Screening Criteria Evaluation for Expansion in Pulmonary Neoplasias (SCREEN)

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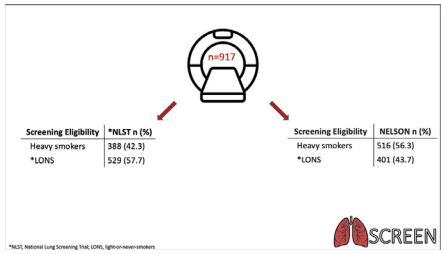
The SCREEN study investigated screening eligibility and survival outcomes between heavy smokers and light-or-never-smokers with lung cancer to determine whether expanded risk factor analysis is needed to refine screening criteria. SCREEN is a retrospective study of 917 lung cancer patients diagnosed between 2005 and 2018 in Nova Scotia, Canada. Screening eligibility was determined using the National Lung Screening Trial (NSLT) criteria. Mortality risk between heavy smokers and light-or-never-smokers was compared using proportional-hazards models. The median follow-up was 2.9 years. The cohort was comprised of 179 (46.1%) female heavy smokers and 306 (57.8%) female light-or-never-smokers. Light-or-never-smokers were more likely to have a diagnosis of adenocarcinoma [n=378 (71.6%)] compared to heavy smokers [n=234 (60.5%); $P< 0.001$]. Heavy smokers were more frequently diagnosed with squamous cell carcinoma [n=111 (28.7%)] compared to light-or-never-smokers, [n=100 (18.9%); $P< 0.001$]. Overall, 36.9% (338) of patients met NLST screening criteria. There was no difference in 5-year survival between light-or-never-smokers and heavy smokers [55.2% (338) vs 58.5% (529); $P = 0.408$; HR 1.06, 95% CI 0.80-1.40; $P = 0.704$]. Multivariate analysis showed that males had an increased mortality risk [HR 2.00 (95% CI 1.57-2.54); $P< 0.001$]. Half of lung cancer patients were missed with the conventional screening criteria. There were more curable, stage 1 tumors among light-or-never-smokers. Smoking status and age alone may be insufficient predictors of lung cancer risk and prognosis. Expanded risk factor analysis is needed to refine lung cancer screening criteria.

Semin Thoracic Surg 35:769–780

Keywords: Lung neoplasms, Early detection of cancer, Mass screening, Risk factors, Smokers, Non-smokers



Roughly half of all lung cancer patients are missed with conventional screening criteria.

Central Message

Half of all lung cancer patients are missed with conventional screening criteria. Age and smoking status alone may be insufficient predictors of lung cancer risk and prognosis.

Perspective Statement

Most lung cancer patients have poor survival outcomes. National guidelines recommend lung cancer screening for heavy smokers to reduce mortality, but many lung cancer patients are not heavy smokers. We must determine whether screening using age and smoking status sufficiently predicts lung cancer risk and prognosis, or if expanded risk factor analysis is needed to refine lung cancer screening criteria.

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Read at the AATS 102nd Annual Meeting, May 14-17, 2022, Boston, MA.

Disclosures: None.

Funding: This work was supported by a Beatrice Hunter Cancer Research Institute Summer Studentship and the Dalhousie Medical Student Society Student Innovation and Research Award. The study funders did not participate in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflicts of Interest: None

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1043-0679/$–see front matter

https://doi.org/10.1053/j.semtcvs.2022.06.018

Lung cancer is the leading cause of cancer death globally.[1,2] Approximately 70% of lung cancers are diagnosed at advanced stages (III-IV), with a 5-year survival rate of 20%.[1] Several randomized controlled trials affirm that low-dose-CT (LDCT) screening detects more lung cancers overall and at earlier, curable stages.[3-8] Notably, the National Lung Screening Trial (NSLT) demonstrated a 20% reduction in mortality with annual LDCT screening compared to chest radiography in heavy smokers.[4] Similarly, the NELSON trial found a reduction in lung-cancer mortality of 24% with LDCT screening compared to no screening in heavy smokers.[3] LDCT screening for lung cancer detection has also been demonstrated to be feasible and cost-effective.[9] Several national organizations in both the United States and Canada recommend LDCT screening to detect lung cancer in heavy smokers.[1,10-14]

The NLST and NELSON trials identified high-risk patients as those aged 55-74 and 50-74 years of age respectively, with an extensive smoking history (Table 1, Supplementary Table A1).[3, 4] However, the NLST screening criteria was based on age and smoking status, stemming from prior studies including the Prostate, Lung, Cervical, and Ovarian (PLCO) Cancer Screening Trial.[15] Similarly, the patient population from NELSON stemmed from a pilot study which determined expected lung cancer mortality based on age and smoking status only.[16] Female sex, family history, and environmental exposures including exposure to radon have also been associated with the development of lung cancer.[2] Long-term indoor radon exposure is responsible for 16% of lung cancer deaths in Canada[17] and is the leading cause of lung cancer among non-smokers in the United States.[17,18] Predictive success of rigorous risk prediction models for lung cancer development suggest that the selection of patients based on age and pack-years alone is insufficient.[19,20]

Nova Scotia's economy has traditionally been supported by the heavy industries such as coal mining resulting in industrial exposure to carcinogens.[21] Environmental studies have demonstrated high levels of radon in Nova Scotia,[22] contributing to a population with the lung cancer risk factors outside of smoking history. While most lung cancer cases have traditionally been in heavy smokers, the proportion of never smokers with the lung cancer has increased to comprise 15%-40% of all cases globally.[23] This increased incidence of lung cancer among never smokers persists even after controlling for race or ethnicity.[24] Additionally, it is unclear whether survival differs in lung cancer patients between the heavy smokers and the light-or-never-smokers. There may be a need to account for extraneous factors aside from the smoking status and the age when screening guidelines are applied locally. Thus, the objective of this study was to retrospectively determine the proportion of lung cancer patients that would have been missed with the conventional lung cancer screening criteria, as well as explore whether survival differs between the light-or-never-smokers and the heavy smokers.

Table 1. NLST Screening Criteria for Heavy Smokers

*NLST Criteria
• 55-74 years of age.
• Current or ex-smokers within 15 years.
• 30 pack-year history or greater.

*National Lung Screening Trial

MATERIAL AND METHODS

This study was approved by the Nova Scotia Health Research Ethics Board (File No.1025892) on August 21st, 2020. The requirement to obtain informed consent was waived under Section 2.1c of the Tri-Council Policy Statement. This study adhered to STROBE guidelines for cohort studies.

Study Design, Data Sources, & Participants

SCREEN is a retrospective cohort study comparing screening eligibility and the survival outcomes between the heavy smokers and the light-or-never smokers. The Nova Scotia Cancer Registry collects data for individuals diagnosed with lung cancer and captures all mortalities in the province. This registry was linked with the Queen Elizabeth II (QEII) Lung Tumor Bank, a clinical and molecular database of patients undergoing lung resection.[25] The study population consisted of lung cancer patients diagnosed between January 2005 and December 2018 at the QEII Health Sciences Center in Halifax, Nova Scotia, Canada. Patients with benign lesions were excluded from the study. The date of resection was considered the date of diagnosis. Among patients with the synchronous tumors diagnosed on different dates, the earliest lung tumor diagnosed was captured for the study and the subsequent samples excluded as the first tissue diagnosis would have been detected through screening. For synchronous tumors known on the date of the first surgery, the tumor associated with the highest stage was selected.

Primary Outcomes

The primary outcome of the SCREEN study was to retrospectively determine the percentage of lung cancer patients that would have met the screening criteria based on age and the smoking status for heavy smokers using the NLST and NELSON trial screening criteria, independently. Patients that smoked less than the criteria for enrollment in the NLST or NELSON trials were considered light-or-never-smokers regardless of age. Patients that met the smoking criteria but did not meet age criteria were excluded from the study. The patient characteristics of heavy smokers were compared to light-or-never-smokers. Furthermore, the SCREEN study investigated whether there were overall survival differences between the heavy smokers and the light-or-never-smokers using the NLST criteria, adjusting for clinical variables of interest. Similar comparisons between the heavy smokers and the light-or-never-smokers were conducted using NELSON trial criteria.

Secondary Outcomes

This study also examined the distribution of cancers by histological diagnosis and stage among the heavy smokers and the light-or-never-smokers defined by NLST criteria. This was repeated by using NELSON criteria to define heavy smokers and light-or-never-smokers. The distribution of lung cancers was determined based on the geographical radon levels (low, medium, and high).

Quantitative Variables

Clinical variables of interest included age, sex, previous cancer history, family history of cancer, symptoms, histological cancer diagnosis, grade, laterality, stage, urban versus rural environment, and geographic radon levels. Clinical information for the patients described above such as smoking history, prior cancer history, and family history of cancer were extracted from the QEII Lung Tumor Bank, which stemmed from the patient charts. Geographic location was determined using postal code information from the NS Cancer Registry, and the provincial Radon Risk Map was searched to correlate relative radon risk with the place of residence.

Statistical Methods

Descriptive statistics to summarize baseline demographic information included mean ± standard deviation for continuous data, in addition to frequencies and percentages for the categorical data. Patient characteristics were compared between the heavy smokers and the light-or-never-smokers defined by screening criteria using Student's t-test for continuous variables and Chi-square tests for categorical variables. Survival from the date of diagnosis to death or date of last follow-up was analyzed using Kaplan-Meier plots and log-rank tests to compare the survival distribution between groups. Kaplan-Meier survival estimates were also generated at 1-year and 5-year time points with 95% confidence intervals and point-wise *P*-values were generated to compare survival estimates between the groups. Cox proportional hazards models were used to estimate hazard ratios. Multivariate models were developed adjusting for a priori determined variables including age, sex, prior lung cancer history, family history of lung cancer, symptom presentation, histological diagnosis, differentiation, laterality, stage, geography by region, and radon level by region. Patients with all available case data were included in the analysis. Statistical analysis was performed using SAS software version 9.4 (The SAS Institute, Cary, NC). A *P*-value of less than 0.05 was considered to indicate the statistical significance.

RESULTS

The SCREEN study included 917 patients with a median length of follow-up of 2.9 (IQR 1.4-5.4) years. Projected internal data would estimate a lung cancer incidence of 13,000 during this study period. Demographics, oncology characteristics, and univariate survival analysis are listed for NLST in Table 2. Overall, 388 (42.3%) patients met NLST screening criteria with a mean age of 65.7 years ± SD 5.3, while 529 (57.7%) patients were light-or-never-smokers that did not meet criteria with a mean age of 68.8 ± 10.3 (Fig. 1). There were 179 (46.1%) female heavy smokers and 306 (57.8%) female light-or-never-smokers defined by NLST screening criteria. Adenocarcinoma was more commonly diagnosed among light-or-never-smokers that did not meet NLST screening criteria [n=378 (71.6%)] compared to heavy smokers [n=234 (60.5%); *P*< 0.001]. Heavy smokers that met NLST screening criteria were more frequently diagnosed with squamous cell carcinoma [n=111 (28.7%)] compared to light-or-never-smokers, [n=100 (18.9%); *P*< 0.001]. Heavy smokers were also more likely to have poorly differentiated or undifferentiated tumors [n=217 (59.0%)] compared to light-or-never-smokers that did not meet NLST screening criteria, [n=232 (46.3%); *P*<0.001]. light-or-never-smokers that did not meet NLST criteria were more likely to have a history of prior cancer, [n=138 (26.3%)] compared to heavy smokers [n=79 (20.4%); *P* = 0.040]. There was no difference in survival between heavy smokers and light-or-never-smokers defined by NLST criteria (Table 2). The demographic characteristics, oncology characteristics and univariate survival analysis are listed for NELSON in Supplementary Table A2. In the NELSON analysis, there was a higher proportion of patients with stage 1 lung cancer in those meeting NELSON screening criteria [n=216 (58.7%)] compared to those that did not [n=244 (51.8%); *P* = 0.047].

Screening Criteria and Overall Survival

Univariate analysis demonstrated that overall survival did not differ between heavy smokers and light-or-never-smokers defined by NLST criteria, *P* = 0.657 (Fig. 2). At one year, there was no difference in survival for light-or-never-smokers compared to heavy smokers defined by NLST [0.92 (0.89 -0.94); 0.90 (0.88-0.94); *P* = 0.586] criteria. At 5 years, there was no difference in survival between the light-or-never-smokers and the heavy smokers using NLST [0.59 (0.54 -0.64); 0.55 (0.50-0.61); *P* = 0.408] criteria.

Similarly, survival curves for patients analyzed using NELSON criteria are found in Supplementary Figure A, while univariate survival outcomes obtained using NELSON criteria are listed in Supplementary Table A3.

Univariate analysis showed that females had a lower rate of mortality (HR 0.48, 95% CI 0.39-0.59; *P*<0.001) compared to males in the general cohort (Table 3). Additionally, those with a family history of cancer had a higher rate of mortality compared to those without a family history of cancer (HR 1.34, 95% CI 1.04-1.73; *P* = 0.023). Patients with a prior cancer had a higher rate of mortality compared to those without a history of cancer (HR 1.30, 95% CI 1.04-1.53; *P* = 0.022). Those with poorly differentiated or undifferentiated tumors had a higher rate of mortality (HR 1.60, 95% CI 1.11-2.30; *P* = 0.012) compared to those with more well-differentiated tumors. Those with advanced stage IV lung cancer had a higher mortality rate compared to their counterparts (HR 3.03, 95% CI 2.08-4.41; *P*<0.001). Patients with symptoms of hemoptysis or weight

Table 2. Demographics by NLST Criteria

	†,*NLST		*P*-value
	‡HS (n=388)	§LONS (n=529)	
Age			<0.001
Mean (SD)	65.7 (5.26)	68.8 (10.31)	
Smoking Status, n (%)			<0.001
Never smoked	0 (0.0%)	72 (13.6%)	
Current Smoker	193 (49.7%)	133 (25.1%)	
Past Smoker	195 (50.3%)	324 (61.2%)	
Sex, n (%)			<0.001
Female	179 (46.1%)	306 (57.8%)	
Male	209 (53.9%)	223 (42.2%)	
Family History n (%)	70 (18.2%)	85 (16.3%)	0.435
Cancer history, n (%)	79 (20.4%)	138 (26.3%)	0.040
Symptoms, n (%)	70 (18.0%)	81 (15.6%)	0.323
Adenocarcinoma, n (%)	219 (59.3%)	362 (71.5%)	<0.001
Squamous cell carcinoma, n (%)	110 (29.8%)	92 (18.2%)	<0.001
Neuroendocrine Tumor, n (%)	40 (10.8%)	52 (10.3%)	0.789
Differentiation, n (%)			<0.001
G1	25 (6.8%)	61 (12.2%)	
G2	126 (34.2%)	208 (41.5%)	
G3/G4	217 (59.0%)	232 (46.3%)	
Location, n (%)			0.250
Main bronchus	0 (0.0%)	2 (0.4%)	
Upper lobe	265 (68.3%)	324 (61.2%)	
Middle lobe	14 (3.6%)	27 (5.1%)	
Lower lobe	102 (26.3%)	164 (31.0%)	
Overlapping	2 (0.5%)	2 (0.4%)	
Diagnosis, n (%)			0.307
Stage I	190 (53.8%)	270 (55.6%)	0.619
Stage II	87 (24.6%)	121 (24.9%)	
Stage III	51 (14.4%)	75 (15.4%)	
Stage IV	25 (7.1%)	20 (4.1%)	
Radon risk, n (%)			0.971
Low	129 (33.2%)	176 (33.3%)	
Medium	107 (27.6%)	142 (26.9%)	
High	152 (39.2%)	210 (39.8%)	
Rural, n (%)	237 (61.1%)	318 (60.1%)	0.767
Survival, n (%)	162 (41.8%)	209 (39.5%)	0.494

*National Lung Screening Trial
†Patients that met NLST criteria based on both age and smoking status
‡Heavy smokers
§(LONS) light-or-never-smokers

loss had a higher rate of mortality compared to those without symptoms (HR 1.32, 95% CI 1.02-1.70; $P = 0.034$).

The Independent Contribution of Smoking Status on Survival

Results from the multivariate analysis are listed in Table 4 and a Forest plot is presented in Figure 3. Survival did not differ between heavy smokers meeting NLST criteria, and light-or-never-smokers (HR 0.86, 95% CI 0.64-1.16; $P = 0.325$). Males were at an increased risk of mortality (HR 2.03, 95% CI 1.60-2.57; $P<0.001$) compared to females. Another independent risk factor for mortality included higher stage tumors (Fig. 3).

Results of the multivariate analysis using NELSON criteria can be found in Supplementary Figure A2.

DISCUSSION

This study demonstrated that roughly half of all lung cancer patients would have been missed using conventional screening criteria stemming from 2 major trials.[3,4] There was no statistical difference in survival between the heavy smokers and the light-or-never-smokers. Male sex contributed to an increased rate of mortality, which has been demonstrated previously.[2]

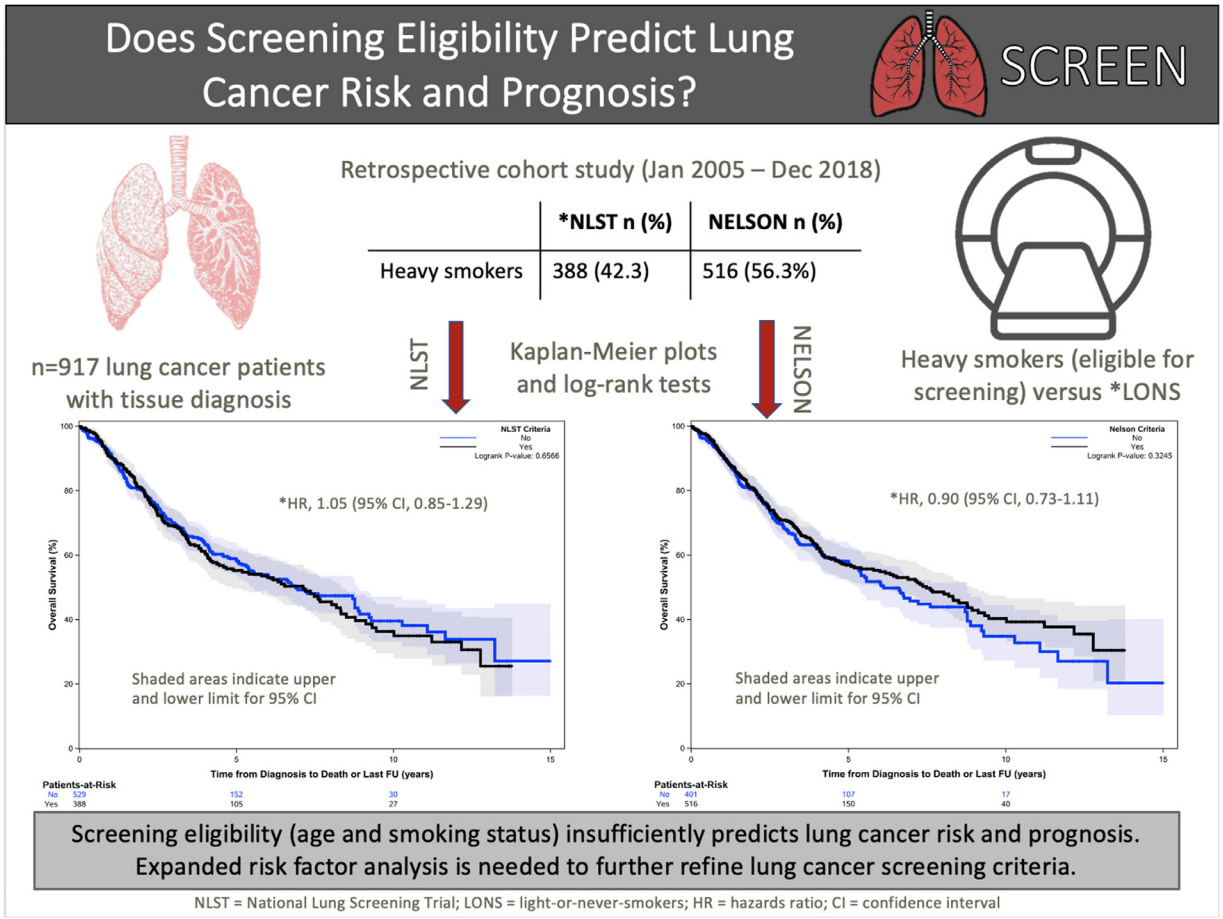

Figure 1. Graphical Abstract. The SCREEN Study found that 50% of lung cancer patients were ineligible for screening, and that there were no differences in 1- and 5-year survival between heavy smokers and light-or-never-smokers when defined using conventional screening criteria. *Colour*.

Light-or-never-smokers were more likely to be diagnosed with adenocarcinoma, while heavy smokers were more frequently diagnosed with squamous cell carcinoma. The same relationships are described by Dias et al. who also found that never smokers were more likely to be females,[26] reflected in our study among light-or-never-smokers. While screening all-comers above the age of 50 years would be ineffective, the efficacy of integrating lung cancer risk factors in addition to age and smoking status in screening criteria is an important area of future study.

Lung Cancer Screening Guidelines & Hesitance

In 2016, the Canadian Task Force on Preventive Health Care released a recommendation for LDCT screening using NLST screening criteria (Table 1) and protocol.[4,14] The U.S. Preventive Services Task Force (USPSTF) released a recommendation in 2021 for annual LDCT screening to detect lung cancer among asymptomatic adults aged 50-80 years with a least a 20 pack-year history that smoke or quit within 15 years.[1] The criteria for heavy smokers in the USPSTF criteria is now more aligned with LDCT screening criteria from the NELSON trial in 2020, which defined heavy smokers with a lower threshold of >15 pack-year smoking history (Supplementary Table A1).[3] NLST & NELSON screening protocols prevent 1 lung cancer death per 323 patients screened, and one lung cancer death for every 130 patients screened, respectively.[27]

Common causes for LDCT screening hesitance include concern for false-positive tests, overdiagnosis, radiation exposure, the negative psychological impact of screening, and a lack of screening-supportive infrastructure.[28] However, substantial heterogeneity in methodology among trials supporting these concerns disrupts the translation of results between screening populations.[28] Additionally, for every 1,000 patients screened, false-positive results lead to 17 invasive procedures, and fewer than one major complication.[27] Moreover, pulmonary nodule management guidelines intended to standardize lung cancer screening care have been shown to decrease false-positive rates, while volumetric assessments and nodule risk scoring has been shown to boost sensitivity and specificity of screening.[29,30] Furthermore, definitions for "overdiagnosis" fail to account for aggressiveness of tumours which impacts their subsequent management, contributing to wide variation in reported rates of overdiagnosis and complicating its translation to patient care.[27] Similarly, psychological distress rates fluctuate greatly

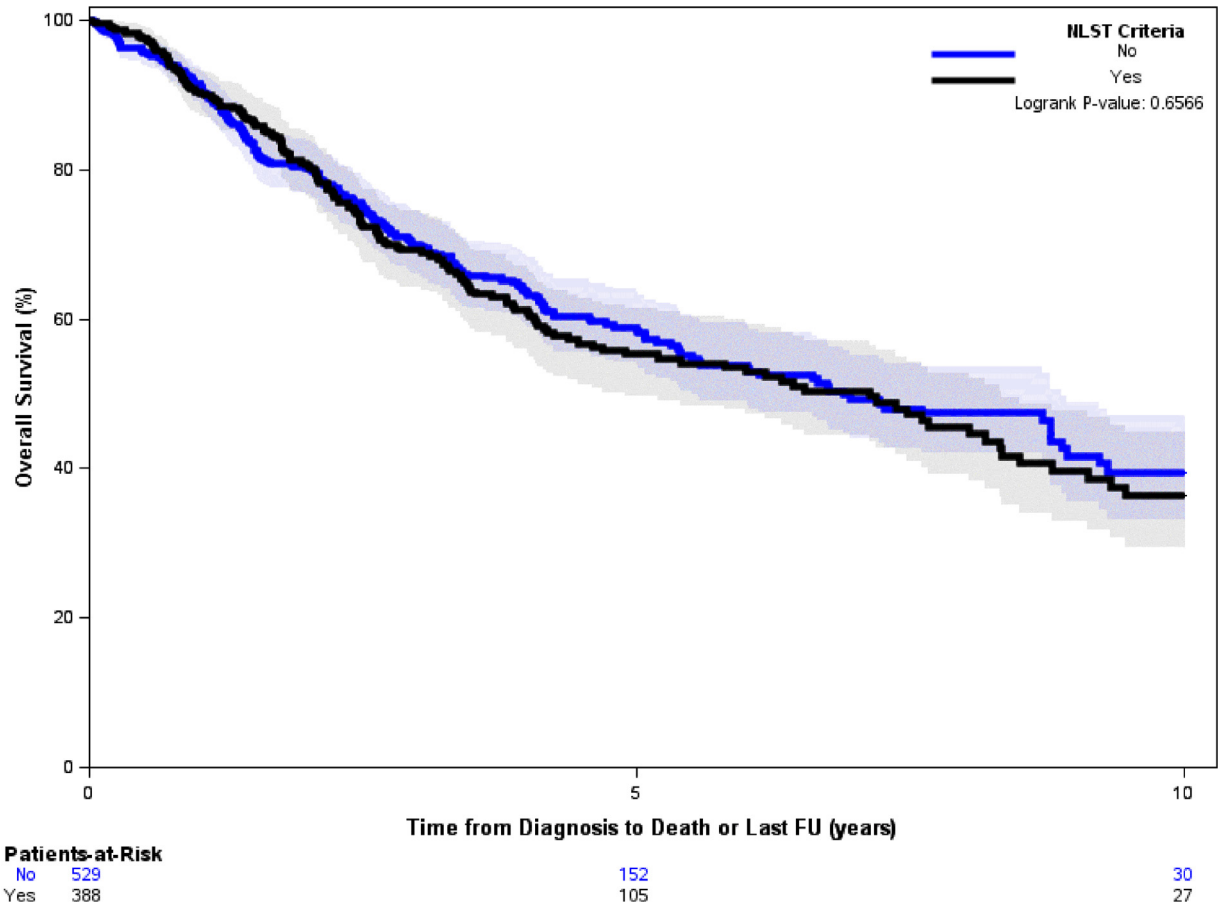

Figure 2. Overall survival does not differ between light-or-never-smokers and heavy smokers as defined by National Lung Screening Trial criteria (HR, 1.05; 95% CI, 0.85-1.29). *Colour*.

among lung cancer screening studies.[27] Finally, it is estimated that 108 lung cancers detected over 10 years of annual screening results in one case of radiation-induced cancer.[31] The benefits of lung cancer screening are dependent on an individual's underlying the risk of lung cancer and the competing causes of death. Overall, variability in generally low harm rates demonstrate a gap in higher quality studies and supports the need for individualized risk-benefit assessments, as the benefits of lung cancer screening may still outweigh the harms for many patients.

Lung Cancer Screening & Smoking

Currently, there are no guidelines to recommend LDCT screening to detect lung cancer among light-or-never-smokers. While the link between the lung cancer and the smoking is irrefutable, lung cancer in light or never smokers is not uncommon. Moreover, never smokers that develop lung cancer take longer to seek medical attention after symptom onset compared to smokers.[26] One recent study of 12,114 patients found that 70% of lung cancer patients may be missed when excluding light-or-never-smokers using the NLST criteria to select heavy smokers for LDCT screening.[32] However, the ability to extrapolate this data to North American patients was unclear, as study participants were Japanese. Our Canadian data demonstrated that roughly half of the patients would not have been screened. This slight variance may be attributable to genetic differences between populations. Nevertheless, never smokers comprise a significant proportion of lung cancer patients. Taken together, there persists a need to investigate methods to reduce lung cancer-related mortality among a growing proportion of patients with lung cancer that are willing to undergo lung cancer screening compared to their smoking counterparts.[33]

Lung Cancer Screening in Light or Never Smokers

Smoking history is self-reported, and its unreliability is well-established.[34] Our study showed that smoking status and age alone are inadequate predictors of lung cancer risk. As regional screening programs are developed to target geographic and demographic groups, using the simple methodology from the SCREEN study can help determine the applicability of conventional screening criteria to a given group is advantageous. One observational study by Kang and colleagues found that LDCT screening in never-smokers detects a significant number of early-stage lung cancers.[35] In our study, light-or-never-smokers had a higher rate of stage 1 cancers compared to heavy

Table 3. Univariate Predictors of Mortality

	Event/ Total	Median (95% CI) †	Hazard Ratio (95% CI) ‡	Survival Estimates (95% CI) †	Covariate Level *P*-Values	*P*-Value
Primary outcomes						
*NLST criteria						0.6566§
Yes	162/388	7.1 (4.9-8.3)	1.05 (0.85, 1.29)	1: 0.90 (0.88-0.94) 5: 0.55 (0.50-0.61)	–	
Secondary outcomes						
Sex						<.0001§
Female	139/485	11.7 (8.5-NE)	0.48 (0.39-0.59)	1: 0.93 (0.91-0.96) 5: 0.70 (0.65-0.75)	<.0001‖	
Male	232/432	4.1 (3.4-5.0)	Reference	1: 0.89 (0.86-0.92) 5: 0.44 (0.39-0.50)	–	
Radon risk						0.2516§
High	157/362	5.6 (4.5-7.6)	1.21 (0.95-1.54)	1: 0.90 (0.87-0.93) 5: 0.54 (0.48-0.60)	0.1208‖	
Medium	101/249	7.4 (5.5-9.3)	1.04 (0.80-1.37)	1: 0.92 (0.89-0.96) 5: 0.59 (0.52-0.67)	0.7549‖	
Low	113/305	8.9 (6.2-NE)	Reference	1: 0.91 (0.88-0.95) 5: 0.59 (0.53-0.66)	–	
Family historycancer						0.0226§
Yes	74/155	4.7 (3.8-8.2)	1.34 (1.04-1.73)	1: 0.88 (0.82-0.93) 5: 0.49 (0.41-0.59)	–	
Cancer history						0.0219§
Yes	104/217	5.3 (4.0-7.5)	1.30 (1.04-1.63)	1: 0.92 (0.88-0.96) 5: 0.53 (0.45-0.61)	0.0223‖	
Differentiation						0.0005§
G1	34/86	9.1 (6.3-NE)	Reference	1: 0.94 (0.89-0.99) 5: 0.70 (0.61-0.82)	–	
G2	112/334	8.7 (6.9-12.2)	1.06 (0.72-1.56)	1: 0.95 (0.92-0.97) 5: 0.62 (0.56-0.69)	0.7550‖	
G3/G4	201/449	5.3 (4.0-7.1)	1.60 (1.11-2.30)	1: 0.89 (0.86-0.92)	0.0115‖	
Diagnosis						<.0001§
Stage I	159/460	8.9 (8.2-11.1)	Reference	1: 0.95 (0.93-0.97) 5: 0.67 (0.62-0.72)	–	
Stage II	90/208	5.4 (4.2-NE)	1.35 (1.05-1.75)	1: 0.94 (0.90-0.97) 5: 0.54 (0.47-0.63)	0.0215‖	
Stage III	80/126	2.6 (1.8-3.9)	2.67 (2.04-3.50)	1: 0.79 (0.72-0.87) 5: 0.32 (0.24-0.43)	<.0001‖	
Stage IV	33/45	2.1 (1.2-6.3)	3.03 (2.08-4.41)	1: 0.76 (0.64-0.89) 5: 0.35 (0.23-0.54)	<.0001‖	
Symptoms						0.0337§
Yes	74/151	5.1 (4.1-8.0)	1.32 (1.02-1.70)	1: 0.88 (0.83-0.94) 5: 0.51 (0.42-0.61	0.0341‖	
Histology						0.1960§
Adenocarcinoma	213/581	7.7 (6.5-9.3)	0.81 (0.64-1.03)	1: 0.92 (0.90-0.94) 5: 0.59 (0.54-0.64)	0.0866‖	
Neuroendocrine tumor	39/92	6.0 (3.2-NE)	0.95 (0.66-1.38)	1: 0.90 (0.84-0.96) 5: 0.55 (0.44-0.68)	0.8029‖	
Squamous cell carcinoma	99/202	5.6 (4.5-8.2)	Reference	1: 0.90 (0.86-0.94) 5: 0.55 (0.48-0.63)	–	
Rural						0.0865§
Yes	213/555	8.0 (6.3-9.3)	Reference	1: 0.92 (0.90-0.94) 5: 0.59 (0.54-0.64)	–	

*National Lung Screening Trial
†Kaplan-Meier method
‡Cox model
§Logrank test
‖Wald Chi-Square test;

Table 4. Multivariate Predictors of Mortality using NLST Criteria

	Hazard Ratio (95% CI)	*P*-Value
NLST criteria		
(Yes vs No)	0.86 (0.64-1.16)	0.3245†
Sex	2.03 (1.60-2.57)	<.0001†
(Male vs Female)		
Family history cancer		
(Yes vs No)	1.01 (0.75-1.35)	0.9570†
Cancer history	1.20 (0.93-1.56)	0.1641†
(Yes vs No)		
Symptoms	1.18 (0.89-1.56)	0.2598†
(Yes - Symptoms vs No Symptoms)		
Histology		0.4426‡
Neuroendocrine tumor vs Adenocarcinoma	1.02 (0.65-1.59)	0.9279†
Squamous cell carcinoma vs Adenocarcinoma	1.19 (0.91-1.56)	0.2058†
Differentiation		0.0152‡
G2 vs G1	0.96 (0.63-1.45)	0.8407†
G3/G4 vs G1	1.38 (0.92-2.08)	0.1215†
Laterality	0.92 (0.73-1.16)	0.4995†
(Left vs Right)		
Diagnosis		<.0001‡
Stage II vs Stage I	1.43 (1.07-1.91)	0.0142†
Stage III vs Stage I	2.92 (2.14-3.97)	<.0001†
Stage IV vs Stage I	3.68 (2.40-5.65)	<.0001†
RURAL (Yes vs No)	0.93 (0.74-1.17)	0.5547†
Radon risk		0.5952‡
Medium vs Low	0.91 (0.68-1.22)	0.5371†
High vs Low	1.05 (0.81-1.38)	0.7021†

*National Lung Screening Trial
†Covariate Wald p-value
‡Type 3 Wald *P*-value

smokers defined by NELSON criteria. This is supported by preliminary results from the TALENT trial by Yang et al which demonstrated that LDCT screening of 12, 011 high-risk never-smokers achieved a higher T0 lung cancer detection rate than the NLST study with 96.5% of patients with potentially surgically curable disease at stage 0 or 1.[36] Furthermore, although there are models to account for the increased risk experienced in those with a family history of lung cancer and/or an increased risk due to race, scant data are available regarding environmental/industrial exposures. This data can be obtained by reviewing regional cancer registries with an approach similar to the methodology used in this work.

Survival did not differ between heavy smokers and light-or-never-smokers, reflected in other studies.[37,38] It is possible that the mortality benefit demonstrated among smokers is also realized by never-smokers. The subjective nature of smoking history may lead to the mislabeling of patients as either heavy smokers or light-or-never-smokers, resulting in overlap in survival between the groups. A study by ten Haaf and de Koning was designed to assess the impact of lung cancer screening on survival in never smokers based on data and major risk prediction models.[39] Their simulation models demonstrated that both the detection of early-stage lung cancers and lung cancer mortality would be increased among never smokers when compared to heavy smokers defined by previous USPSTF guidelines, which correspond to NLST criteria.[39] However, they found a lesser number of life-years gained among never smokers compared with ever-smokers.[39] This was attributed to increased survival rates among lung cancer patients that are never smokers compared to ever smokers due to the detrimental effects of smoking.[39] In contrast, the SCREEN study demonstrated no survival differences between lung cancer patients that are heavy smokers and light-or-never-smokers. SCREEN provides primary data which refutes the assertion that light-or-never-smokers would derive lesser benefit from lung cancer screening compared to heavy smokers due to innate differences in survival between the two groups.

One retrospective review by Kondo and colleagues found that LDCT screening improved survival and decreased the rate of advanced cancers in never-smokers.[40] Early data is promising for the utility of lung cancer screening in light-or-never-smokers, but further research is required. There are currently large-scale trials evaluating the efficacy of LDCT screening for light-or-never-smokers in Asia,[36,41,42] but North American trials are needed to inform the development of local lung cancer screening programs. While screening all individuals above 50 years of age is likely not beneficial, the use of additional lung cancer risk factors in screening criteria must be studied.

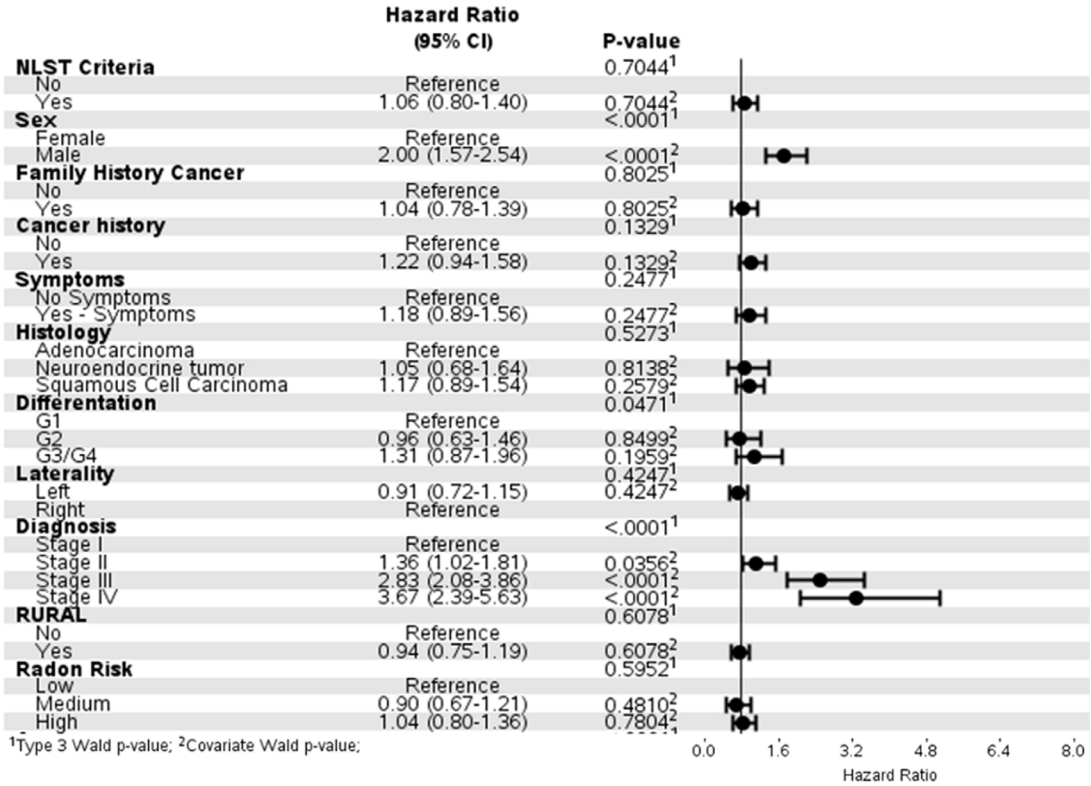

Figure 3. Multivariate analysis demonstrates no difference in survival between light-or-never-smokers and heavy smokers as defined by National Lung Screening Trial criteria. *Colour*.

This supports the need for large-scale trials to investigate the utility of lung cancer screening among patients with an array of evidence-based risk factors, to examine whether current lung cancer screening criteria should be expanded beyond age and smoking status alone.

Limitations

This study was conducted at a single center, though most lung cancer referrals in Nova Scotia are seen at the QEII Health Sciences Centre. Moreover, the patients in our cohort comprised approximately 7% of all lung cancer patients in the province due to limitations pertaining to the robustness of local databases. It is probable that patients without tissue diagnosis were frailer and/or had more advanced disease. Heavy smokers outside of age criteria according to the NLST and NELSON trials were not included in our study, and our data should be interpreted accordingly. It is also possible that compared to lung cancer patients in general, our study population included a larger proportion of light-or-never-smokers. Furthermore, detailed information about associated risk factors for lung cancer development such as ethnicity, exposure to cooking oils, and comorbidities such as COPD were lacking among our cohort. Additionally, radon risk was approximated based on their residing county at the time of diagnosis, which is a crude metric of radon exposure. The median follow-up was short and is another limitation of the study. Furthermore, residing county was determined using postal code and only approximates living region. Finally, this was not a prospective study of lung cancer patients that received LDCT screening, and our data must be interpreted accordingly.

CONCLUSIONS

Light-or-never-smokers comprise a significant proportion of patients with lung cancer. While screening all-comer never smokers for lung cancer would be ineffective, there may be an opportunity to reduce both mortality and healthcare utilization among a growing proportion of lung cancer patients. Among patients with lung cancer in our cohort, heavy smokers would have obtained no additional mortality benefit compared to light-or-never-smokers when defined using NLST or NELSON screening criteria. Our findings suggest that smoking status and age alone may be insufficient predictors of lung cancer risk and prognosis. Additional research is needed to examine the utility of additional lung cancer risk factors such as sex, environmental exposures such as radon, and other factors in comprising lung cancer screening eligibility criteria and expand risk factor analysis to help lung cancer screening be more effective and equitable.

WEBCAST

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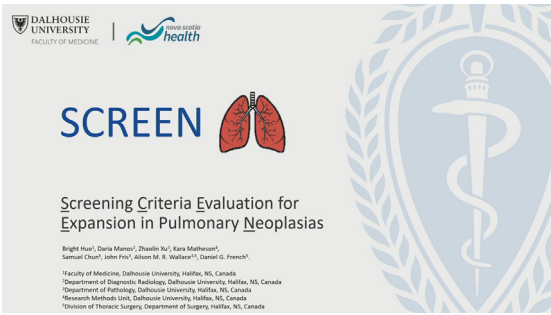

SUPPLEMENTARY MATERIAL

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DISCUSSION

AATS 2022 Annual Meeting

Screening Criteria Evaluation for Expansion in Pulmonary Neoplasias (SCREEN)

Presenter: Mr. Bright Huo

Invited Discussant: Dr. Sandra Starnes

Dr. Sandra Starnes (Cincinnati, Ohio):

Well, I'd like to thank the association for the opportunity to discuss this paper and for the authors for sending me their manuscript well in advance. Great job. So, while screening with low-dose CT has been shown to decrease lung cancer mortality in higher-risk patients, we still don't know the optimal selection criteria to prevent the most deaths while optimizing the risk-benefit ratio, as we've heard multiple times today. The authors demonstrate that there was a large number of patients who are diagnosed with lung cancer that do not meet current screening criteria both on the NLST and the Nelson study, so there is still work to do to refine our eligibility. I have 3 questions and I'll ask them in order. The first question is do you have data on lung cancer-specific mortality in this population?

Mr. Bright Huo (Nova Scotia, Canada): Thank you, Dr. Starnes. Due to the retrospective approach that we took, our cancer registry, unfortunately, does not capture disease-specific mortality, so we don't have access to that data.

Dr. Starnes: And then as we've again heard multiple times today, lung cancer screening remains significantly underutilized, around 6% of the United States. So, do you think we should focus on screening the high-risk patients that we know have a benefit versus broadening our eligibility criteria?

Mr. Huo:

Yeah, thanks. That's a great question. It's unfortunate that lung cancer screening uptake is inadequate. Data from Canada unfortunately we are not privy to as screening programs are in early phases of being implemented. But to your point about the high-risk patients, it's absolutely important not to broadly screen all light or never smokers but rather identify those at highest risk. We want to emphasize that our methodology pertaining to using a cancer registry, retrospectively assessing that registry, and identifying whether the screening criteria applies or not to a specific population can be used.

For example, if you wanted to look at veterans that have provided service in other countries, you could apply this methodology and identify how well the criteria applies. Using this, it's possible that there could be light or never smokers that could be considered high risk depending on whether or not they have significant industrial or occupational in addition to heavy smokers.

Dr. Starnes:

So, that's a great segue into my last question. So, how can we use your data? Is there available data in your large cohort that would allow us to refine eligibility?

Mr. Huo:

Yeah, thanks. That's another strong question, Dr. Starnes. The primary purpose of our study was not to do that, but however, we do have access to molecular data as well as postal code data, which gives us geographic location, and we also have clinical variables. So, moving forward, our next steps are to identify the relationship between these variables with the ultimate goal, hopefully, the long-term goal of identifying those that are at highest risk to enable targeted screening because I think that's the way to go.

Dr. Starnes:

Thank you and congratulations. Great job, Bright.

Mr. Huo:

Thanks, Dr. Starnes.

Unidentified Speaker:

Dr. Cook?

Dr. David Cooke (Sacramento, California): David Cooke, Sacramento. Thank you for this wonderful presentation and congratulations on being a medical student presenting in this form. The Taiwanese TALENT trial looked at low-dose CT screening in never and remote smokers and found that first-degree relatives showed benefit from low-dose CT scan, specifically mother, brother, sister, at rates similar to the NLST. Do you have that level of family history granularity in your dataset?

Mr. Huo:

Yeah, thank you for the very strong point. The TALENT trial I am a bit familiar with, and I believe that they used family history within the third degree and unfortunately, we don't have access to that data due to our cancer registry, but it's a very important point to consider within family history itself, so thank you for bringing that up.

Dr. Cooke:

Very good. Thank you.