Resected Lung Cancer Patients Who Would and Would Not Have Met Screening Criteria

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Background. **Current eligibility criteria for lung cancer screening may underestimate the risk of malignancy for some individuals. We compared the predicted risk of lung cancer among patients who would have met screening criteria to those who would not have despite being at moderate-risk.**

Methods. **A retrospective cohort study of resected lung cancer patients was performed. The screen eligible group was based on criteria provided by the United States Preventive Services Task Force; age 55 to 80 and a 30 or greater pack-year smoking history. The screen ineligible group was based on criteria provided by the National Comprehensive Cancer Network for a moderate-risk individual not recommended screening; age greater than 50 years, greater than 20 pack-year smoking history, and no history of asbestos exposure or chronic obstructive pulmonary disease. A recently validated risk-prediction model was used to compare the risk of lung cancer across eligibility groups based on measured and imputed patient-level variables.**

Results. **Screen ineligible patients (n = 88) had a lower estimated probability of lung cancer than screen eligible patients (n = 419); 1.3% versus 3.1%, p value less than 0.001. However, 20% of screen ineligible patients had a predicted probability of lung cancer greater than or equal to the prevalence of lung cancer (3.7%) among National Lung Screening Trial participants; 17% of screen ineligible patients had a predicted probability of lung cancer greater than or equal to the American Association for Thoracic Surgery threshold (5%) defining high-risk individuals.**

Conclusions. **Current eligibility criteria for lung cancer screening underestimate the risk of lung cancer for some individuals who might benefit from lung cancer screening.**

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The National Lung Screening Trial (NSLT) demonstrated a significant reduction in lung cancer mortality attributable to screening high-risk individuals with low-dose computed tomography (LDCT) [1]. People eligible for study were 55 to 74 years old, current or former smokers who quit within the last 15 years, and had at least a 30 pack-year smoking history. In 2013, the United States Preventive Services Task Force (USPSTF) recommended screening of high-risk individuals as defined by NLST inclusion criteria, but extended the age range to 80 years based on modeled analyses of risks and benefits [2]. As a result, commercial insurers are required (by law) to fully cover the costs of LDCT screening for this high-risk population starting in 2015. The availability of lung cancer screening is one of the most significant advances in thoracic oncology in a generation. Yet most guidelines for screening, including the USPSTF, have limited themselves to the inclusion criteria of the NLST, which were developed in order to accomplish a randomized clinical trial and do not assert that they represent an exclusive risk profile for development of lung cancer. The NLST utilized only age and smoking exposure in order to simplify patient recruitment and did not study other known risk factors for lung cancer. Because it is unlikely that large randomized trials will assess other at-risk populations, it is important to consider whether there are opportunities to extend the benefits of early detection to other high-risk individuals.

The current approach to determining screen eligibility omits other known risk factors for lung cancer and imposes arbitrary bounds on age and tobacco exposure. In response to this criticism, investigators developed a risk-prediction model for lung cancer among smokers enrolled in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), and validated model performance in NLST participants [3]. One can use the publicly available prediction model to estimate the risk of lung cancer for a hypothetical individual under various assumptions about their risk profile. This exercise demonstrates that an individual can be ineligible for screening based on USPSTF criteria, but have a similar or even higher risk of lung cancer than NLST participants. Current eligibility criteria for screening may underestimate the risk of lung cancer for some individuals.

To provide empirical evidence of this concern, the goal of this investigation was to compare the predicted risk of lung cancer among operatively managed lung

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cancer patients who would and would not have met screening eligibility criteria. Screen eligibility was based on the USPSTF criteria. A meaningful comparator group would ideally consist of individuals at risk for lung cancer but not recommended screening. Accordingly, we identified a group based on criteria provided by the National Comprehensive Cancer Network (NCCN) for individuals at moderate risk not recommended to undergo screening [4].

Material and Methods

A retrospective study was conducted of lung cancer patients treated with pulmonary resection between 1999 and 2008 with follow-up through 2012. Subjects included in this study were asymptomatic adults with solitary, primary lung cancer detected by computed tomography and meeting screen eligibility or ineligibility criteria as defined in the next paragraph. The source of patient information was a single-institution surgical quality improvement database maintained by Memorial Sloan-Kettering Cancer Center. This database contains information on the following: patient, cancer, and treatment characteristics; early postoperative events; and long-term survival available through a linkage with the Social Security Death Index. An institutional review board approved this investigation and waived the need for consent.

Patients considered screen eligible were 55 to 80 years of age and had a 30 or greater pack-year smoking history. This group was based on eligibility criteria provided by the USPSTF. Former smokers in this database had information on number of years quit recorded as a categoric variable: 1 to 4 weeks; 1 to 6 months; 6 to 12 months; 1 to 5 years; 6 to 10 years; and 10 or greater years. As it was not possible to measure the number of years quit more granularly, the number of years quit was re-coded assuming the following: quit 1 year ago if quit 1 to 4 weeks, 1-6 months, or 6 to 12 months ago; quit 5 years ago if quit 1 to 5 years ago; quit 10 years ago if quit 6 to 10 years ago; and quit 15 years ago if quit greater than 10 years ago. Patients considered screen ineligible were 50 or greater years of age, had a 20 or greater pack-year smoking history, and no additional documented risk factor. Selection of this comparator group was based on criteria outlined by the NCCN for an individual at moderate risk for lung cancer but not recommended screening, yet excluding clearly low-risk patients that would not provide a legitimate comparison. Lung cancer risk factors routinely recorded in the database were a documented history of chronic obstructive pulmonary disease and asbestos exposure. The screen eligible and ineligible groups were mutually exclusive. For instance, a 57-year-old 32 pack-year current smoker was classified as screen eligible.

The primary aim of this study was to compare the predicted risk of lung cancer across eligibility groups using a validated prediction model [3]. Tammemägi and associates [3] developed and validated a risk-prediction model among 80,375 patients enrolled in the PLCO trial based on the following variables: age; race; education; body mass index; chronic obstructive pulmonary disease; personal history of cancer; family history of lung cancer; smoking status (current versus former); duration of smoking intensity; and smoking quit time. The performance of this model was validated in an independent cohort of individuals from the NLST. Published coefficients from this model were used to estimate the probability of lung cancer for each subject in our study based on his or her unique set of risk factors [3]. Variables recorded in our database and allowed to vary at the patient-level included age, race, smoking status, average number of cigarettes smoked per day, years smoked, and years quit. The database recorded pack-years of cigarette exposure. In order to use this information for risk-prediction, as specified by the model with 2 different variables for cigarette exposure, pack-years was disaggregated to cigarettes per day and years smoked under the assumption that all patients smoked 1 pack per day. Variables not recorded in the database were imputed and set to the same value for all patients as such: body mass index of 27; some college education; no personal history of malignancy; and no family history of lung cancer. In order to anchor risk estimates to an external reference, we calculated the proportion of patients with an estimated risk of lung cancer equal to or above several thresholds including the following: (1) the prevalence of lung cancer among NLST participants [1]; (2) the thresholds for detecting 80% and 90% of lung cancers as reported by the authors of the validated risk-prediction model [3]; and (3) the threshold for a high-risk individual proposed by the American Association of Thoracic Surgery (AATS) lung cancers [5]. The STATA/SE 12.1 was used for all analyses (StataCorp LP, College Station, TX). Median values were compared using the Kruskal-Wallis equality-of-populations rank test, categoric variables were compared using the Fisher exact test, and survival rates were compared using Kaplan-Meier methods and a log-rank test. Confidence intervals [CI] for binary variables were estimated using binomial exact methods. The p values less than 0.05 were considered significant.

Results

Compared with screen eligible patients, screen ineligible patients were more frequently women, had fewer pack-years of tobacco exposure, were less likely to have cardiac comorbid conditions, and had higher median predicted diffusion capacity of carbon monoxide levels (Table 1). The distribution of screen eligible and ineligible patients did not change over time ($p = 0.585$).

As expected, the median predicted probability of lung cancer was significantly lower among screen ineligible versus screen eligible patients (1.3% [range, 0.3% to 14%] vs 3.1% [range, 0.7% to 15%], $p < 0.001$). The distributions of the predicted probability lung cancer by eligibility status are shown in Figure 1. Among patients in the screen ineligible group, 20% (95% CI, 13% to 30%) had a similar or higher predicted risk of lung cancer than the prevalence of lung cancer (3.7%) among NLST