Smoking Cessation and Relapse during a Lung Cancer Screening Program

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Abstract

Background: The potential for negative screening to reduce smoking cessation and long-term abstinence is a concern in lung cancer screening. We examine whether consistently negative results during long-term participation in a lung cancer screening program reduce cessation or increase relapse.

Methods: Participants (N = 2,078) in the Early Lung Cancer Action Program received annual screenings and periodic smoking behavior surveys over a follow-up period as long as 12 years. Point abstinence and prolonged abstinence were examined among 730 baseline smokers. Relapse was examined among 1,227 former smokers who quit for 1 year or more at enrollment, 121 recent quitters at enrollment, and 155 baseline smokers who quit during follow-up. Abstinence and relapse for participants with consistently negative computerized tomography scan results were compared with those with non-cancer–positive results using stratified Cox models.

Introduction

Lung cancer is the largest cause of cancer death in the United States, and the late stage of disease at diagnosis results in 5-year survival rates of only 15% (1). This reality makes lung cancer an attractive target for early detection, and screening approaches have been proposed initially with chest X-rays and sputum cytology and more recently with computerized tomography (CT) of the chest. However, there is concern that screening for lung cancer might diminish smoking cessation (2, 3). More specifically, there is concern that the reassurance provided by screening, and particularly by a negative screening result, might reduce motivation to quit smoking among current smokers or lead to resumption of smoking among former smokers.

Evidence on cessation activity from studies of screened populations is sparse, and follow-up is limited to 3 years. Populations participating in lung cancer screening have high rates of smoking cessation activity (4, 5) and point abstinence (6-10) during the first 1 to 3 years of screening participation. Because a positive screening result requires additional testing to determine whether it is malignant, the reassurance of a negative screening result has been examined by comparing individuals with negative scans to those with positive scans. A positive finding on screening has been associated with increased rates of cessation in the year following the delivery of the positive screening result (9, 10).

Data on relapse are even more limited. Townsend and colleagues (10) followed a lung cancer screening population for 3 years and found that a negative screening result was not associated with increased relapse among those who had quit for less than 12 months. Very low relapse rates of 3% (after 3 years) for former smokers of more than 12 months abstinence at enrollment precluded evaluation of the effect of screen positivity.

We examine a large population of current and former smokers participating in a lung cancer screening program, the Early Lung Cancer Action Program (ELCAP), who received annual screening for up to 12 years. This longer duration of follow-up allows the evaluation of the effect of negative screen results on prolonged abstinence long-term rates of relapse.

The reassurance provided by lung cancer screening is assessed by comparing smoking behaviors of those with negative scans to those with positive (but not cancer)
scans. Those with negative scans were reassured that they had no findings of concern and were told to come back in 1 year, whereas those with a positive scan had findings requiring further evaluation to determine whether it was a malignancy and were brought in for further testing as a part of the study. These individuals were ultimately found not to have cancer and so were in some sense reassured as well; however, it is likely that the level of reassurance experienced by those who are told that they might have cancer and need further testing is substantively different from that of participants who are given a clean bill of health. Our objective is to define whether consistently negative screening results are associated with less cessation and more relapse over a 6-year interval in a population undergoing annual CT screening for lung cancer.

**Materials and Methods**

**Population.** From 1993 to 1999, participants were enrolled in ELCAP at New York University Medical Center and New York Hospital-Cornell University Medical Center. Participation was limited to the ELCAP population rather than the larger international study (I-ELCAP) to ensure that similar smoking cessation advice was provided to participants. After 1999, additional participants were enrolled at New York Hospital-Cornell University Medical Center.
Cessation in Lung Cancer Screening

Center. Enrollees were symptom-free volunteers who had at least a 10 pack-year history of cigarette smoking, had no prior cancer history, and were fit to undergo thoracic surgery. Upon enrollment, subjects received an initial screening chest CT and completed a baseline survey to determine medical condition, medical history, demographic characteristics, and smoking behavior. Annual repeat screening with chest CT and periodic follow-up smoking behavior assessments were conducted for all participants. Participants identified as current smokers were advised to quit smoking and were provided contact information for a telephone quitline.

By the end of 2004, at least one follow-up smoking assessment was available for 2,083 participants who did not have a malignant diagnosis, including 730 current smokers at the time of the baseline screen; 1,227 long-term, former smokers who had quit 1 or more years before enrollment; and 121 former smokers (recent quitters) who had quit within 1 year of enrollment. Five participants were excluded from the analysis because one or more of the covariates was missing. Seventy-eight percent of enrollees received at least one follow-up smoking assessment within 18 months of their enrollment. Institutional review board approval was obtained for this study at New York Hospital-Cornell University Medical Center and New York University Medical Center.

The analysis was restricted to participants who did not receive a malignant diagnosis because these individuals are likely to have a high rate of cessation following diagnosis (11-13) and their inclusion would lead to an overestimation of cessation and abstinence for participants who do not develop lung cancer. More detailed information about the population and protocol for evaluation are documented elsewhere (14).

Outcomes. Figure 1 presents a flow diagram of the smoking status changes in the study population that led to the different outcomes. Subjects were initially classified as baseline smokers, long-term former smokers, or recent quitters. Long-term former smokers were those who reported not having smoked for at least 1 year before enrollment. Recent quitters were those who had quit within 1 year before enrollment but not in the 30 days before enrollment. Those who had smoked in the 30 days before enrollment were defined as current smokers.

Analyses of new abstinence were restricted to those who enrolled in ELCAP as current (baseline) smokers. Abstinence at follow-up was defined as a self-report of no smoking in the 30 days preceding the follow-up evaluation (point abstinence). A quit date was recorded for those who reported becoming a former smoker since their last assessment. Two measures of cessation outcomes were evaluated. Cessation activity was measured as the cumulative fraction of baseline current smokers who reported point abstinence on one or more follow-up evaluations (cumulative point abstinence). This measure does not require prolonged abstinence because participants continued to be included in the measure even if they reported a subsequent relapse. Prolonged abstinence was defined as abstinence for at least 1 year plus abstinence in all subsequent reports. This measure reflects achievement of longer-term abstinence.

Relapse was defined as any self-reported smoking in the 30 days before the follow-up assessment for participants who had previously reported abstinence. Relapse was examined in three groups: 1,227 former smokers who reported being abstenent for at least 12 months at baseline evaluation (long-term former smokers), 121 former smokers who had quit for more than 30 days but less than 12 months at baseline (recent quitter), and those who quit during the follow-up. Of the 730 baseline smokers, 256 had at least one point abstinence within 72 months of trial enrollment. Of these, 61% had at least one follow-up after reporting new abstinence (n = 155). Analyses of relapse among those who quit during follow-up were confined to this group of 155 individuals. Smoking status information at annual follow-up was not collected uniformly throughout the study period, with less data available for the early years of the study and more complete data available in recent years.

The cumulative probability of achieving prolonged abstinence among ELCAP participants was compared with that of the U.S. population using the National Health Interview Surveys to estimate long-term (2+ years) successful cessation rates for white males and females born during the same years as the ELCAP participants. The long-term successful cessation rates for 5-year birth cohorts of white males and females by calendar year were calculated using the methodology described in National Cancer Institute Tobacco Control Monograph 8 (15). The rates were directly adjusted to match the age and sex composition of the ELCAP sample, and each birth cohort-specific annual quit rate was applied in the corresponding calendar year to calculate the estimated cumulative abstinence for current smokers in the U.S. population over the duration of follow-up.

Statistical Analysis. Cox proportional hazards models incorporating the results of the CT scans as a dichotomous, time-dependent covariate were used to test for differences between groups. Static Kaplan-Meier estimates were presented graphically to allow consideration of unadjusted differences in the outcome measures between those with positive and negative scans at different points in time. Among baseline smokers, time to cessation was measured from enrollment in ELCAP to the self-reported quit date. A quit date was missing for 26.7% of baseline smokers who quit during the study, and the date of the interview at which the subject reported having quit smoking was used as proxy for those subjects with missing quit dates. Conducting the analyses excluding those with missing quit dates did not substantively alter the results.

Participants were not asked to provide a date of relapse; thus, the relapse date was fixed at the midpoint between the last self-reported abstinence and the first self-reported resumption of smoking. The time to relapse for long-term former smokers and recent quitters was the number of months from study enrollment to the relapse date. Participants who died during the study or were lost to follow-up were censored at their last smoking assessment, and participants with outcomes that occurred after 72 months were censored at 72 months (44.2%).

The proportional hazards models incorporated the results of the CT scans as a dichotomous, time-dependent covariate. A positive scan was attributed to each participant who received a positive screening result before cessation or relapse. Participants who did not receive any positive CT scan results or who reported new
abstinence (or new relapse in the analyses of relapse) before the conversion of their scan result from negative to positive were classified as having negative CT scans. Positive scan results were those requiring additional interval evaluation with repeat CT to evaluate whether the nodule was growing consistent with a malignancy. A positive scan was one that showed solid or part-solid noncalcified nodule(s) of size 5.0 mm or larger, or nonsolid noncalcified nodule(s) of size 8 mm or larger. All other results were classified as negative CT scans. Participants whose positive scans led to a diagnosis of lung cancer were excluded from the analyses. This allowed screened recipients to be separated into two groups, those with a negative screen who were reassured and told to come back in 1 year and those with a positive screen who were told that further evaluation was needed to assess whether their nodule might be a malignancy.

Of those who enrolled in the study 6 or more years before the end of follow-up (and therefore could have been followed for 6 years), 68.4% received smoking assessments at 6 or more years of follow-up and they had received on average 5.4 CT scans. For the entire study population, including those who enrolled less than 6 years before the end of the follow-up and who therefore could not have achieved the 6-year point, 46.1% reached the 6-year follow-up point.

The models controlled for the baseline characteristics of duration of smoking, smoking intensity (packs smoked per day), age, gender, and race as well as time to positive scan. Most subjects were white (93.9%); thus, participants were classified as either white or other. The relapse models for long-term former smokers also included duration of abstinence.

Post hoc power calculations for this study indicate that there was 90% power to detect hazard ratios (HR) for higher rates of relapse among those who had positive scans of 0.42 for long-term former smokers and 0.51 for those recent quitters, suggesting ample power to detect a substantive effect. The level for current smokers who quit during the study was 0.26 consistent with the smaller number of individuals in this group and suggesting that differences of 3- to 4-fold in HRs for relapse rates might have escaped detection by chance in analyses of this group.

Results

Demographic characteristics and smoking behaviors of study participants are presented in Table 1. There are slightly more males among long-term former smokers than among baseline smokers, and long-term former smokers are somewhat older than baseline smokers or recent quitters. A higher proportion of both baseline smokers and recent quitters reported smoking one-half pack to 1 pack per day (ppd) of cigarettes. A higher proportion of long-term former smokers reported smoking more than 1 ppd (50.7%). The analyses presented in this article are confined to the first 6 years of follow-up to reduce the potential bias introduced by examining data only from long-term continuing study participants.

Kaplan-Meier survival analyses estimate that 35.1% of baseline current smokers reported smoking abstinence on at least one follow-up smoking assessment, and 29.0% reported prolonged abstinence. Prolonged abstinence for an age and gender matched sample of the U.S. population (National Health Interview Surveys data) was 23%. The screened population is not directly comparable with national estimates and the national estimate is presented only as a benchmark.

The Effect of Consistently Negative Screening Results on Point and Persistent Abstinence among Baseline Smokers. The question of whether a consistently negative screening result reduces cessation activity or long-term successful abstinence is examined by comparing the likelihood of point and prolonged abstinence for those who had a consistently negative screening result to the same likelihood for those who had a positive screening requiring further evaluation to establish whether it was a malignancy. Table 2 presents the HRs from the univariate Cox proportional hazards models of the likelihood of reporting at least one point abstinence during the 6 years of follow-up. Subjects who received negative CT scan results had a 28% lower likelihood of achieving point abstinence at one or more follow-up, compared with those who had positive result (HR, 0.72; P < 0.004). Kaplan-Meier curves for the cumulative percentage of baseline smokers reporting at least one point abstinence over time reveal that much of this effect is manifest in the early period of the follow-up when the largest number of new positive screens would have occurred (Fig. 2). By

Table 1. Description of ELCAP participants

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>$\chi^2 (P)$</th>
<th>Smoking status at baseline</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline smokers ($n = 730$)</td>
</tr>
<tr>
<td>Male</td>
<td>10.6* (0.005)</td>
<td>44.8 (41.2-48.4)</td>
</tr>
<tr>
<td>White</td>
<td>4.1 (0.13)</td>
<td>93.8 (91.8-95.5)</td>
</tr>
<tr>
<td>Smoking intensity (ppd)</td>
<td>34.3* (&lt;0.0001)</td>
<td>14.1 (11.7-16.8)</td>
</tr>
<tr>
<td>1/2</td>
<td>1/2-1</td>
<td>48.6 (44.9-52.3)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>56.3 (33.7-40.8)</td>
<td>50.7 (32.4-50.6)</td>
</tr>
<tr>
<td>Age</td>
<td>38.32* (&lt;0.0001)</td>
<td>59.9 (9.2)</td>
</tr>
<tr>
<td>Duration of smoking</td>
<td>283.77* (&lt;0.0001)</td>
<td>41.8 (10.1)</td>
</tr>
<tr>
<td>Duration of abstinence</td>
<td></td>
<td>16.3 (10.5)</td>
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</tbody>
</table>

*Significant ($P < 0.05$).
the 6th year of follow-up, statistical significance disappeared, suggesting that being informed of a positive scan might lead to increased quitting in the short-term but that the effect on cessation activity diminishes with time following the initial positive screening result.

Any effect of cessation on disease rates would be mediated through an effect on long-term abstinence. When prolonged abstinence was examined using the univariate Cox proportional hazard models, a consistently negative scan was not associated with a lower likelihood of prolonged abstinence at 6 years of follow-up (HR, 1.34; \( P = 0.15 \); Table 2) or in the Kaplan-Meier plots (Fig. 3). Results are similar when the follow-up is extended to 12 years. Because no covariates were statistically significant for prolonged abstinence in the univariate model, multiple-covariate Cox models were only examined for point abstinence. When considered simultaneously in the Cox proportional hazards model of point abstinence, neither CT scan results nor smoking greater than 1 ppd were significant.

**Smoking Relapse.** We examined the possibility that a consistently negative screen result might influence the likelihood of smokers relapsing back to smoking for three groups of former smokers: those who were long-term abstinent at baseline, those who had quit from 30 days to 12 months before enrollment, and those who quit during the follow-up period. Cox proportional hazard models were used to compare the likelihood of relapse for those with a consistently negative scan to those with a positive scan.

The HRs from univariate Cox proportional regression modeling of relapse for the three groups of former smokers, subset by baseline smoking status, are presented in Table 3. Long-term former smokers at baseline had very low cumulative rates of relapse (4.4%) at 6 years of follow-up and the HRs for those with a consistently negative scan were not significantly different from those with a positive scan, suggesting that screening and the reassurance of a negative screen had little effect on relapse among long-term former smokers.

There were also no significant differences in likelihood of relapse between those with positive and negative scans among recent quitters, or among baseline smokers who quit during the study.

Because the mean duration of abstinence was long (16 years) in former smokers and an effect on relapse might be more evident among those with more recent onset of abstinence, we also conducted an analysis of relapse for those abstinent for 1 to 3 years at enrollment. The HR for a positive scan compared with a negative scan...
in univariate analyses was 1.32 [95% confidence interval (95% CI, 0.39-4.49)]. Thus, the effect in this shorter duration of abstinence group was both not significant and in the direction of a higher likelihood of relapse for those with a positive scan. Results for former smokers of 3+ years abstinence at enrollment remained not significantly different by scan result. Among recent quitters at enrollment, 42.2% resumed smoking during 72 months of follow-up, but those with consistently negative scans did not have higher rates of relapse than those with positive scans (HR, 0.88; 95% CI, 0.42-1.82; Table 3; Fig. 4). Among baseline smokers who quit during the study, 33.5% resumed smoking within 72 months of enrollment; and a consistently negative scan was not associated with relapse (HR, 1.61; 95% CI, 0.39-6.70; Table 3; Fig. 5). There is a wide confidence interval for those who quit during the study, suggesting that an effect of moderate size could have been missed in this group. Finally, multiple covariate modeling of relapse did not show a statistically significant effect of scan results for any of the relapse groups.

**Discussion**

In a review of lung cancer screening in 1989, David Eddy (2) speculated that the reassurance provided by a negative screening outcome might result in lower rates of smoking cessation. Current recommendations by the U.S. Preventive Services Taskforce (3) echo those concerns and they are voiced in literature on lung cancer screening (4, 7, 10). Existing observations from lung cancer screening studies suggest that participants have high rates of smoking cessation (point abstinence) during the initial few years of screening (4, 5, 7-10) and that a positive screening result is associated with higher point abstinence in short-term follow-up. We provide evidence that replicates this short-term effect on point abstinence. We also provide evidence indicating that a consistently negative result in a lung cancer screening program is not associated with a reduced likelihood of achieving long-term smoking abstinence or increased relapse back to smoking over a 6-year period of follow-up. To our knowledge, this is the first

![Figure 4](https://example.com/f4.png)  
**Figure 4.** Kaplan-Meier estimates of the percentage of recent quitters at enrollment who relapse by baseline CT scan result.

![Figure 5](https://example.com/f5.png)  
**Figure 5.** Kaplan-Meier estimates of the percentage of baseline smokers quitting during follow-up who relapse by duration of abstinence and baseline CT scan results.

### Table 3. Univariate Cox modeling of the likelihood of relapse back to smoking among former smokers subset by baseline smoking status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Long-term former smokers</th>
<th>Recent quitters</th>
<th>Baseline smokers who quit during follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person-years HR (95% CI)</td>
<td>Person-years HR (95% CI)</td>
<td>Person-years HR (95% CI)</td>
</tr>
<tr>
<td>CT scan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonpositive results Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive results 0.51 (0.20-1.29)</td>
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<tr>
<td>Duration of smoking 1.01 (0.99-1.03)</td>
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<tr>
<td>Duration of abstinence 0.90* (0.87-0.94)</td>
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<tr>
<td>Cigarettes smoked daily (ppd)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/2 575 Reference</td>
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<td></td>
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<tr>
<td>1 2,085 1.40 (0.54-3.65)</td>
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<tr>
<td>&gt;1 2,878 0.96 (0.37-2.53)</td>
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</tr>
<tr>
<td>Sex Male 2,941 Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female 2,598 0.83 (0.49-1.43)</td>
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<tr>
<td>Age 0.92* (0.90-0.95)</td>
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<td></td>
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<tr>
<td>Race Not white 232 Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White 5,306 1.16 (0.28-4.76)</td>
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<tr>
<td>*Significant (P &lt; 0.05).</td>
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</table>
examination of smoking cessation outcomes in a population of individuals being screened for lung cancer with follow-up smoking assessments over a period longer than 3 years.

Because everyone who participated in EL Cap received at least one CT scan, the study design precludes direct evaluation of the effect of participating in a screening program on abstinence or of receiving lung cancer screening compared with not being screened. Individuals who elected to participate in the EL Cap program may be more health conscious and more interested in cessation, raising concerns about direct comparisons with smokers and former smokers in the general population. We present data on prolonged abstinence among baseline smokers among the screening participants that reveal a rate of prolonged abstinence as high as or higher than an age- and gender-matched sample of the U.S. population. Because these populations are not comparable, these abstinence rates are presented as a benchmark comparison only and we do not attempt a statistical evaluation.

As reported by others (9, 10), a positive (but noncancer) chest CT is associated with point abstinence early in the follow-up period, suggesting that an abnormal finding may act as a trigger for cessation. Our results replicate this short-term effect but reveal no continuing effect of a positive scan on the cumulative likelihood of reporting one or more point abstinences at 6 or 12 years of follow-up. These results suggest that the effect of a positive scan on point abstinence may be largely confined to the period immediately following notification of the initial positive screening result and that scan positivity may not exert a persistent effect on cessation activity as screening continues.

Consistent with the absence of a longer-term effect on cessation, prolonged abstinence is not statistically different for those with a consistently negative scan and those with a positive screening result, suggesting that the reassurance provided by a negative scan may not be a factor determining long-term abstinence.

Expressions of concern about the demotivating effect of a negative screen result on cessation seem to be largely limited to lung cancer screening programs. A parallel body of literature exists, examining whether screening for tobacco-related lung disease influences cessation, but the hypothesis tested is usually whether provision of screening can enhance cessation (16-18). Although there is insufficient evidence to establish a benefit for cessation of spirometric and other screenings for tobacco-related damage (16), the evidence does not suggest a deleterious effect on cessation. These observations are consistent with our findings.

Townsend and colleagues (10) reported no association of screening results with relapse back to smoking among those who had quit for less than 12 months at enrollment. Low rates of relapse at 3 years of follow-up among longer-term abstinent smokers precluded assessment of scan effects for that group. Our data replicate Townsend and colleagues’ results for smokers with less than 12 months of abstinence at enrollment and extend the absence of an association to 6 years of follow-up. A statistically significant association of scan positivity and relapse is also absent in our data for a large group of longer-term former smokers (n = 1,227) over a 6-year period of follow-up. No association of a positive scan with relapse was found for current smokers at enrollment who quit during the study, but the small number of observation and limited power to show an effect for this group requires caution in drawing inference. Data on follow-up of the EL Cap population include individuals followed for as long as 12 years, but accrual to the population has continued since 1993 and the bulk of the population have less than 12 years of follow-up. As the length of follow-up is extended in the analysis, the number of individuals available shrinks due to study participants dropping out and more recent enrollees not having achieved that length of follow-up. For this reason, we have limited the presentation of our statistical and graphic comparisons to the first 6 years of follow-up. We have conducted similar analyses of the full 12-year follow-up data and the results do not alter the interpretation evident from the 6-year follow-up; thus, they are not presented in detail.

Study Limitations. For the analysis of relapse, 39% of baseline smokers who reported at least one point abstinence during the follow-up were excluded from the analysis of relapse because these subjects did not have any additional smoking assessments after their report of abstinence. Although this percentage represents a sizable proportion of the study population, they were not different demographically or in their smoking behavior from the group included in the analysis.

Some imprecision in estimating cessation and relapse resulted from interval censoring. Because the EL Cap study was not designed to evaluate changes in smoking behavior, information on smoking behavior was not captured continuously or uniformly. Early in the study, subjects were not asked about changes in smoking behavior at their follow-up appointments for CT scans. Later, subjects were asked if they had smoked in the month preceding their appointment and when they had quit smoking, but participants were not asked for the dates that they resumed smoking. To estimate the relapse date, this study used a conservative approach of using the midpoint between the last known abstinence and the first report of relapse.

The data used to assess abstinence and relapse are self-reported, and it is possible that participants may have misreported their smoking status. These concerns are somewhat mitigated by recent studies using biochemical verification that show the validity of self-reported smoking status (19), including self-report in the context of a lung cancer screening study (20). Finally, given the lack of a control condition of individuals who did not enroll in a lung cancer screening program, the study design precludes direct evaluation of the effect of receiving lung cancer screening on cessation outcomes.

The data presented are not representative of the general population, particularly for race/ethnicity, and this means that generalization of the results to all smokers in the U.S. population should be done with considerable caution.

Screening programs provide opportunities to change the smoking behavior of participants (5). The evidence presented suggests that a consistently negative scan during long-term participation in a lung cancer screening program is not associated with reduced long-term abstinence or greater smoking relapse.
Disclosure of Potential Conflicts of Interest

C.I. Henschke (CIH) and D.F. Yankelevitz (DFY) have pending and awarded patents on CT scanning. Both CIH and DFY received royalty payments from Cornell through Cornell’s licensing agreement with GE for software consistent with the Bayh Dole act. CIH has subsequently divested herself from receiving any payments. DFY was a medical advisor and stockholder in PneumRX a company that made biopsy needles. DFY discontinued being an advisor nearly a year ago, and gave his stock to charity. In neither instance did the amounts exceed $10,000. D.M. Burns has testified in litigation against the tobacco industry including on issues related to lung cancer screening.

Acknowledgments

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C.M. Anderson and R. Yip conducted analyses of the data presented. Dr. Burns and C.M. Anderson drafted the initial manuscript. D.M. Burns, C.I. Henschke, D.F. Yankelevitz, and J.S. Ostroff developed the study design and reviewed and revised the manuscript.

References

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