Screening Criteria Evaluation for Expansion in Pulmonary Neoplasias (SCREEN) II

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Background: There is a need to expand eligibility criteria for lung cancer screening beyond age and smoking history. In this study, we sought to assess whether light-or-never-smokers and heavy smokers differ in molecular and immunologic markers based on conventional lung cancer screening criteria.

Methods: We conducted a retrospective review of lung cancer cases from 2005 to 2018 at a tertiary Canadian institution. We used multivariable logistic regression to compare the rate of molecular mutations (*KRAS*, *EGFR*, *BRAF*, *PIK3CA*, *ALK*, and PD-L1 [< 1%, 1%–49%, ≥ 50%]) and survival between light-or-never-smokers and heavy smokers.

Results: We included 1156 patients with lung cancer. Overall, 46.4% (National Lung Screening Trial [NLST], n = 536) and 63.3% (Nederlands–Leuvens Longkanker Screenings Onderzoek [NELSON], n = 732) of the patients were heavy smokers. Using NELSON criteria, screen-ineligible light-or-never-smokers were more frequently from areas at high risk for radon exposure (n = 175 [41.3%]) than screen-eligible heavy smokers (n = 285 [38.9%]). Light-or-never-smokers were more likely to be *EGFR*-positive in both NLST (odds ratio [OR] 0.79, 95% confidence interval [CI] 0.21–1.37; p = 0.008] and NELSON (OR 0.79, 95% CI 0.28–1.31; p = 0.002) models. Female light-or-never-smokers were more likely than male light-or-never-smokers to be *EGFR*-positive in NELSON (OR 0.59, 95% CI 0.06–1.12; p = 0.03] but not NLST (OR 0.51, 95% CI 0.02–1.05; p = 0.06) models. Light-or-never-smokers were more often *PIK3CA*-positive using NLST (OR 1.33, 95% CI 0.54–2.13; p = 0.001) and NELSON (OR 1.19, 95% CI 0.49–1.90; p = 0.001) models. Light-or-never-smokers in the NELSON model were at higher risk of death.

Conclusion: Screen-ineligible light-or-never-smokers had a higher rate of *EGFR*- and *PIK3CA*-positive lung cancers than screen-eligible heavy smokers when defined using trial-based lung cancer screening eligibility criteria. Molecular profiling, particularly where targeted therapy is available, should be considered in future studies establishing criteria for lung cancer screening.

Contexte : Il faut élargir les critères d'admissibilité au dépistage du cancer du poumon au-delà de l'âge et des antécédents tabagiques. Dans cette étude, nous avons voulu vérifier s'il y a des différences entre les personnes dont le tabagisme est léger, voire nul (groupe 1) et celles qui fument beaucoup (groupe 2) au plan des marqueurs moléculaires et immunologiques selon les critères classiques de dépistage du cancer du poumon.

Méthodes : Nous avons procédé à une revue rétrospective des cas de cancer du poumon de 2005 à 2018 dans un établissement de soins tertiaires canadien. Nous avons utilisé la régression logistique multivariée pour comparer les taux de mutations moléculaires (*KRAS*, *EGFR*, *BRAF*, *PIK3CA*, *ALK* et PD-L1 [< 1 %, 1 %–49 %, ≥ 50 %]) et la survie entre les 2 groupes.

Résultats : Nous avons inclus 1156 cas de cancer du poumon. En tout, 46,4 % (étude NLST [National Lung Screening Trial], n = 536) et 63,3 % (étude NELSON [Nederlands–Leuvens Longkanker Screenings Onderzoek], n = 732) des malades étaient de gros fumeurs. À partir des critères de l'étude NELSON, le groupe 1, non admissible au dépistage, venait de secteurs à risque élevé d'exposition au radon (n = 175 [41,3 %]) comparativement au groupe 2, admissible au dépistage (n = 285 [38,9 %]). Le groupe 1 était plus susceptible d'être *EGFR*-positif, tant selon le modèle NLST (rapport des cotes [RC] 0,79, intervalle de confiance [IC] de 95 % 0,21–1,37; p = 0,008), que le modèle NELSON (RC 0,79, IC de 95 % 0,28–1,31; p = 0,002). Dans le groupe 1, les femmes étaient plus susceptibles que les hommes d'être *EGFR*-positives selon le modèle NELSON (RC 0,59, IC de 95 % 0,06–1,12; p = 0,03), mais non selon le modèle NLST (RC 0,51, IC de 95 % 0,02–1,05; p = 0,06). Le groupe 1 avait plus

tendance à être *PIK3CA*-positif selon les modèles NLST (RC 1,33, IC de 95 % 0,54–2,13; p = 0,001) et NELSON (RC 1,19, IC de 95 % 0,49–1,90; p = 0,001). Selon le modèle NELSON, le groupe 1 était exposé à un risque de mortalité plus élevé.

Conclusion : Les personnes dont le tabagisme est léger voire nul qui ne sont pas admissibles au dépistage ont présenté un taux plus élevé de cancer du poumon *EGFR*- et *PIK3CA*-positifs comparativement aux gros fumeurs, lorsqu'on appliquait les critères d'admissibilité au dépistage du cancer du poumon des 2 essais cités. Il faudrait envisager un profilage moléculaire lors des prochaines études qui porteront sur les critères d'admissibilité au dépistage du cancer du poumon, surtout lorsqu'il existe des modalités thérapeutiques ciblées.

The National Lung Screening Trial (NLST) and Nederlands–Leuvens Longkanker Screenings Onderzoek (NELSON) trials have established that lung cancer screening effectively reduces lung cancer mortality by at least 20%.[1,2] Despite its efficacy, conventional screening criteria excludes a substantial proportion of patients who develop lung cancer, with recent concerns including gender disparities.[3] Epidemiologic studies suggest that only 27% of patients with lung cancer meet NLST criteria for age and smoking status.[4,5] There is a need to better capture a wider range of patients that represent the diverse population at risk for developing lung cancer.

The 2021 US Preventive Services Taskforce guidelines addressed the wider inclusion of patients in lung cancer screening by expanding age and smoking status to increase eligibility.[6] Still, many risk factors for lung cancer are excluded. Risk prediction models have been developed to incorporate factors outside of age and smoking history, including race, level of education, chronic obstructive pulmonary disease status, and family history of lung cancer, to identify the highest-risk patients for lung cancer screening.[7] However, to our knowledge, the application of risk prediction models in practice is limited outside of the Canadian context. Furthermore, molecular and immunologic markers are not currently considered in eligibility criteria for low-dose computed tomography (CT) screening.

Lung cancer genomics contribute to lung cancer incidence and mortality, with higher rates of mutations across varying demographic populations.[8] As most lung cancers harbour mutations, targeted therapies have been developed to improve outcomes in lung cancer therapy.[8] However, the rate of molecular and immunologic mutations in the development of lung cancer in screen-ineligible patients has yet to be established. Furthermore, novel techniques are in development to detect lung cancer at the prediagnosis stage.[9] If the rates of molecular markers differ based on screening eligibility, molecular marker analysis may play an important role in broadening screening eligibility criteria. Thus, the objective of this study was to assess the molecular and immunologic profile between screen-eligible heavy smokers and screen-ineligible light-or-never-smokers, defined by conventional screening criteria. Our hypothesis was that molecular and immunologic profiles differ between lung cancers found in screen-eligible heavy smokers and screen-ineligible light-or-never-smokers.

Methods

Data source and participants

This was a retrospective assessment of molecular and immunologic mutations among tumours found in screen-eligible heavy smokers and screen-ineligible light-or-never-smokers. Building on the original Screening Criteria Evaluation for Expansion in Pulmonary Neoplasias (SCREEN) study,[10] we report molecular and immunologic profiles on an expanded cohort of patients with lung cancer aged 18 years and older diagnosed between January 2005 and December 2018 at the Queen Elizabeth II Health Sciences Centre (QEII) in Halifax, Nova Scotia, Canada. The QEII is the only thoracic surgical centre in the province of Nova Scotia, serving a population of more than 1 million people. Data were obtained from the provincial cancer registry, which contains data related to geographical location by postal code and lung cancer incidence and mortality for patients in Nova Scotia. Clinical, molecular, and immunologic data were gathered from the QEII Lung Tumour Bank, which captures the clinical and molecular information for patients with tissue samples from biopsy or lung resection. The provincial radon risk map was used to capture relative radon risk with place of residence by postal code in Nova Scotia. Patients with benign lesions were excluded. Those who met smoking but not age criteria were excluded from the study.

Variables and outcomes

The primary outcome was to determine the rate of molecular and immunologic markers among screen-eligible heavy smokers and screen-ineligible light-or-never-smokers, defined by trial-based lung cancer screening criteria. We applied eligibility criteria based on age and smoking status from the NLST and NELSON trials, respectively (Table 1). Patients who smoked less than the criteria for enrolment in these trials were considered screen-ineligible light-or-never-smokers. Clinically significant variables were considered, including sex, family history of lung cancer to the

Table 1. Conventional lung cancer screening criteria for heavy smokers

NLST	NELSON
• Age 55–74 yr • Current or former smoker < 15 yr • History of ≥ 30 pack-year	• Age 50–75 yr • Current or former smoker < 10 yr • > 15 cigarettes/d > 25 yr OR > 10 cigarettes/d > 30 yr

NELSON = Nederlands–Leuvens Longkanker Screenings Onderzoek Trial, NLST = National Lung Screening Trial.

first degree, any patient-reported previous cancer history, TNM staging, rurality, geographical radon risk, and immunologic mutations including PD-L1. Postal code was used to infer geographical place of residence, which was referenced with the provincial radon risk map to correlate with areas of low, medium, and high risk for radon exposure. The radon risk map defines these levels as the proportion of buildings that exceed the radon guideline in the region, corresponding to ratings of low (> 5%), medium (> 14%), and high (> 40%). We also report the rates of histologic diagnosis and molecular mutations such as *KRAS*, *EGFR*, *PIK3CA*, *BRAF*, *ALK*, human epidermal growth factor receptor 2 (HER2), *AKT1*, *NRAS*, and *FGF1* between eligible heavy smokers and ineligible light-or-never-smokers. The population-adjusted rate of molecular mutations was assessed by county. The earliest tumour diagnosed was captured among patients with synchronous tumours on different dates. Higher stage tumours were selected for synchronous tumours diagnosed on the same date. We considered the date of resection or biopsy as the date of diagnosis.

Statistical methods

We used descriptive statistics to summarize baseline demographic information, including mean and standard deviation (SD) for continuous data, in addition to frequencies and percentages for categorical data. We compared patient characteristics between screen-eligible heavy smokers and screen-ineligible light-or-never-smokers defined by screening criteria using the Student *t* test for continuous variables and the χ^2 test for categorical variables. We used univariate analysis to assess the relation between molecular mutations, heavy smokers, and light-or-never-smokers defined by NELSON and NLST criteria. We used Cox proportional hazards models to estimate hazard ratios. Multivariable models were developed to explore the association of molecular mutations while adjusting for a priori determined clinically significant variables. We included patients with all available case data in the analysis. For each outcome, all variables were entered simultaneously into an initial model, and a backward elimination procedure was applied using the Akaike information criterion.[11] We performed statistical analysis using R software version 4.3.0. We considered a p value of less than 0.05 to indicate statistical significance.

Ethics approval

This study was approved by the Nova Scotia Health Research Ethics Board (no. 1025892) and adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies.[12]

Results

NLST criteria

We included 1156 patients with lung cancer. Using the NLST criteria, there were 536 (46.4%) screen-eligible heavy smokers with a mean age of 65.9 (SD 5.2) years and 258 (48.1%) females, and 620 (53.6%) screen-ineligible light-or-never-smokers with a mean age of 69.0 (SD 10.4) years ($p < 0.001$) and 278 (44.8%) females ($p < 0.001$). Demographic, molecular, and immunologic characteristics are listed in Table 2. Overall, there were 782 (67.6%) adenocarcinomas, 257 (22.2%) squamous cell carcinomas, and 9 (0.8%) large cell carcinomas in our cohort. There were 334 (28.9%) *KRAS*-, 84 (7.3%) *EGFR*-, and 38 (3.3%) *PIK3CA*-positive lung tumours. There was a higher rate of *EGFR* mutations among screen-ineligible light-or-never-smokers (n = 70 [11.3%]) relative to screen-eligible heavy smokers (n = 14 [2.6%], $p < 0.001$). Light-or-never-smokers also had a higher rate of *PIK3CA* mutations (n = 28 [4.5%]) than heavy smokers (n = 10 [1.9%], $p = 0.02$). There was no difference in *KRAS* mutations among heavy smokers (n = 174 [32.5%]) compared with light-or-never-smokers (n = 160 [25.8], $p = 0.5$). A total of 123 (10.6%) patients had PD-L1-positive lung cancers. There was no difference in the rate of PD-L1 markers of 50% or greater between eligible heavy smokers (n = 63 [11.8%]) and light-or-never-smokers (n = 60 [9.7%], $p = 0.1$). Mortality did not differ between the 2 groups (Table 2) ($p = 0.8$).

Regression analysis using NLST criteria showed that patients with a family history of lung cancer had a 1.8-times higher odds of having a *KRAS* mutation (Table 3). Light-or-never-smokers were more likely to be *EGFR*-positive than heavy smokers identified using NLST criteria (odds ratio [OR] 0.79, 95% confidence interval [CI] 0.21–1.37, $p = 0.008$). Those with adenocarcinoma and squamous cell carcinoma were also more likely to have a *KRAS* mutation. Patients with PD-L1 of 50% or greater were at 3.2-times higher odds of having a *KRAS* mutation. Screen-ineligible light-or-never-smokers were at 3.1-times and 2.4-times greater odds of having an *EGFR* mutation and *PIK3CA* mutation, respectively (Table 3).

NELSON criteria

Using the NELSON criteria, 732 (63.3%) patients were heavy smokers. Results for screen-eligible heavy smokers and ineligible light-or-never-smokers as defined by

Table 2. Characteristics of screen-eligible and screen-ineligible patients with lung cancer

Characteristic	NLST; no. (%) of patients			NELSON; no. (%) of patients		
	Heavy smokers *n* = 536	Light-or-never-smokers *n* = 620	*p* value	Heavy smokers *n* = 732	Light-or-never-smokers *n* = 424	*p* value
Age, mean ± SD, yr	65.9 ± 5.2	69.0 ± 10.4	< 0.001	64.9 ± 6.3	72.1 ± 9.9	< 0.001
Smoking status			< 0.001			< 0.001
Never smoked	0 (0)	98 (15.8)		0 (0)	98 (23.1)	
Current smoker	232 (43.3)	160 (25.8)		312 (42.6)	80 (18.9)	
Past smoker	304 (56.7)	355 (57.3)		420 (57.4)	233 (55.0)	
Sex			< 0.001			0.4
Female	258 (48.1)	364 (58.7)		387 (52.9)	235 (55.4)	
Male	278 (51.9)	256 (41.3)		345 (47.1)	189 (44.6)	
Family history of lung cancer	87 (16.2)	99 (16.0)	> 0.9	123 (16.8)	63 (14.9)	0.5
Previous cancer history	113 (21.1)	167 (26.9%)	0.02	157 (21.4)	123 (29.0)	0.002
Histology						
Adenocarcinoma	332 (61.9)	450 (72.6)	< 0.001	476 (65.0)	306 (72.2)	0.01
Squamous cell carcinoma	150 (28.0)	107 (17.3)	< 0.001	181 (24.7)	76 (17.9)	0.01
Large cell carcinoma	23 (4.3)	17 (2.7)		30 (4.1)	10 (2.4)	
Neuroendocrine tumour	9 (1.7)	0 (0)		9 (1.2)	0 (0)	
Grade			< 0.001			< 0.001
G1	35 (6.5)	60 (9.7)		53 (7.2)	42 (9.9)	
G2	177 (33.0)	354 (57.1)		254 (34.7)	277 (65.3)	
G3	280 (52.2)	184 (29.7)		371 (50.7)	93 (21.0)	
G4	12 (2.2)	1 (0.2)		13 (1.8)	0 (0)	
Location			0.4			0.6
Main bronchus	0 (0)	1 (0.2)		1 (0.1)	0 (0)	
Upper lobe	356 (66.4)	389 (62.7)		478 (65.3)	267 (63.0)	
Middle lobe	22 (4.1)	33 (5.3)		35 (4.8)	20 (4.7)	
Lower lobe	151 (28.2)	190 (30.6)		209 (28.6)	132 (31.1)	
TNM staging			0.1			0.01
Stage I	258 (48.1)	341 (55.0)	0.06	355 (48.5)	244 (57.5)	0.01
Stage II	126 (23.5)	123 (19.8)	0.9	170 (23.2)	79 (18.6)	
Stage III	67 (12.5)	83 (13.4)		92 (12.6)	58 (13.7)	
Stage IV	26 (4.8)	20 (3.2)		36 (4.9)	10 (2.4)	
Radon risk			0.7			
Low	170 (31.7)	197 (31.8)		241 (32.9)	126 (29.7)	(Ref.)
Medium	153 (28.5)	163 (26.3)	0.6	198 (27.0)	118 (27.8)	< 0.001
High	209 (39.0)	251 (40.5)	0.05	285 (38.9)	175 (41.3)	< 0.001
Rural	325 (60.6)	359 (57.9)	0.5	441 (60.2)	243 (57.3)	0.4
Mortality	181 (33.8)	204 (32.9)	0.8	235 (32.1)	150 (35.4)	0.3
Molecular markers						
KRAS	160 (29.9)	174 (28.1)	0.5	226 (30.9)	108 (25.5)	0.06
EGFR	14 (2.6)	70 (11.3)	< 0.001	24 (3.3)	60 (14.2)	< 0.001
PIK3CA	10 (1.9)	28 (4.5)	0.02	18 (2.5)	20 (4.7)	0.06
BRAF	5 (0.9)	11 (1.8)	0.3	7 (1.0)	9 (2.1)	0.2
ALK1H	2 (0.4)	2 (0.3)	> 0.9	3 (0.4)	1 (0.2)	> 0.9
HER2	1 (0.2)	1 (0.2)	> 0.9	2 (0.3)	0 (0)	0.8
AKT1	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
NRAS	1 (0.2)	0 (0)	0.9	1 (0.1)	0 (0)	> 0.9
FGFR1	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
PD-L1, %			0.1			0.4
< 1	153 (28.5)	199 (32.1)	0.2	226 (30.9)	126 (29.7)	0.5
1–49	122 (22.8)	127 (20.5)		164 (22.4)	85 (20.0)	
≥ 50	63 (11.8)	60 (9.7)		86 (11.7)	37 (8.7)	

HER2 = human epidermal growth factor receptor 2; NA = not applicable; Ref. = reference category; NA = not applicable; NELSON = Nederlands–Leuvens Longkanker Screenings Onderzoek Trial; NLST = National Lung Screening Trial; SD = standard deviation.

Table 3. Regression analysis demonstrating risk factors for developing molecular mutations using National Lung Screening Trial criteria

Variable	OR	2.50%	97.50%	*z* value	*p* value
KRAS					
(Intercept)	0.36	0.00	157742.50	–0.15	0.9
Heavy smokers NLST	1.36	0.93	1.98	1.58	0.1
Sex (male)	0.70	0.48	1.02	–1.87	0.06
Family history of cancer (yes)	1.80	1.09	2.97	2.29	0.02
Previous cancer history (yes)	0.69	0.43	1.09	–1.61	0.1
Stage at diagnosis (stage 2/3/4)	0.99	0.67	1.45	–0.07	0.9
Urban v. rural (urban)	1.35	0.00	567045.80	0.05	> 0.9
Radon risk (low)	1.47	0.00	622910.70	0.06	> 0.9
Radon risk (medium)	1.04	0.00	435731.00	0.01	> 0.9
Adenocarcinoma (yes)	5.34	2.53	11.25	4.40	< 0.001
Squamous cell carcinoma (yes)	0.11	0.03	0.43	–3.18	< 0.001
PD-L1 (< 50%)	0.31	0.19	0.52	–4.50	< 0.001
EGFR					
(Intercept)	0.06	0.00	Inf.	0.00	> 0.9
Heavy smokers NLST	0.32	0.16	0.65	–3.15	< 0.001
Sex (male)	0.71	0.38	1.35	–1.04	0.3
Family history of cancer (yes)	1.48	0.677	3.26	0.99	0.3
Previous cancer history (yes)	1.77	0.92	3.41	1.70	0.09
Stage at diagnosis (stage 2/3/4)	0.80	0.42	1.53	–0.67	0.5
Urban v. rural (urban)	0.37	0.00	Inf.	0.00	> 0.9
Radon risk (low)	0.35	0.00	Inf.	0.00	> 0.9
Radon risk (medium)	0.44	0.00	Inf.	0.00	> 0.9
Adenocarcinoma (yes)	3.42	0.80	14.73	1.65	0.1
Squamous cell carcinoma (yes)	0.00	0.00	Inf.	–0.02	> 0.9
PD-L1 (< 50%)	2.51	0.87	7.28	1.69	0.09
BRAF					
(Intercept)	0.03	0.00	Inf.	0.00	> 0.9
Heavy smokers NLST	0.78	0.18	3.25	–0.35	0.7
Sex (male)	0.74	0.18	3.03	–0.42	0.7
Previous cancer history (yes)	0.76	0.09	6.36	–0.25	0.8
Family history (yes)	0.99	0.20	4.92	–0.01	> 0.9
Stage at diagnosis (stage 2/3/4)	0.44	0.09	2.20	–1.00	0.3
Rural (yes)	1.88	0.00	Inf.	0.00	> 0.9
Radon risk (low)	2.18	0.00	Inf.	0.00	> 0.9
Radon risk (medium)	0.70	0.00	Inf.	0.00	> 0.9
Adenocarcinoma (yes)	1.06	0.13	8.77	0.05	> 0.9
Squamous cell carcinoma (yes)	0.00	0.00	Inf.	–0.01	> 0.9
PD-L1 (> 50%)	0.59	0.12	2.97	–0.63	0.5
P1K3CA					
(Intercept)	0.13	0.00	180.58	–0.552	0.6
Heavy smokers NLST	0.42	0.18	1.00	–1.959	0.05
Sex (male)	0.80	0.35	1.82	–0.525	0.6
Previous cancer history (yes)	1.51	0.60	3.83	0.875	0.4
Family history (yes)	1.16	0.47	2.88	0.323	0.7
Stage at diagnosis (stage 2/3/4)	1.58	0.71	3.56	1.117	0.3
Rural (yes)	0.71	0.001	843.86	–0.094	0.9
Radon risk (low)	0.91	0.001	1113.38	–0.025	> 0.9
Radon risk (medium)	0.26	0.00	305.61	–0.376	0.7
Adenocarcinoma (yes)	0.64	0.18	2.32	–0.679	0.5
Squamous cell carcinoma (yes)	1.58	0.40	6.26	0.651	0.5
PD-L1 (> 50%)	0.61	0.24	1.53	–1.046	0.3

Inf. = infinity; NLST = National Lung Screening Trial; OR = odds ratio; SCC = squamous cell carcinoma.

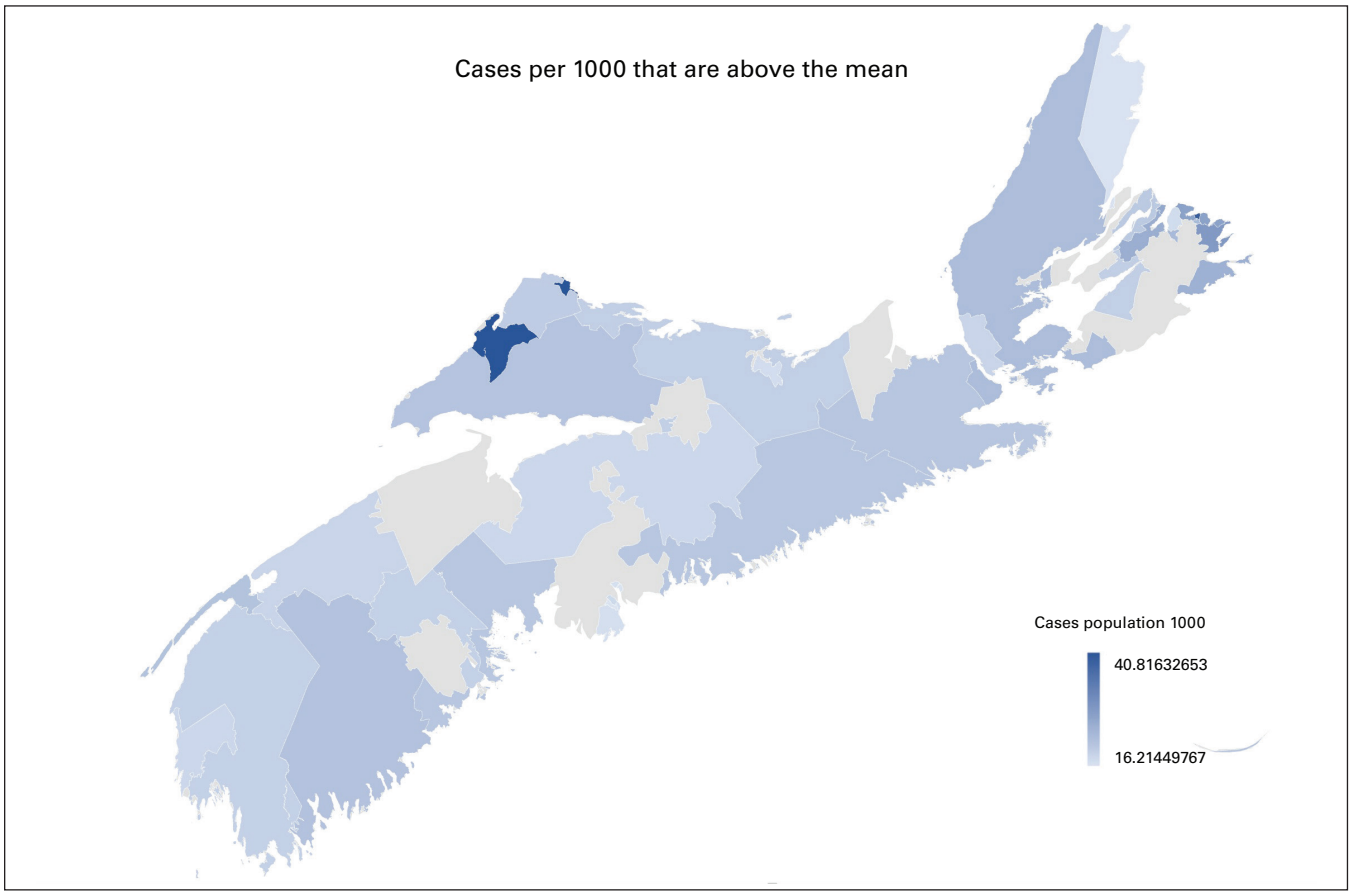

Fig. 1. Map of Nova Scotia showing the annual incidence of lung cancer cases per 1000 individuals relative to the provincial mean during the study period.

NELSON criteria are shown in Table 2. Using NELSON criteria, screen-ineligible light-or-never-smokers were more frequently from areas at high risk for radon exposure (n = 175 [41.3%]) than eligible heavy smokers (n = 285 [38.9%], p < 0.001). Screen-ineligible light-or-never-smokers had a higher rate of stage I tumours (n = 244 [57.5%]) relative to eligible heavy smokers (n = 355 [48.5%], p = 0.01). Light-or-never-smokers were at a higher risk for death relative to heavy smokers (hazard ratio 1.53, 95% CI 1.10–2.10, p = 0.01). Results of regression analyses using NELSON criteria are shown in Appendix 1 (available at www.canjsurg.ca/lookup/doi/10.1503/cjs.015223/tab-related-content). Light-or-never-smokers were more likely to be *EGFR*-positive than heavy smokers in the NELSON model (OR 0.79, 95% CI 0.28–1.31, p = 0.002). Additionally, female light-or-never-smokers were more likely than male light-or-never-smokers to be *EGFR*-positive in the NELSON model (OR 0.59, 95% CI 0.06–1.12, p = 0.03]. Finally, light-or-never-smokers were more often *PIK3CA*-positive using NELSON criteria (OR 1.19, 95% CI 0.49–1.90, p = 0.001).

Figure 1 shows the number of lung cancer cases per 1000 people by region with respect to the mean number for the province for all 1156 patients. Figure 1 highlights regions with an increased number of cases per 1000 people in the province of Nova Scotia during the study period, including Cumberland, Cape Breton, and Guysborough.

Discussion

This study examined the rates of molecular and immunologic mutations between screen-eligible heavy smokers and screen-ineligible light-or-never-smokers defined by conventional eligibility criteria for lung cancer screening. Our cohort had a higher proportion of adenocarcinoma relative to squamous cell carcinoma, congruent with existing literature.[13] As Nova Scotia has among the highest rates of radon exposure in Canada,[14] this may be expected, as incremental rises in radon levels are associated with an increased rate of adenocarcinoma.[15] The rates of *KRAS* and *PIK3CA* mutations were comparable with epidemiologic data.[16,17] The rate of *EGFR* mutations was lower than expected, though our population has a low proportion of people with Asian descent, and significantly lower levels are known to occur among those with European ancestry.[18] When defined by NLST or NELSON criteria, light-or-never-smokers had a higher rate of *EGFR* and *PIK3CA* mutations. There was no difference in the rate of *ALK*, *BRAF*, or PD-L1 mutations.

Eligibility criteria for lung cancer screening using age and smoking history fails to capture a substantial proportion of patients[5,10] and may contribute to racial disparities in lung cancer screening.[19] Risk prediction models have been shown to improve racial disparities compared with eligibility criteria of the US Preventive Services Taskforce.[20] In Ontario, the pilot screening program successfully employs the Prostate, Lung, Colorectal and Ovarian $(PLCO)_{m2012}$ risk model for lung cancer screening eligibility.[21] However, the use of risk prediction models is limited elsewhere as their practicality limits their implementation,[3] and the 2021 US Preventive Services Taskforce Guidelines recommend the use of smoking and age criteria owing to the inconsistent benefits shown with existing risk prediction models.[19] There is a need to identify additional factors for consideration in establishing eligibility criteria for lung cancer screening. We found a higher rate of *EGFR* and *PIK3CA* mutations among screen-ineligible light-or-never-smokers than screen-eligible heavy smokers. Prior studies suggested an association between *EGFR* mutations and smoking status,[18] but not screening eligibility. Earlier studies suggested that *EGFR* mutations in patients with non–small cell lung cancer are associated with higher aggressivity and reduced survival.[22] With the development of newer targeted therapies showing advantages such as prolonged progression-free survival and improved quality of life compared with standard chemotherapy,[23] there is potential benefit in detecting these tumours early. Moreover, early evidence suggests that the treatment of lung tumours positive for both *EGFR* and *PIK3CA* mutations with targeted therapy leads to decreased overall survival,[24] further emphasizing the importance of identifying both markers when detecting early lung tumours.

Racial differences in tumour molecular profiling are well-established,[8] but race is not currently used to determine eligibility for screening. The US Preventive Services Taskforce made a first step toward improving the racial disparities in lung cancer screening by broadening its age and smoking history criteria for lung cancer screening in 2021.[19] Further attempts have been made to directly assess the influence of race using risk prediction models. For instance, $PLCO_{m2012}$ is the most globally validated risk prediction model and considers race by using the labels White, Black, Hispanic, Asian, American Indian or Alaskan Native, and Native Hawaiian or Pacific Islander.[25] Despite this advancement, the broad nature of these groupings has limitations. As molecular mutations account for genetic factors influenced by race, there is a potential role for the use of molecular mutations in further improving racial disparities in lung cancer screening as advances are made in serum biomarker screening.

In our cohort, 15%–20% of screen-ineligible light-or-never-smokers were *EGFR*- or *PIK3CA*-positive, suggesting that further study is needed to assess the role of screening for early lung tumours using molecular markers. Novel techniques such as liquid biopsy are being developed to help detect and manage early-stage lung tumours. Sorber and colleagues enrolled 388 patients with pathological stage I non–small cell lung cancer and found that the detection of *EGFR* mutations using liquid biopsy was associated with improved overall survival and progression-free survival.[26] The 2021 International Association for the Study of Lung Cancer Consensus Statement recommends that liquid biopsy using plasma cell tumour DNA be considered for the genotyping of newly diagnosed patients with advanced non–small cell lung cancer.[27] Moreover, Sozzi and colleagues demonstrated that the detection of plasma-based micro-RNA combined with low-dose CT resulted in a fivefold decrease in false-positive lung cancer detection at 3.7% compared with low-dose CT screening alone (19.4%).[28] Similarly, Pastorino and colleagues found that 20.1% of patients with positive serum micro-RNA as well as low-dose CT were diagnosed with lung cancer at 4 years, compared with 10.8% in patients who were low-dose CT–positive only.[29] The authors also found that patients who were micro-RNA and low-dose CT–positive had the highest lung cancer mortality (10.1%) relative to those who were low-dose CT–positive only (4.1%).[29] Additionally, the detection of protein-based biomarkers are being studied. Fahrmann and colleagues found that the combination of a 4-marker serum protein test and the $PLCO_{m2012}$ model improved sensitivity by 9.9% and specificity by 6.9% of lung cancer detection relative to US Preventive Services Taskforce 2021 criteria.[30] The utility of detecting various serum markers in lung cancer screening is still being explored but remains a promising future area of research. Point-of-care testing using rapid next-generation sequencing has been shown to detect cancer efficiently (in less than 3 days) in a community setting, including for non–small cell lung cancer. As these techniques improve, point-of-care testing for non–small cell lung cancer and molecular analysis at the prediagnosis stage is a promising area for future work and will be crucial in evaluating the utility of molecular analysis in broadening lung cancer screening eligibility criteria.

Radon exposure and geographical incidence in screen-ineligible patients

Radon is the second leading cause of lung cancer after smoking[31] and is the leading cause of lung cancer in never-smokers worldwide.[32] Gaskin and colleagues estimated that among 66 countries globally, radon accounted for 226 057 lung cancer deaths in 2012.[31] Despite the linear relation between radon exposure and lung cancer incidence,[31] radon is not considered in guideline recommendations for identifying high-risk individuals for lung cancer screening.[19] The National Comprehensive Cancer Network 2022 Guideline Update[33] states that while age and smoking history are used for risk assessment, radon exposure can be considered

during shared decision-making for lung cancer screening. Using low-dose CT, Panina and colleagues screened 3671 participants aged 40–74 years irrespective of smoking status who were living in regions with excessive radon levels; they produced a lung cancer detection rate of 2.0%, comparable to findings from the NLST.[34] In our cohort, 2.4% of screen-ineligible light-or-never-smokers were also more frequently living in areas at high risk for radon exposure relative to screen-eligible heavy smokers. Our data support that the use of targeted lung cancer screening must be evaluated in regions with high geographical exposure to radon to ascertain the clinical significance of our findings. While limitations exist to quantifying and characterizing the nature of radon exposure for individuals with various past dwellings, accurate estimates occur when living spaces are occupied for 10 years or longer, and the measurement of indwelling radon exposure is convenient, reliable, and inexpensive.[35] Prospective randomized trials are needed to further clarify the role of radon exposure in risk factor–based lung cancer screening. Moreover, the regional analysis of lung cancer cases used in this study enables a detailed assessment of the incidence of cases adjusted per capita in any given zone. Similar studies have mapped the rates of *EGFR* mutations, but on a global scale.[36] The methodology used in this study may be replicated elsewhere, particularly when there is interest in the initiation of a lung cancer screening program. Furthermore, identification of high-risk areas allows for further investigation of genetic and environmental factors. Zhu and colleagues[37] assessed the geographic variation and clustering of lung cancer incidence rates in Philadelphia and its surrounding areas and identified high-risk areas that were associated with lower socioeconomic status and potential sources of pollution. Physicians and policy-makers will benefit from understanding which regions have an increased incidence of lung cancer, as well as an augmented exposure risk for radon, to help inform targeted screening as lung cancer screening programs are established.

Limitations

This was not a prospective study for patients receiving lung cancer screening, and the findings must be interpreted accordingly. The generalizability of our findings must be considered as this was a single-centre study, though our institution is the sole provider for thoracic surgery care for our province and neighbouring provinces.

The low rate of *EGFR* mutations found in our cohort may reflect that our findings are more applicable to predominantly White populations. Moreover, patients without a tissue diagnosis were not captured in the data, and these patients may have held poorer health status. The cohort comprised roughly 9% of all patients with lung cancer in the province owing to database limitations, with a projected estimate of 13 000 cases during this period. Furthermore, a detailed history including emphysema status and exposure to cooking oils was unavailable. In particular, ethnicity has been found to play a major role in the prevalence of certain mutations, including *EGFR*.[35] This remains a major limitation of our data set. Furthermore, screen-ineligible patients were older in our study and this was not adjusted for in the regression analysis as age is part of the definition of group allocation. The findings must be interpreted accordingly.

Radon exposure risk for patients was estimated based on their postal code at the time of diagnosis. This is a crude estimate of radon exposure and has important limitations, particularly at the individual level. Work is currently underway to calculate lifetime exposure of radon at the individual level and to better characterize the distribution of radon in Nova Scotia.

Patients treated with immunotherapy were not reflected in this cohort. Moreover, regional comparisons of molecular and immunologic mutation rates were likely limited in power, and findings must be interpreted appropriately. Finally, techniques for lung cancer detection and molecular analysis are not yet ready for reliable clinical use for lung cancer screening but remain a promising area of future research.

Conclusion

Screen-ineligible light-or-never-smokers had a higher rate of *EGFR*- and *PIK3CA*-positive lung cancers than screen-eligible heavy smokers when defined using trial-based eligibility criteria for lung cancer screening. There was no difference in PD-L1 between ineligible light-or-never-smokers and eligible heavy smokers. There is a need to prospectively investigate the role of molecular markers in identifying the patients with highest risk who may benefit from low-dose CT screening. The use of blood-based markers is a promising area of study and may facilitate the assessment of molecular markers associated with the development of early lung cancers. Mapping lung cancer incidence based on geographic location may further inform targeted efforts, particularly at the initiation of a lung cancer screening program.

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