardized collection of tobacco information in clinical trials, the reporting of this information may vary as seen in our review. Some trials report only smoking status at diagnosis or trial entry, whereas others may capture and report additional measures such as dose-intensity, quit attempts, and nicotine dependence level. Developing a common standardized way to report tobacco use in trials may be required. Furthermore, none of the trials included in this review reported second-hand smoke exposure, which may negatively impact patient outcomes and quit rates.[124,125] With the recent increased prevalence of electronic cigarettes and cannabis use, these additional forms of tobacco, nicotine, and combustibles exposure will also need to be assessed and evaluated in relation to cancer outcomes.

There are limitations to our study. First, we focused on reporting tobacco use in clinical trials based on their publications, but some studies may have collected this information in their protocol and not reported on it, leading to an underestimate. Reported information, however, is what readers can access to understand the effects of tobacco use on trial outcomes. Our included studies spanned a wide range of starting years which may make these results difficult to interpret. This range and variation, however, does have an advantage as it enables us to evaluate trials which were initiated over multiple time periods including before and after the Surgeon General's Report in 2014. Third, our inclusion criteria focused on studies with $\geq$100 patients, which therefore excluded small early-phase trials where more detailed assessments including pharmacokinetics are likely to have been evaluated. Many early-phase studies, however, are of treatments that do not ultimately proceed to later-phase trials. Furthermore, given the strict inclusion and exclusion criteria, some trials may not have been included in our review. In addition, our review focused primarily on radiation and systemic therapy trials and did not include surgical trials. Tobacco is known to potentially negatively impact surgical outcomes,[3,4] however, and a future review focusing reporting of tobacco use and their analyses in surgical oncologic trials should be completed.

In conclusion, only about one-third of cancer cooperative group clinical trial publications report any tobacco use information. When reported, it was predominantly in trials involving lung or head and neck cancers. Trials reporting tobacco use information showed significant heterogeneity in how smoking status was reported, as well as variability in reporting dose-intensity measures. Most of these studies did not evaluate the impact of tobacco use on trial outcomes. Future cancer cooperative clinical trials should routinely incorporate standardized methods to assess, collect, and evaluate the impact of tobacco use on clinical outcomes.

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