CT SCREENING FOR LUNG CANCER (W SCOTT, SECTION EDITOR)

Importance of Smoking Cessation in a Lung Cancer Screening Program

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Abstract Early detection of lung cancer and smoking cessation interventions can decrease lung cancer mortality, but information on the effectiveness and interaction between smoking cessation and lung cancer screening is sparse and inconsistent. This review aims to synthesize recent studies in two major areas of interest. First, we explore the interactions and potential for synergies between lung cancer screening programs and smoking cessation by summarizing reported changes in smoking behavior observed in major screening trials in the US and Europe, as well as attempts to use smoking cessation interventions to augment the benefits from lung cancer screening programs. Second, we review the interaction between smoking habits and pre-/post-operative pulmonary resection outcomes, including changes in smoking behavior post-diagnosis and post-treatment. Information from these areas should allow us to maximize benefits from smoking cessation interventions through the entire lung cancer screening process, from the screen itself through potential curative resection after diagnosis.

Keywords Smoking cessation · Lung cancer · CT screening · Lung cancer screening · Resection · Screening trial · Postoperative complications · Quit smoking · NLST · Tobacco policy

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Introduction

In 2011, the National Lung Screening Trial reported that screening heavy smokers annually with three low-dose CTs reduced lung cancer mortality by 20 % compared to screening with three chest radiographs [1••]. CT screening has become a prominent focus in combating lung cancer (with USPSTF draft recommendations released in July 2013 [2, 3•]) because screening increases the likelihood of early detection and successful treatment of early stage lung cancers. Prognosis for lung cancer deteriorates rapidly over time, with estimates of 10-year survival rates for stage I screen-detected lung cancer at over 80 % [4], while 5-year survival estimates for advanced (stage IV) lung cancer are around 10–15 % [5]. These factors contribute to making lung cancer the leading cause of cancer death in the US.

Cigarette smoking causes around 90 % of lung cancers [6]. Despite recent declines in smoking, 19 % of adult Americans were current smokers in 2011 [7], making smoking cessation interventions another important strategy for decreasing lung cancer mortality. Though the reduction in smoking attributed to tobacco control has prevented an estimated 800,000 lung cancer deaths in the US between the period 1975 and 2000 [8•], a large portion of the population remains at risk. Early detection of lung cancer and smoking cessation interventions can decrease lung cancer mortality, but information on the effectiveness and interaction between smoking cessation and lung cancer screening is sparse and inconsistent. This review aims to synthesize recent studies in two major areas of interest. First, we will explore the interactions and potential for synergies between lung cancer screening programs and smoking cessation. We summarize reported changes in smoking behavior observed in major screening trials in the US and Europe, as well as attempts to use smoking

cessation interventions to augment the benefits from lung cancer screening programs. Second, we will review the interaction between smoking habits and pre-/post-operative pulmonary resection outcomes, including changes in smoking behavior post-diagnosis and post-treatment. Information from these areas of interest should allow us to maximize benefits from smoking cessation interventions through the entire lung cancer screening process, from the screen itself through potential curative resection after diagnosis.

Impact of Screening Trials on Smoking Habits

The outcomes of a lung cancer screen exam may have a significant impact on a participant's motivations and actions. A positive lung cancer screen can provide participants with a phenomenon known as "a teachable moment [9, 10••]," defined as a health event that motivates an individual to adopt risk-reducing health behaviors. The proportion of trial participants with positive CT screening exams depended on the trial design, but averaged 20 %, and most (over 90 %) of these positive screens were false-positive, ultimately benign findings [1••, 11]. Thus, for many screened individuals, the scare of a positive test, fear of a potential lung cancer diagnosis, and education from a physician about lung cancer and the dangers of smoking could provide motivation to give up or reduce their smoking habits. On the other hand, a negative screen result may create the opposite effect in which a participant gets a false sense of security from a negative screen result and either continues to smoke or resumes smoking after having previously quit without worry about future consequences. A number of recently completed lung cancer screening trials quantified smoking outcomes in the context of trial results. Later, we will explain the reasons that the analyses below have provided varied, inconsistent results across trials in both the US and Europe.

Eight major randomized trials or cohort studies of lung cancer screening in the past decade, six in the US and two in Europe, have so far reported followed-up smoking outcomes. Key descriptions and results for each of these are given in Table 1. The Early Lung Cancer Action Program (ELCAP) was a study ($n = 2,078$) at New York Presbyterian Hospital that looked at participants that were at least 60 years old with a minimum of 10 pack-years of smoking. In 2001, Ostroff et al. [12] reported that 23.1 % of participants reported they had quit smoking (defined in this report as 30-day abstinence), while 26.1 % had decreased smoking and 2.9 % increased smoking. In the same ELCAP participants, Anderson et al. [13] reported that at 6 years of follow-up, 14 % had quit smoking (defined as 30-day abstinence) and that 4.4 % of former smokers at

enrollment had relapsed. A study of 313 current and former smokers referred to as the lung screening study (LSS, a feasibility study for the NLST) assessed current and former smokers' motivations and interest in smoking cessation. In 2007, Taylor et al. [9] reported quit rates (defined as point abstinence) in the LSS of 6.6 % for current smokers and 4.1 % for former smokers at 1-month follow-up. Quit rates in the NLST portion of the study were 7.2 % for current smokers and 4.7 % for formers smokers at follow-up, while the relapse rate was 4 %. The Mayo CT study enrolled participants who were at least 50 years old with less than 10 years since quit and greater than 20 pack-years of smoking history. Cox et al. [14] reported a 14 % quit rate (7-day abstinence) at 1-year follow-up. A later study by Townsend et al. [15] with longer follow-up reported 22 and 23 % quit rates (7-day abstinence) at 2 and 3 years, respectively. Relapse rates were as high as 31 % for recent quitters during the study and 3 % for former smokers after 3 years of follow-up. The Pittsburgh Lung Screening Study (PLuSS) enrolled participants 50–70 years of age with a minimum of 0.5 packs/day for 25 years and a maximum 10 years since quit. Styn et al. [16] reported a 16 % quit rate (30-day abstinence) and a 12 % relapse rate for recent quitters at a 1-year follow-up interview.

Two major trials in Europe examined smoking abstinence in the presence of CT lung cancer screening. The ongoing Dutch-Belgian NELSON trial enrolled 50–75-year-old participants with a minimum of 15 cigarettes/day for at least 25 years or a minimum of 10 cigarettes/day for at least 30 years with a maximum of 10 years since quit. Van der Aalst et al. [17, 18] reported an insignificant 13 % quit rate (7-day abstinence) in the CT group and 15 % in the control group at 2-year follow-up. In further follow-up within the CT group, there was an insignificant 8.9 % quit rate in the CT group with negative results compared to 11 % in the group with indeterminate results. The Danish Lung Cancer Screening Trial (DLCST) enrolled participants between the ages of 50–70 with greater than 20 pack-years and maximum years since quit of 10. Ashraf et al. [19] reported quit rates of 11.9 % in the CT group and 11.8 % in the control group (4-weeks abstinence), with relapse rates of 10 and 10.5 %, respectively.

While the previous analyses were done in trials comparing CT to chest radiograph or to usual care, two other trials comparing chest radiographs to usual care also reported changes in smoking status. Though the difference in smoking outcomes between CT and radiograph screening is unclear, we might speculate there will be higher quit rates in a CT screening arm with more detected nodules and false positives. The PLCO compared chest radiograph screening to usual care in a group with no eligibility requirement (including non-smokers). Barry et al. [20•] followed up participants 4–14 years after enrollment and

Table 1 Overview of smoking status changes during major lung cancer screening trials and studies in the US and Europe

Screening trial	N	Eligibility criteria	Smoking endpoints reported	Source(s) for smoking endpoints
ELCAP	134 (40.3 % male)	Age > 60, pack-years (PY) > 10	Quit rate: 23.1 %	Ostroff et al. [12]
			Relapse rate: 3 % "increased" smoking	
ELCAP	2,078 (44.8 % male)	Age > 60, PY > 10	Quit rate: 14 % (up to 6 years)	Anderson et al. [13]
			Relapse rate: 4.4 % (former smokers)	
			34–42 % for recent quitters	
Mayo CT (1 year F/U)	1,475 (49.7 % male)	Age > 50, PY > 20, years since quit (YSQ) < 10	Quit rate: 14 % (1 year)	Cox et al. [14]
			Relapse rate: N/A	
Mayo CT (3 years F/U)	1,520 (51.7 % male)	Age > 50, PY > 20, YSQ < 10	Quit rate: 22 % (2 years); 24 % (3 years)	Townsend et al. [15]
			Relapse rate: 2.3 %, 2.7 %, 3.0 % (at 1, 2, 3 years)	
			26–32 % for recent quitters	
NLST/LSS feasibility study	LSS: 144 (51.8 %)	NLST: age 55–75, PY > 30, YSQ < 10	Quit rate: 6.3 % (NLST); 4.8 % (LSS)	Taylor et al. [9]
	NLST: 169 (57 %)		Relapse: 4.4 % (NLST); 3.3 % (LSS)—former smokers	
DLCST	4,104 (55 % male)	Age: 50–70, PY > 20 YSQ < 10	Quit rate (1 year F/U): 11 % (CT group), 10 % (control)	Ashraf et al. [46]
			Relapse rate: 9.3 % (CT group), 9.3 % (control)	
PLuSS	2,094 (49.3 % male)	Age: 50–79, YSQ < 10, min 0.5 packs per day for 25 years	Quit rate: 16 % (1 year)	Styn et al. [16]
			Relapse rate: 12 % for recent quitters	
NELSON (analysis of smokers at baseline questionnaire)	1,284	Age: 50–75	Quit rate: 13 % (CT group), 15 % (control)—2 years F/U	van der Aalst et al. [18]
Mayo lung project (CXR)	9,211	Smokers age > 45	Quit rate: 7.5 % (intervention), 7.5 % (control)—1 year F/U	Shi et al. [21]
PLCO screening trial (CXR)	6,807 (current), 31,694 (former)	Age: 55–74	Quit rate: 34.8 % (current at baseline)	Barry et al. [20•]
			Relapse rate: 3.3 % (former at baseline)	

Except where noted, the screen modality was CT

ELCAP Early Lung Cancer Action Program, *NLST* National Lung Screening Trial, *LSS* lung screening study, *DLCST* Danish Lung Cancer Screening Trial, *PLuSS* Pittsburgh Lung Screening Study, *PLCO* Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

reported that 65.2 % of current smokers had continued smoking, while 3.3 % of former smokers had relapsed. Shi et al. [21] reported no significant difference in smoking status between the chest radiograph and control groups (quit rate of 7.5 % in both groups at 1-year follow-up) in the Mayo Lung Project, which compared chest radiographs to usual care in older smokers.

Numerous differences across these analyses make it very difficult to compare them directly. In many cases, comparisons of quit rates by arm are insignificant, but the power to detect changes in behavior is limited because of small sample sizes. Furthermore, criteria such as the definition of "quitting" are arbitrary and vary widely across

trials. For example, the Mayo CT defined quitting as a 7-day abstinence from smoking, while ELCAP used 30 days as a guideline. The NELSON trial also used 7 days, but additionally required fewer than five cigarettes smoked since 2 weeks after the quit date. In the Healthy People 2020 Objectives, the definition of "recent smoking cessation" is a former smoker who has quit in the past year and has not smoked for more than 6 months prior to interview [22]. Also, as mentioned in the trial participation criteria, age ranges, minimum pack-years, and minimum cigarettes per day varied within the trials. Finally, these studies looked at volunteer populations, many of which enrolled in trials with no usual care arm, so observed

smoking cessation rates may not be completely applicable to the general population in which individuals meeting the screening eligibility criteria are referred for screening by their primary care physicians.

Smoking Cessation Combined with Lung Cancer Screening

While some questions remain on the effectiveness of a lung cancer screening program in changing participants' smoking habits, there is very little information on the effectiveness of smoking cessation therapies combined with screening. The NELSON trial analyzed the effectiveness of a smoking cessation intervention integrated with the screening trial. Van der Aalst et al. [23••] reported that a group ($n = 642$) given a tailored self-help cessation intervention had lower, though insignificant, rates of prolonged (defined as smoking less than five cigarettes per day for 2 weeks after quit date) abstinence (12.5 %) compared to a control group ($n = 642$) that received standard brochures (15.6 %). Unfortunately, only 23 % of the participants in the tailored information group returned their questionnaire and received tailored advice, making results difficult to interpret. Clark et al. [24] found that smokers undergoing CT for lung cancer screening in the Mayo CT were more likely to make a quit attempt after having received Internet-based resources (68 %) compared to those who received standard self-help materials (48 %, $p = 0.011$). However, the study found no significant difference in 7-day abstinence between the two groups. A pilot test by Ferketich et al. [25•] that included a tobacco dependence treatment along with lung cancer screening reported a quit rate (defined as 7-day abstinence) of 33.3 % in the arm that provided the intervention prior to screening compared to 22.2 % after screening, suggesting that delivery of cessation interventions may be more effective prior to lung cancer screening. In addition to trial result analyses, McMahon et al. [26•] used a microsimulation model to estimate the cost-effectiveness of lung cancer screening in combination with smoking cessation therapies. They predicted costs well over $100,000/QALY for screening/cessation combination programs compared to no intervention. However, they concluded that the ability of CT lung cancer screening programs to influence participants' smoking cessation rates would play a significant role in determining the cost-effectiveness of the screening program overall.

Impact on Surgery

Because of trial participation eligibility requirements, lung cancer screening trial participants are much heavier smokers than smokers in the general population and at a higher risk of lung cancer. Though former smokers were eligible, many participants in the trials described above were current heavy smokers (approximately 48 % in the NLST [1••]). As a result, discovery of nodules and potential lung cancers through trial screening and follow-up protocols leads to an increased number of lung cancer surgeries. Recent studies described below suggest that current smokers have a higher likelihood of postoperative complications (including mortality [27]) compared to former smokers, often resulting in decreased quality of life [28, 29]. More broadly, ever-smokers have a higher likelihood of postoperative complications compared to never-smokers.

In 2013, Seok et al. [30••] looked at 232 cancer patients between 2005 and 2009 and found that smoking was not a risk factor for postoperative complications, concluding that delaying surgery in order to get a significant duration of smoking cessation was unnecessary. On the other hand, a 2010 review by Thomsen et al. [31•] analyzed eight trials, including seven that offered or recommended nicotine replacement therapy (NRT) as an intervention, and concluded that preoperative smoking interventions including NRT may reduce postoperative morbidity. Furthermore, a 2011 study by Balducyk et al. analyzing questionnaires given to 20 patients concluded that smoking at the time of surgery was associated with decreased postoperative quality of life and that smoking cessation at any point prior to lung cancer surgery would be beneficial. Mason et al. [32] looked at outcomes from a large group of patients ($n = 7,990$) who had undergone resection between 1999 and 2007 to assess risk of hospital death and complications relative to time of smoking cessation. They found that mortality in the hospital was 1.5 % for patients who had smoked compared to 0.39 % for non-smokers ($p = 0.03$, current smokers). Furthermore, complications occurred in 6.2 % of patients who had smoked compared to 2.5 % of those who hadn't ($p = 0.03$, current smokers). Thus, there is a benefit to quitting, but patients do not always benefit from this information. Cooley et al. [33] collected smoking status and history from 94 patients recovering from lung cancer surgery as part of a multi-hospital (US) study between 2002 and 2006 and reported that only 46 % of patients had received cessation assistance prior to surgery.

Other studies have focused on the timing of smoking cessation interventions relative to surgery. Zaman et al. [34•] analyzed seven studies [35] looking at the interval of smoking cessation prior to surgery and concluded that an "optimal interval of cessation has not been identified." Barrera et al., Groth et al., Sawabata et al., and Shimizu et al. [36–39] each found no significant difference in postoperative pulmonary complications due to differences in timing of smoking cessation. Nakagawa et al. [40] found that smoking cessation resulting in at least 4 weeks of

smoking abstinence prior to surgery showed a reduction in development of complications. Another study by Slatore et al. [41] looked at the cost-effectiveness of a smoking cessation and found it to be cost-effective at both 1 and 5 years after surgery.

While previous studies also discuss the benefit of preoperative smoking cessation efforts and the drawbacks of smoking prior to curative resection, a 2013 review of preoperative smoking cessation effects on lung cancer surgery outcomes by Schmidt-Hansen et al. [42••] reported that "*The included studies were marked by methodological limitations. On the basis of the reported bodies of evidence, it is not possible to make any firm conclusions about the effect of preoperative smoking cessation or of preoperative pulmonary rehabilitation on operative outcomes in patients undergoing surgery for lung cancer.*"

Conclusions

Cooley et al. [43] reported that after diagnosis of cancer, around 50 % of patients were interested in smoking cessation programs, further highlighting the need to develop interventions. While studies vary regarding the degree to which lung cancer screening programs affect smoking cessation, most agree that lung cancer screening programs should promote smoking cessation and that smoking cessation-related interventions are an important factor to consider in any lung cancer screening program.

However, it is difficult to make conclusions based on recent lung cancer screening trials in the US and Europe because of inconsistencies in trial characteristics, lack of smoking history follow-up, small sample sizes, and other limitations. Studies specifically focused on smoking status in the context of smoking cessation interventions as part of lung cancer screening in the community are needed to gain more information on the potential for synergy. Furthermore, these studies need to be consistent in terms of follow-up time, cohort characteristics, definitions of smoking abstinence, and other important factors. Since several organizations such as the American Cancer Society, American College of Chest Physicians, American Society of Clinical Oncology, American Thoracic Society, and National Comprehensive Cancer Network Guidelines have followed up the results of the NLST with recommendations of lung cancer screening closely modeling the NLST, a registry that collects standardized information (screen participation, screen results, smoking behavior at defined intervals, etc.) would be an important tool for researchers to conduct meaningful analyses in this field. Additionally, more information on smoking history changes in the NLST itself should be published in the near future, giving a glimpse into what effects we may expect in this volunteer,

heavy-smoking population. Though smoking cessation interventions were not part of the trial, these analyses should provide information on smoking behavior changes in response to positive and negative screens.

Similar to the issues faced in determining smoking changes in lung cancer screening programs, existing studies focusing on the relationship between smoking and postoperative outcomes were inconsistent and difficult to compare. As a result, conclusions are varied. Though most authors agree that smoking cessation interventions prior to surgery are important and will lead to better outcomes [44, 45], more consistent trials and significant results are required to quantify these effects and make any definitive determinations. Overall, further studies and comparative effectiveness analyses on patient outcomes data that include smoking status are required in order to determine the magnitude of the role that smoking cessation interventions and therapies can play in lung cancer screening programs. Furthermore, these studies should extend to lung cancer surgeries and the differences in outcomes between participants who quit or continue smoking during the course of a trial.

Cigarette smoking is a major contributor to poor health, and several components of the Patient Protection and Affordable Care Act (ACA) target tobacco use. Under the ACA, about 25 million more Americans are expected to gain health insurance, which will include no cost-sharing for tobacco cessation and lung cancer screening (if recommended by the US Preventive Services Task Force with an A or B recommendation, §2713 of ACA). Together, evidence from available studies, improved data collection and outcomes reporting, and changes in access to effective interventions for tobacco cessation will allow physicians to better guide patients through the screening to treatment process and improve patient outcomes along the way.

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