Review Article

The importance of incorporating smoking cessation into lung cancer screening

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Abstract: Lung cancer is the leading cause of cancer-related death in the United States (U.S.) and is the second most common non-skin cancer among men and women, accounting for about 30% of cancer-related deaths. There is clear and accumulating evidence that continued tobacco use has multiple adverse effects on cancer treatment outcomes, including greater probability of recurrence, second primary malignancies, reduced survival, greater symptom burden, and poorer quality of life (QOL). Recent findings suggest an avenue to significantly mitigate the impact of smoking on lung cancer mortality rates through the use of low-dose computed tomography (LDCT) lung cancer screening. Based on the reviewed evidence (type B), the U.S. Preventive Services Task Force (USPSTF) guidelines of 2015 recommend screening combined with smoking cessation interventions for high-risk heavy smokers and recent quitters. These practice changes offer opportunities to develop novel smoking cessation strategies tailored to highly specific settings that aim to amplify the survivorship gains expected from screening alone. However, there is a paucity of research and data that speaks to the feasibility and efficacy of providing smoking cessation treatment specifically within the context of the LDCT lung cancer screening environment. While some studies have attempted to characterize the parameters within which smoking cessation interventions should be implemented in this context, further research is needed to explore relevant factors such as the format, components, and timing of interventions, as well as the influence of risk perceptions and results of the screening itself on motivation and ability to quit smoking.

Keywords: Smoking; smoking cessation; lung cancer screening; low-dose computer tomography (LDCT); review

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Smoking and cancer

Lung cancer is the leading cause of cancer-related death in the United States (U.S.) and it is the most common non-skin cancer affecting both men and women, accounting for an estimated 235,000 new cases in 2018 and about 30% of cancer-related deaths (1). Not surprisingly, cancer patients with smoking-related disease have the highest prevalence of smoking at diagnosis. Among patients with lung or head and neck tumors, smoking prevalence is 40–60% (2-5) and data indicate that 39% of patients with any smoking-related cancer (other than lung cancer) are current smokers (6). Some estimates suggest that up to 50% of patients either do not quit after diagnosis, or relapse following initial quit attempts (2). There is a causal relationship between continued cigarette smoking and all-cause and cancer-specific mortality, higher risk of progression, and increased risk for tobacco-related second primary cancers in cancer patients and survivors (7).

It is estimated that smoking prevalence in the first year

following a cancer diagnosis is 23.3% and declines to around 19% in the years following diagnosis (8,9). Tobacco plays a causal role in at least 15 types of cancer (10,11) and accounts for 85% of lung cancer cases (12) and around 30% of the attributable risk for overall cancer mortality (13). There is clear and accumulating evidence that continued tobacco use has multiple adverse effects on cancer treatment outcomes. The 2014 Surgeon General's Report (7) is the first comprehensive, large-scale review of evidence to report a causal relationship between continued tobacco use and adverse outcomes in cancer patients and survivors. This report concludes that the summarized evidence "*documents that cigarette smoking has a profound adverse impact on health outcomes in cancer patients*" (14).

Further, in the 2014 report the evidence was suggestive that cigarette smoking increases the risk for recurrence, decreases response to treatment and increases toxicities related to cancer treatments (7). These findings provide clear clinical implications for the importance of addressing tobacco in the oncology setting (7). The evidence reviewed suggests that the overall risk of dying could be reduced by 30–40% if patients quit at the time of diagnosis; and smoking cessation in cancer patients may have benefits that are equal to or exceed those of the best cancer treatments available (15). Other potential benefits of cessation include increased physiological and psychological functioning (16-18). However, the accuracy of findings on the benefits of cessation are limited by the quality of tobacco use assessments and accuracy of patient self-report (19), which may underrepresent the extent of adverse effects related to smoking as well as the benefits of cessation (15). The Surgeon General's Report notes that current smoking status in cancer patients warrants the full attention of the health care team, given evidence that it is a powerful indicator for risk of complications and altered response to treatment.

In particular, continued smoking during cancer treatment is associated with greater probability of recurrence (20,21), second primary malignancies (22-25), reduced survival (26-29), greater symptom burden (30), and poorer quality of life (QOL) (31). Smoking is also associated with deleterious consequences during the perioperative period such as pulmonary embolism, infection, poor wound healing, increased risk of anesthesia and cardiovascular events (32-39) as well as diminished response and complications of radiotherapy (40,41). Conversely, smoking cessation increases the survival from a diagnosed lung cancer (42-44), reduces the risk of complications after primary lung resection (45), and increases QOL in lung cancer patients (46). Taken together, these findings provide a compelling rationale for assuring that these patients are provided with treatment options that have been shown to be efficacious for smoking cessation. Unfortunately, there is a lack of well-controlled prospective studies within the treatment context of the cancer patient (7), particularly lung cancer patients; therefore, aggressive research steps are needed to optimize specific cessation approaches for these patients and settings.

Recent advances in early detection suggest an avenue to significantly mitigate the impact of smoking on lung cancer mortality rates through the use of low-dose computed tomography (LDCT) in lung cancer screening, which has resulted in a 20% reduction (compared to annual chest radiography) in lung cancer mortality rates and a 6.7% reduction in all-cause mortality rates (47). The U.S. Preventive Services Task Force (USPSTF) then issued a set of recommendations for yearly LDCT screening for select high risk individuals (current and former heavy smokers) (48,49). More specifically, high risk individuals were defined as adults aged 55–74 years who have a 30-pack-year smoking history and currently smoke or have quit within the past 15 years (49). Later data modeling suggested that benefits of screening may extend up to 80 years of age, thus the expanded age range was revised to be 55–80 years (50). Similar recommendations were subsequently issued by a variety of other agencies, including the American Association for Thoracic Surgery (51), American Cancer Society (52), American College of Chest Physicians (53,54), American Lung Association (53,55), American Society of Clinical Oncology (53), and the American Thoracic Society (56).

Advantages of early detection and intervention in lung cancer

Early detection and intervention has been and continues to be the clinical mantra for most cancers for several decades now, albeit some exceptions (e.g., slow growing prostate cancer, where close observation and regular monitoring is now advocated instead of aggressive intervention). A favorable balance between benefit and risk of an early detection test or procedure (e.g., exposure to radiation or procedures due to false positives) have to be confirmed before recommending it on the population level. As a result of the estimated overall 20% reduction in mortality from lung cancer, the American Cancer Society screening guideline emphasizes that clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should ascertain the smoking status and smoking

history of their patients ages 55 to 74 years and should initiate a discussion about lung cancer screening with those patients who have at least a 30-pack/year smoking history, currently smoke or have quit within the past 15 years, and are in relatively good health (11). Interestingly, a recent study suggested that a further expansion of the recommended lung cancer screening population criteria using a more personalized risk-based model may offer even greater overall reductions in mortality benefits as the number of eligible high-risk current and former smokers declines over time (57). A logical next step that is not in debate is the need and benefit of providing the best possible smoking cessation treatments for those who have a positive LDCT; unfortunately, these treatments may or may not be delivered due to different barriers (logistical, economic, and others). On the other hand, helping those who have a negative LDCT (the vast majority of those screened with LDCT) to quit smoking has the potential of an exponential improvement in surviving a lung cancer that is not yet detectable, or even better the prevention of one. Thus, adapting and tailoring the standard smoking cessation interventions to these patients' needs and circumstances can have major positive effects on those patients' health and wellbeing as well as the overall public health.

Lung cancer screening results, risk perception, and smoking behavior

Lung cancer screening guidelines have also emphasized that smokers or recent quitters in these programs should be carefully counseled to ensure that the screening itself is not perceived as an adequate replacement for smoking cessation (52) that might lead to patients being less motivated to quit smoking or more likely to relapse, particularly after a negative screening test (58). The Danish Lung Cancer 5-Year Screening Trial, one of the early studies to publish specific smoking data of lung cancer screening patients, randomized 4,120 patients to receive either annual LDCT screening or no intervention. Findings indicated no significant differences in annual smoking status between the two groups, though the overall sample annual point-prevalence quit rates increased from 11% to 24% by year 5 (59). Relapse rates were also similar across both groups. Patients in both groups were provided with brief cessation counseling but were not offered pharmacotherapy. Of further interest, initial analyses of these patients after 1 year of screening showed a significant increase in cessation attempts and decrease in relapse to smoking among patients with a positive scan versus those with a negative scan (60), but this effect was not observed when all 5 years of screening were analyzed (59). In a study that was limited to a cohort of male lung cancer screening with a similar design, patients reported similar quit rates and no differences were observed between smokers who were screened with an LDCT and the control group that was not screened, though a significantly higher number of quit attempts were reported in smokers with a positive screening result (61).

Another study in which researchers interviewed 313 current and former smokers from two lung screening studies [the National Lung Screening Trial (NLST) and the Lung Screening Study (LSS)] before and 1-month following screening reported that NLST participants endorsed greater readiness to quit smoking ($P<0.05$) at the 1-month follow-up, though the screening result did not moderate this finding. Of importance, among younger participants (≤64) in the LSS sample, an abnormal screening result was significantly associated with increased readiness to quit, whereas a normal result was associated with becoming less ready to quit ($P=0.02$) (62). A study that included 15,489 patients from the NLST reported that participants with new or unstable screening findings that were suspicious for lung cancer had an odds ratio (OR) for continued smoking of 0.663 (95% CI: 0.607–0.724; $P<0.001$) when compared to participants with normal screening results (63). An expansion of these findings in a recent study during a 5-year follow-up of this sample, it was reported that any false positive screening result was associated with greater point prevalence as well as greater 6-month sustained abstinence in smokers, and that recent quitters with more than one false positive screening result were less likely to relapse than those with a negative result. Among longer-term former smokers, the screening result was not associated with greater relapse (64). Taken together, the handful of studies to date do not robustly support the supposition that participation in lung cancer screening itself promotes cessation, though the evidence is mixed. However, these data do suggest that positive or false positive screening results may be associated with greater motivation to quit and a higher likelihood of quitting and staying quit (62, 65-67).

A large survey conducted with a variety of cancer patients observed that patients may substantially overestimate the benefit of cancer screening and may have misperceptions about the harm reduction incurred through screening itself (68). In fact, in a study conducting in-depth interviews with a small sample (n=45) of lung cancer screening patients, most patients reported an increased reflection

on the harms and long-term consequences of smoking as a result of screening, while as many as half of the patients reported a decrease in the motivation to quit smoking following screening, and described misperceptions such as "undergoing screening yields the same benefits as smoking cessation" and "everyone who undergoes screening will benefit" (69). A similar qualitative study investigating risk perceptions associated with lung cancer screening among screening participants reported that while most patients endorsed high-risk perceptions for lung cancer and other smoking related diseases, these did not translate into quitting behaviors or even increases in motivation to undergo lung screening (70).

Similarly, in a study of 430 NLST patients conducted 1-year following lung cancer screening, patients reported no significant changes in risk perceptions from baseline and no significant changes in risk perceptions were associated with screening results. More significantly, risk perceptions were not associated with smoking behavior (quit rates or relapse rates) and only 10% of these patients reported quitting at the 1-year follow-up (71).

Overall, evidence to date suggests that screening itself does not necessarily promote long term cessation, though participants in screening programs may quit at slightly higher rates than the general population of smokers partly due to demographic or motivational differences in these populations (58,60,72). Research on the role of lung cancer screening results and lung cancer screening-associated risk perceptions on smoking cessation and relapse suggests that these factors may have at least short-term influence on smoking behavior but studies are inconsistent with regard to lasting effects. Thus, there is a tremendous need not only for new interventions that facilitate smoking cessation among lung cancer screening patients, but also for intervention components that address risk perceptions and explicitly, cognitive biases and misperceptions in the lung screening context (69). Moreover, interventions addressing smoking-related risk perceptions should not be limited to lung cancer specifically, but would need to include the other devastating effects of smoking-related diseases, risks, and the reversible health consequences after quitting.

Smoking cessation in the LDCT screening environment

In addition to the established short-term efficacy, several studies in the general population have shown that extended counseling and/or pharmacotherapy enhances treatment outcome and sustained abstinence relative to brief, time limited approaches (73). To achieve similar outcomes among lung cancer screening patients, a more aggressive stance may be needed that would include offering continuous engagement with lung cancer screening patients who recently quit and those who continue to smoke. In line with the U.S. Public Health Service (PHS) Tobacco Clinical Practice Guidelines (73) that recommend consistent assessment and treatment for every tobacco user seen in health care settings, LDCT lung cancer screening provides a clear opportunity to deliver evidence-based smoking cessation treatments to a captive audience of smokers at high risk for lung cancer.

While acknowledging the relative lack of data specific to this population and context, the Society for Research on Nicotine and Tobacco (SRNT) as well as the Association for the Treatment of Tobacco Use and Dependence (ATTUD) have provided preliminary recommendations for the delivery of smoking cessation interventions to smokers engaging in lung cancer screening that include encouraging patients to quit smoking at every visit regardless of screening results, arranging for behavioral and pharmacological cessation treatments outlined in the PHS Tobacco Clinical Practice Guidelines (73) as well follow-up contacts to support these efforts, and providing evidence-based interventions to increase motivation in patients unwilling to make a quit attempt (74). It is possible that this population of older smokers, albeit at high risk for developing lung cancer, may vary considerably in their motivation to quit (75,76), though the currently available evidence is mixed (77). This population may also perceive little health benefit from cessation given their age (78). What is clearly needed is a treatment strategy that goes well beyond simply advising a patient to quit smoking that is routinely integrated into the screening process to ensure that those who initially quit will not relapse; and that those who initially fail to quit will be repeatedly presented with opportunities to do so in a supportive clinical environment.

This approach was supported in a nested case-control design study conducted with patients enrolled in the NLST. This study assessed the association between reported delivery of the recommended minimal intervention when a smoker is identified in a medical consultation (73), known as the 5As (ask, advise, assess, assist/discuss quitting, and arrange/follow-up), and smoking cessation behaviors (79). The smoking cessation literature generally recommends the use of the 5As for all smokers in the context of any visit with a medical provider, though data suggest that the more effective components of the

model, assist and arrange, are less commonly implemented (80). This study included 3,336 participants from 23 American College of Radiology Imaging Network (ACRIN)-NLST sites. The authors reported that while assist and arrange follow-up delivered by primary care providers was associated with increased quitting (OR =1.40, 95% CI: 1.21–1.63; OR =1.46, 95% CI: 1.19–1.79, respectively), the less intensive interventions (ask, advise, and assess) were not. Moreover, the rates of assist, and especially arrange follow-up, were relatively low (assist 56.4%; arrange 10.4%).

The Lung Health Study (81) was the first randomized controlled trial (RCT) to demonstrate a mortality benefit for tobacco cessation in a sample of 5,887 current smokers who received either usual care versus 10 weeks of cessation treatment that included physician messaging, group counseling sessions, and nicotine replacement therapy (NRT), then followed for 14.5 years. All-cause mortality rates were significantly higher in the usual care group *vs.* the intervention group (10.38 *vs.* 8.83 per 1,000 person-years; P=0.03). Moreover, the difference in mortality rates favoring sustained cessation was even more pronounced when patients were analyzed by smoking patterns following the interventions. Mortality rates were 6.04 per 1,000 person-years in sustained quitters *vs.* 7.77 per 1,000 person-years in intermittent quitters *vs.* 11.09 per 1,000 person-years in continuing smokers.

There is little data that speaks to the feasibility and efficacy of smoking cessation treatment that occurs specifically within the context of an LDCT scanning environment. Treatment factors that have not yet been well-studied include format, treatment components, and timing of the intervention; and whether behavioral, pharmacological, or a combination of both are provided, though a handful of recent studies have begun to explore these issues in more depth. Two recent studies attempted to incorporate very basic cessation interventions into lung cancer screening settings with discouraging results, reinforcing the need for more intensive treatment strategies in the lung screening setting. In the first study, 171 current smokers were randomized to written materials versus the provision of a list of 10 internet sites with cessation resources. Results indicated that while the internet group was more likely to attempt to quit, there were no differences in abstinence rates at 1 year (between 5% and 10%) (82). van der Aalst and colleagues (61) randomized 1,284 smokers to receive a brochure or a tailored guide to quit smoking but reported no significant difference in abstinence rates at 2 years (tailored 12.5% *vs.* brochure 15.6%). Of importance, none of the interventions used in these studies were commensurate with the standard counseling and pharmacotherapy recommended by the PHS Tobacco Clinical Practice Guidelines (73).

Conversely, in a small 12-week smoking cessation counseling program combined with varenicline that targeted thoracic oncology patients, smoking abstinence rates at the 12-week follow-up were higher in the intervention group (n=32) as compared to the control group (n=17; 34.4% *vs.* 14.3%; OR =3.14, 95% CI: 0.59–16.62, P=0.18).

Clinicians were proactive in reaching out to patients during clinic visits to discuss tobacco treatment and participation in the research study. All sessions were structured according to the 5As counseling model (73), included cancer-specific and general smoking cessation topics, were initiated within the first three clinic visits, and were conducted both in-person and by phone (83).

This type of integrated care model could potentially be adapted for a lung cancer screening setting. For example, one small pilot feasibility study initiated a 12-week treatment protocol (including telephone-delivered behavioral therapy and NRT or varenicline) targeting both tobacco cessation and participation in lung cancer screening (84). The study also tested the effects of conducting tobacco dependence treatment before (BCT group) or after (ACT group) the lung scan (randomly assigned) and reported the following results: at 4 months CO confirmed quit rates were 33.3% in the BCT arm and 22.2% in the ACT arm (27.8% overall), and all but one patient made a 24-hour attempt to quit. At 6 months the confirmed abstinence rates decreased to 22.1% in the BCT arm and 11.1% in the ACT arm (16.7% overall). These preliminary results demonstrate that integrated, intensive cessation treatment can significantly impact abstinence rates in lung screening patients and that these rates can be affected by the parameters of the intervention delivery. Tobacco cessation research in oncology settings more generally supports the need of using more than minimal cessation interventions to achieve meaningful reductions in smoking prevalence with cancer patients (85).

Conclusions

It has been well established that tobacco use accounts for 85% of lung cancer cases (12) as well as almost 32% of the attributable risk for overall cancer mortality (13). There is also clear and accumulating evidence that continued tobacco use in cancer patients has multiple adverse effects on cancer treatment outcomes. The implementation of a wide variety of agency guidelines will provide opportunities

to significantly impact lung cancer mortality rates through early detection and the use of LDCT lung cancer screening. These practice changes also offer opportunities to develop novel smoking cessation strategies tailored to highly specific settings that may amplify the gains in survival that would be expected from screening alone whether an LDCT is positive or not. Smokers in this context may differ in important ways from the general population of smokers and more research is needed to understand the unique characteristics of this population as well as the context within which treatment should be provided. There is little data that speaks to the feasibility, efficacy, and cost-effectiveness of smoking cessation treatment specifically within the context of the LDCT lung cancer screening environment, including factors such as the optimal treatment provider; format, components, and timing of interventions; and the influence of risk perceptions and results of the screening itself on motivation and ability to quit smoking, though efforts are underway to address these and other important parameters.

In 2015, the *J Natl Cancer Inst* announced a funding opportunity (R01; RFA-CA-15-011) supporting projects that specifically test smoking cessation interventions in the context of lung cancer screening, with the goal of bolstering the intervention and dissemination effectiveness evidence base, identifying barriers, and estimating feasibility, acceptability, and cost-effectiveness of various approaches. A total of eight trials were ultimately included in this collaboration, entitled the Smoking Cessation and Lung Cancer Screening (SCALE) collaborative (including one study funded by the Veterans Health Administration). The aims and background for each of these trials is summarized in a recent paper by Joseph and colleagues (86). This type of initiative is an example of an aggressive effort to advance the understanding of the complex issues surrounding the treatment of smokers and recent quitters at high risk for the development of lung cancer in the context of lung cancer screening, which has the potential for further reductions in the morbidity and mortality associated with lung cancer as well as the myriad of other smoking-related diseases.

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Footnote

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