CHEST

Performance of Risk Factor-Based Guidelines and Model-Based Chest CT Lung Cancer Screening in World Trade Center-Exposed Fire Department Rescue/Recovery Workers

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BACKGROUND: Lung cancer is a leading cause of cancer incidence and death in the United States. Risk factor-based guidelines and risk model-based strategies are used to identify patients who could benefit from low-dose chest CT (LDCT) screening. Few studies compare guidelines or models within the same cohort. We evaluate lung cancer screening performance of two risk factor-based guidelines (US Preventive Services Task Force 2014 recommendations [USPSTF-2014] and National Comprehensive Cancer Network Group 2 [NCCN-2]) and two risk model-based strategies, Prostate Lung Colorectal and Ovarian Cancer Screening (PLCOm2012) and the Bach model) in the same occupational cohort.

RESEARCH QUESTION: Which risk factor-based guideline or model-based strategy is most accurate in detecting lung cancers in a highly exposed occupational cohort?

STUDY DESIGN AND METHODS: Fire Department of City of New York (FDNY) rescue/recovery workers exposed to the September 11, 2001 attacks underwent LDCT lung cancer screening based on smoking history and age. The USPSTF-2014, NCCN-2, PLCOm2012 model, and Bach model were retrospectively applied to determine how many lung cancers were diagnosed using each approach.

RESULTS: Among the study population (N = 3,953), 930 underwent a baseline scan that met at least one risk factor or model-based LDCT screening strategy; 73% received annual follow-up scans. Among the 3,953, 63 lung cancers were diagnosed, of which 50 were detected by at least one LDCT screening strategy. The NCCN-2 guideline was the most sensitive (79.4%; 50/63). When compared with NCCN-2, stricter age and smoking criteria reduced sensitivity of the other guidelines/models (USPSTF-2014 [44%], PLCOm2012 [51%], and Bach[46%]). The 13 missed lung cancers were mainly attributable to smoking less and quitting longer than guideline/model eligibility criteria. False-positive rates were similar across all four guidelines/models.

INTERPRETATION: In this cohort, our findings support expanding eligibility for LDCT lung cancer screening by lowering smoking history from ≥30 to ≥20 pack-years and age from 55 years to 50 years old. Additional studies are needed to determine its generalizability to other occupational/environmental exposed cohorts. CHEST 2021; 159(5):2060-2071

KEY WORDS: low-dose chest CT; lung cancer screening; occupational lung disease; smoking; World Trade Center

ABBREVIATIONS: EMS = emergency medical service providers; FDNY = Fire Department of the City of New York; LDCT = low-dose chest CT; NCCN-2 = National Comprehensive Cancer Network Group 2; NLST = National Lung Cancer Screening Trial; PLCOm2012 = Prostate Lung Colorectal and Ovarian Cancer Screening; USPSTF = United States Preventive Services Task Force; WTC = World Trade Center; WTCHP = World Trade Center Health Program

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In 2020, lung cancer represents 12.7% of cancer cases and 22.4% of cancer deaths in the United States.[1] The 5-year age-standardized net survival rate in the 2010-2016 timeframe remains only 20.5% despite improved screening and treatment.[1] CT screening leads to earlier detection of lung cancer, improving survival.[2,3] In 2014, the United States Preventive Services Task Force (USPSTF-2014) recommended annual low-dose chest CT (LDCT) lung cancer screening using risk factor-based criteria—age 55 to 80 years old with ≥30 pack-years smoking history who currently smoke or have quit within the past 15 years.[4] The recommendation was based primarily on the 2011 National Lung Cancer Screening Trial (NLST), in which LDCT screening exhibited a 20% relative reduction in lung cancer mortality.[3] A recent meta-analysis pooling results from nine randomized controlled trials confirmed that LDCT improves detection of early-stage lung cancers and reduces lung cancer mortality when compared with usual care/no screening or chest radiography.[5]

The USPSTF recently proposed expanding LDCT lung screening eligibility criteria by lowering entry age to 50 years of age and smoking history to ≥20 pack-years (currently smoking or having quit within 15 years).[6] Neither the current or 2020 proposed USPSTF guideline consider other important risk factors such as occupational exposures. The National Comprehensive Cancer Network-Group 2 (NCCN-2) guidelines do consider occupational exposures and lower eligible screening age from 55 to 50 years and smoking history from ≥30 to ≥20 pack-years, similar to the USPSTF-2020 proposal, but without a 15-year limit on years quit.[7] In contrast to risk factor-based guidelines, risk model-based strategies aim to provide a more precise, cost-effective screening guidance beyond age and smoking history by incorporating demographic, limited occupational, and clinical characteristics.[8-13]

The Fire Department of the City of New York (FDNY) firefighters and emergency medical service providers (EMS) involved in the rescue/recovery effort after the September 11, 2001 terrorist attacks represent a large, occupational cohort in which the performance of multiple lung cancer screening criteria can be directly compared. Relative to their counterparts in the general population, some have that found firefighters have an increased rate of lung cancer, while others have not.[14-18] LDCT lung cancer screening and treatment, both at no cost to the participant, are covered under the federal government's World Trade Center (WTC) Health Program (WTCHP). Thus, FDNY rescue and recovery workers underwent LDCT screening based on their occupational exposures, which included multiple carcinogens from WTC dust/gases such as asbestos, silica, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, and dioxins.[19,20]

Whether risk factor-based guidelines or risk model-based strategies for LDCT lung cancer screening are more accurate and efficient in occupational cohorts is unclear.[8] The current study is, to our knowledge, the first to evaluate the lung cancer screening performance of two risk factor-based guidelines and two risk model-based strategies in the same cohort with occupational exposures (Table 1). The guidelines chosen were USPSTF-2014,[4] the most accepted in the United States, and NCCN-2,[7] which includes other risk factors such as occupational exposures. The chosen risk model-based strategies were: Prostate Lung Colorectal and Ovarian Cancer Screening (PLCOm2012)[12] and Bach models, because they are well validated, and the Bach model includes occupational (asbestos) exposure.

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Methods

Study Population

The source population consisted of 13,910 FDNY-WTC exposed rescue and recovery workers (firefighters/EMS) enrolled in the FDNY-WTCHP who consented for research. Because the broadest

TABLE 1] LDCT Lung Cancer Screening Criteria

LDCT Lung Cancer Screening	Criteria
Risk Factor-Based Guideline	
United States Preventive Services Task Force (USPSTF-2014)[4]	Age 55 to 80; ≥30 pack-year smoking (current or stopped <15 years ago)
National Comprehensive Cancer Network Group 2 (NCCN-2)[7]	Age 50 to 80; ≥20 pack-year smoking (current or stopped anytime); and at least one more risk factor (personal history of cancer or lung disease, family history of lung cancer, occupational carcinogenic exposure, radon exposure).
Risk Model-Based Strategy	
Bach[9]	Composed of two models, one predicting probability of lung cancer over 1 year and one predicting survival in the absence of lung cancer over 1 year. Each were run recursively 6 times to predict 6-year absolute risk, matching the PLCOm2012 model calibrated to this timeframe. Covariates included number of cigarettes per day while smoking, years smoked, years since quit, age, sex, and asbestos exposure. The Bach model assigns a risk factor for smoking that essentially excludes never smokers and includes an occupational exposure (asbestos) for which we substituted any level of WTC exposure. Variable adjustments and weights from Bach et al[9] were applied. As with the PLCOm2012 risk prediction cutoff, participants with a 6-year lung cancer risk >1.3455% were included.
Prostate Lung Colorectal and Ovarian Cancer Screening (PLCOm2012)[12]	Covariates included age, race, education level, BMI, diagnosis of COPD, any previous cancer, family history of cancer, smoking intensity, smoking duration, and years since quit smoking. The PLCOm2012 excluded never smokers and does not include a covariate for occupational exposure. Variable adjustments, weights, and the lung cancer risk threshold of >1.3455% were applied.

LDCT = low-dose chest CT; PLCOm2012 = Prostate Lung Colorectal and Ovarian Cancer Screening; WTC = World Trade Center.

inclusion criteria of the four screening guidelines/models studied required participants to be ≥50 years old, individuals younger than 50 years on December 31, 2018 (end of enrollment) were excluded (n = 3,502). To determine the impact of smoking history on LDCT screening performance, we included all smokers (regardless of amount or quit date), excluding 6,455 never smokers. The final study population was 3,953 FDNY-WTC exposed rescue/recovery workers invited to participate in the FDNY-WTC Chest CT lung cancer screening program between October 2001 and December 2018 (Fig 1). The Montefiore Medical Center/Albert Einstein College of Medicine Institutional Review Board approved this study (#01-12-297/#07-09-320).

Demographic, Exposure, and Clinical Characteristics

Demographic information, including age, race, sex, and education level, were retrieved from the FDNY employee database. Clinical data, including height, weight, BMI (at first CT), self-reported smoking status (current, former, never smoker), smoking intensity (age started, age quit, packs/day), personal history of cancer or lung disease, family history of lung cancer, and WTC exposure intensity, were obtained during annual FDNY-WTCHP monitoring examinations.[21] The first self-reported age at start of smoking was used, as were the highest values ever reported for age at quit and packs/day. Among current smokers, pack-years were calculated, using the difference between age at their first CT and age at start of smoking multiplied by the average packs/day smoked. Among former smokers, cumulative smoking exposure (pack-year history) was calculated, using the difference between the quit and start ages multiplied by the average packs/day smoked. Years since quit was calculated as the difference between age at first CT and age at quitting. WTC exposure intensity was measured using self-reported time of arrival to the WTC disaster site. Intensity hierarchy from greatest to least exposure was based on initial arrival time at the WTC site as follows: arrived morning of September 11, 2001, arrived during the afternoon/evening of September 11, 2001, arrived September 12, 2001, and those who arrived thereafter or with unspecified arrival times.

Physician diagnoses and information from diagnostic tests such as spirometry and chest CT scans were extracted from the FDNY-WTCHP electronic medical record.[22] Lung cancer histologic groupings were created using ICD-O-3 codes.[23] COPD was classified according to the Global Initiative for Obstructive Lung Disease criteria (FEV_1/FVC ratio < 0.7),[24] a stricter definition than that used in many prior LDCT studies.

LDCT Scans

LDCTs were performed at approved radiology facilities, and all received standard radiologic evaluations. Radiologists were blinded to participants' WTC exposure intensity.

Lung Cancer Case Confirmation, False-Positives, and Complications

Individuals with suspicious nodules received diagnostic evaluations and treatment within the FDNY-WTCHP based on Fleischner Society criteria.[25,26] FDNY cancer data are described in detail elsewhere.[27] Briefly, lung cancer diagnoses for all FDNY-WTC exposed rescue/recovery workers were ascertained via two methods: by linkage to state cancer registries[28] and by medical record confirmation of cases reported to the FDNY-WTCHP. A trained clinician (N. J.) contacted eligible participants to obtain any missing medical records for cancers not already identified through state cancer registry matches.[27] Date and stage at diagnosis were obtained from the medical record. Only confirmed lung cancer cases, by

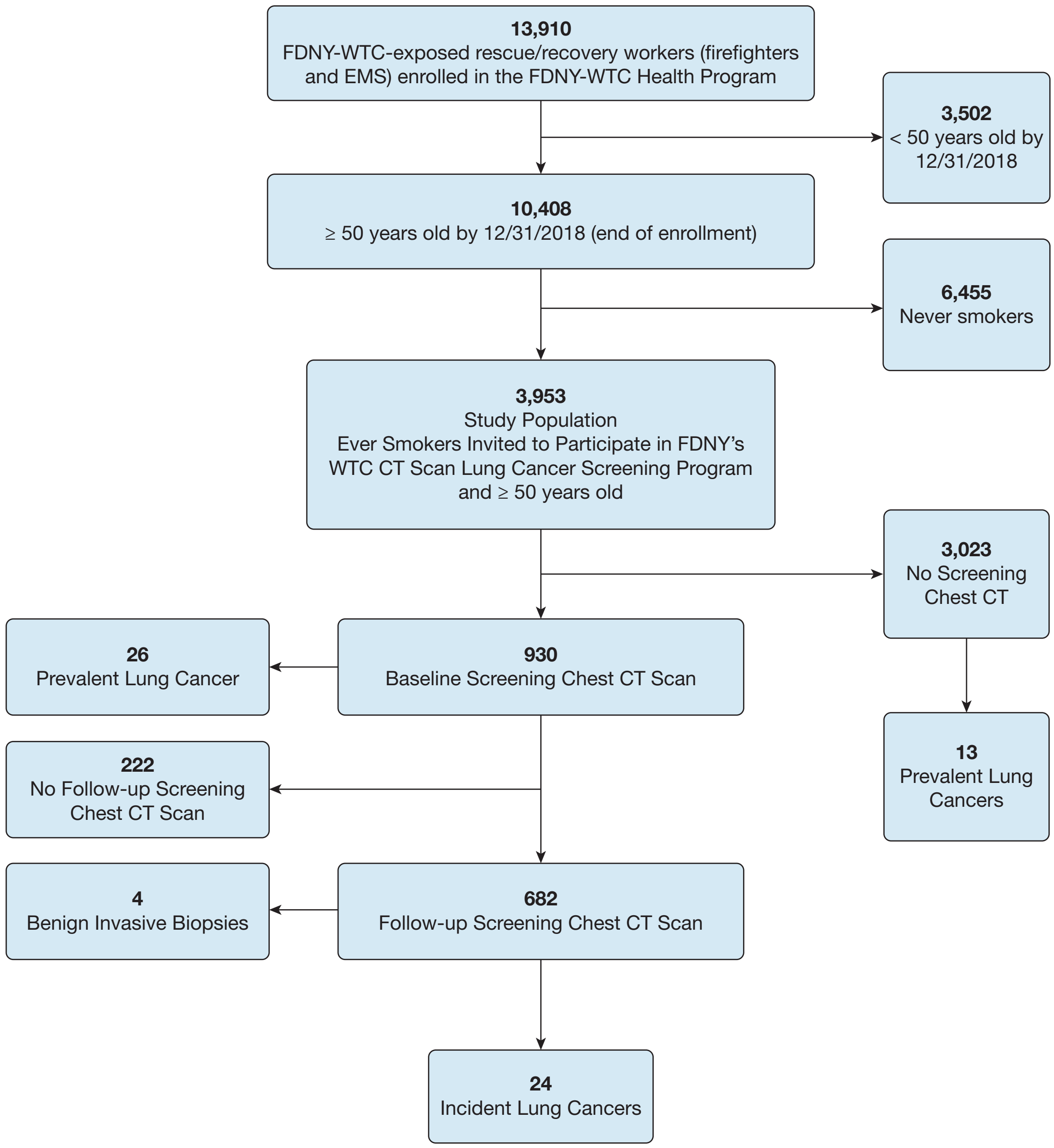

Figure 1 – *Flow diagram of the study population. Shown is the total number of current and former smokers aged 50 years and older invited to participate in the FDNY-WTC CT lung cancer screening program. FDNY-WTC = Fire Department of the City of New York World Trade Center.*

either method described, diagnosed October 1, 2001 through December 31, 2019, were included in this study. Prevalent cancers were those found within 6 months of the first CT scan.

False-positive cases were found via medical record review and defined as the proportion of participants whose suspicious nodules (≥6 mm or increasing in size) required follow-up and were not diagnosed as lung cancer by end-of-study, out of all cases with suspicious nodules on LDCT. We also identified the proportion of participants with suspicious nodules that underwent an invasive procedure for which the biopsy did not reveal lung cancer out of all with biopsied nodules. Diagnostic procedures were obtained from FDNY-WTCHP medical/invoice records. Serious complications were defined as unexpected hospitalization, extended hospital length of stay, or death.

Screening Guidelines and Risk Prediction Models

Participant characteristics and self-reported smoking measures at the time of their first CT scan were used to categorize participants according to the guidelines (NCCN-2 and USPSTF-2014) and models (PLCOm2012 and Bach). Because of overlapping inclusion criteria, many participants were evaluated by more than one set of screening criteria. The application of these guidelines/models to the FDNY-WTCHP cohort is detailed in Table-1.

Statistical Analyses

Overall population demographics and characteristics among the NCCN-2, USPSTF-2014, PLCOm2012, and Bach model screening subgroups were assessed as proportions, medians, and interquartile ranges, or means ± SDs, as appropriate. The number of lung cancers detected within the study population was assessed against the total detected by the NCCN-2, USPSTF-2014, PLCOm2012, and Bach guideline/models. Stage at diagnosis, sensitivities, specificities, and false-positives were descriptively compared across the study population and screening subgroups, when applicable. Logistic models were used to test association between cancer cases among participants and either WTC exposure intensity or occupation (EMS vs firefighter), controlling for age, sex, and smoking status. Finally, among all lung cancers, we used a scatterplot to illustrate the distribution by pack-years and age at diagnoses of those detected by the NCCN-2 guidelines and those who were and were not additionally detected by the USPSTF-2014, PLCOm2012, and Bach guideline/models. Analyses were conducted using SAS 9.4 (SAS Institute).

Results

Among 3,953 FDNY-WTC rescue/recovery workers in the study population, 930 underwent a baseline CT scan and were eligible for one of the four screening guidelines/models. Those who participated in screening were older and more likely to be firefighters, be current smokers, have COPD, or have a personal or family history of cancer compared with the 3,023 who were invited but chose not to participate in LDCT screening (Table 2). Of those who participated, 926 of 930 (99.6%) met NCCN-2 criteria, 392 of 930 (42%) met USPSTF-2014 criteria, 409 of 930 (44%) met PLCOm2012 criteria, and 395 of 930 (42%) met Bach model criteria. Four participants did not meet NCCN-2 criteria but met criteria for either the PLCOm2012 or Bach model because they had less than 20 pack-years smoking (average of 16 years), but in combination with other risk factors were included in the model; none had cancer. Of those who did not participate, 31.8% (960/3023) would have met the broadest eligibility criteria (NCCN-2).

Among the four screening groups, demographic characteristics were similar except the NCCN-2 population was younger and had the lowest mean pack-years (Table-3). Follow-up scans occurred in 73% (682/930) (Fig 1), and 33% of them (228/682) had a new lung nodule on a follow-up scan. Follow-up time was not different between guidelines or models.

Lung Cancer Characteristics and Screening Protocol Performance

There were 63 of 3,953 (1.6%) lung cancer cases during the study period. The median age at diagnosis was 65 years (interquartile range, 57-71). Among the 63 lung cancer cases, 56 (89%) were non-small cell carcinoma (43 adenocarcinomas, 11 squamous cell, and two large cell carcinomas), three (4.8%) were small cell carcinoma, and four (6.3%) were other (eg, carcinoid tumors).

Of the 63 people with lung cancer, 50 were detected among 930 who met criteria for at least one of the screening guidelines or models and 13 diagnosed among the 3,023 who did not participate in LDCT screening—only one of whom met eligibility for at least one screening guideline or model. The NCCN-2 guideline identified the greatest number of cancers (n = 50) and encompassed all of those identified by USPSTF-2014 guideline (n = 28), the PLCOm2012 model (n = 32), and the Bach model (n = 29) (Table 3). The sensitivity of the NCCN-2 guideline was greater than that of the USPSTF-2014, PLCOm2012, and Bach guideline/models, but at the expense of a lower specificity (Table 3). Prevalent and incident cancers identified by screening were split almost evenly at 26/50 and 24/50, respectively (Table 3). Within each screening guideline or model group, those diagnosed with lung cancer had greater mean pack-years of smoking and more years of follow-up than each screening population as a whole, but the median number of scans were similar. Of the 50 cancers detected by LDCT screening, finding localized disease (stage I/II) was similar for all four guidelines or models—NCCN-2 (26/50; 52.0%), USPTSF-2014 (12/28; 42.9%), PLCOm2012 (13/32; 40.6%) and Bach model (11/29; 37.9%) (Table 3). Of the remaining 13 cases in the nonscreened population, 46.1% were localized disease.

False-positive findings (suspicious nodules requiring follow-up that were not diagnosed as lung cancer by the end of the study) ranged from 83.8% to 79.7% (259/309 NCCN-2, 110/138 USPSTF-2014, 129/161 PLCOm2012, and 115/144 Bach). The proportion of invasive procedures that did not result in a lung cancer diagnosis ranged from 5.9% to 7.4% (4/54 NCCN-2, 2/30 USPTSF-2014, 2/34 PLCOm2012, 2/31 Bach). Procedures identifying false-positives were needle biopsy (n = 1) and video-assisted thoracoscopy (n = 3). No serious complications were reported.

Because age and smoking history are the strongest predictors of lung cancer risk, Figure 2 plots age at diagnosis vs pack-years for all 63 lung cancers. The shaded area encompasses indications for LDCT screening based on the NCCN-2 guideline's lower age and smoking history criteria (n = 50), and the red triangles represent lung cancer cases not included in screening. Nearly half of the 50 cancers identified by NCCN-2 were not identified by the other three

TABLE 2] Study Population Characteristics

Characteristic	Screened Population Based on LDCT Criteria		Not Screened Population	
	No.	%	No.	%
Total	930	100	3,023	100
Age at first CT, y				
50-54	293	32	NA	
55-59	231	25		
60-64	185	20		
65-69	106	11		
70-74	79	8		
75+	36	4		
Age at end of 2018, y				
50-54	36	4	695	23
55-59	111	12	649	21
60-64	297	32	691	23
65-69	212	23	447	15
70-74	140	15	278	9
75+	134	14	263	9
Sex				
Male	898	97	2,909	96
Female	32	3	114	4
Race				
White	850	91	2,634	87
Black	33	4	175	6
Hispanic	35	4	180	6
Other	4	0.1	18	1
Missing	8	1	16	1
Smoking status[a]				
Current smokers	268	29	327	11
Former smokers	662	71	2,696	89
Pack-years				
<20 pack-years	4	0.1	2,063	68
20-29 pack-years	294	32	452	15
30+ pack-years	632	68	508	17
Years quit[b]				
≤15 years	774	83	1,281	42
>15 years	156	17	1,742	58
Occupation				
Firefighter	840	90	2,541	84
EMS	90	10	482	16
Medical history				
COPD	361	39	569	19
Previous cancer	213	23	492	16
Family history of cancer	199	21	398	13
Diagnosis of lung cancer	50	5	13	0.1

LDCT = low-dose chest CT.
[a]Smoking status as of first 50+ scan if available or first reported smoking status for those who did not have a CT.
[b]If first 50+ CTs came in 2019, excluded.

TABLE 3] Screening Population Characteristics[a]

Characteristic	NCCN-2				USPSTF-2014				PLCOm2012				Bach			
	Total		Cancer		Total		Cancer		Total		Cancer		Total		Cancer	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Total	926	100	50	5[b]	392	100	28	7[b]	409	100	32	8[b]	395	100	29	7[b]
Age at first CT																
50-54	293	32	10	20	0	0	0	0	61	15	3	9	36	9	2	7
55-59	231	25	12	24	147	38	11	39	110	27	11	34	119	30	10	34
60-64	183	20	8	16	134	34	5	18	120	29	5	16	126	32	4	14
65-69	105	11	9	18	64	16	7	25	64	16	7	22	60	15	7	24
70-74	78	8	8	16	47	12	5	18	47	11	5	16	47	12	5	17
75+	36	4	3	6	0	0	0	0	7	2	1	3	7	2	1	3
Pack-years	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
Pack-years	38.9 (15.2)		44.5 (14.4)		48.2 (14.8)		48.9 (12.5)		48.5 (15.5)		48.8 (12.3)		49.6 (14.7)		50.1 (12.0)	
Follow-up	Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)	
No. of scans	2.0 (1-4)		2.00 (1-4)		3.0 (2-4)		2.00 (1-5)		3.0 (2-5)		2.0 (1-4)		3.0 (2-4)		2.0 (1-4)	
Time of follow-up, y[c]	3.8 (1.7-8.3)		4.7 (1.6-8.2)		3.0 (1.6-6.3)		4.2 (1.3-5.5)		3.5 (1.9-7.8)		4.7 (1.3-6.1)		3.3 (1.7-7.4)		4.3 (1.3-5.5)	
Age at diagnosis, y	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
50-54			3	6			0	0			1	3			1	3
55-59			12	24			7	25			8	25			6	21
60-64			10	20			6	21			7	22			7	24
65-69			9	18			7	25			7	22			6	21
70-74			9	18			4	14			4	13			4	14
75+			7	14			4	14			5	16			5	17
Cancers																
Prevalent cancer			26	52			14	50			16	50			15	52
Incident cancer			24	48			14	50			16	50			14	48
Lung cancer stage																
I			23	46			12	43			13	41			11	38
II			3	6			0	0			0	0			0	0
III			7	14			4	14			6	19			5	17
IV			15	30			10	36			11	34			11	38
Unknown			2	4			2	7			2	6			2	7

(Continued)

TABLE 3] *(Continued)*

Characteristic	NCCN-2				USPSTF-2014				PLCOm2012				Bach			
	Total		Cancer		Total		Cancer		Total		Cancer		Total		Cancer	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Study population (n = 3,953)																
Sensitivity and specificity																
Sensitivity	79.37% (50/63)				44.44% (28/63)				50.79% (32/63)				46.03% (29/63)			
Specificity	77.48% (3,014/3,890)				90.64% (3,526/3,890)				90.31% (3,513/3,890)				90.59% (3,524/3,890)			

NCCN = National Comprehensive Cancer Network Group; PLCOm2012 = Prostate Lung Colorectal and Ovarian Cancer Screening; USPSTF-2014 = United States Preventive Services Task Force.
[a]Some participants fit multiple screening criteria.
[b]Percentage of cancers among the total for each group.
[c]Excludes prevalent cancers and those without follow-up scan.

screening protocols; the USPSTF-2014 did not identify 22 (three <55 years old, 13 quit smoking >15 years ago, and six smoked <30 pack-years); the PLCOm2012 did not identify 18 (13 quit smoking >15 years ago, and seven smoked <30 pack-years); and the Bach model did not identify 21 (13 quit smoking >15 years ago and seven smoked <30 pack-years). Of the 13 people with lung cancer who did not participate in screening, only one may have been eligible for any of the four guidelines or models studied, because the remaining 12 smoked <20 pack-years, eight of whom also quit smoking >15 years ago.

Occupation and WTC Exposure as Screening Criteria

After adjusting for age, sex, and smoking history, there were no significant differences in lung cancer identified by any of the four screening protocols based on occupation (firefighter vs EMS) or WTC exposure intensity.

Discussion

To our knowledge, this study is the first to assess the performance of four LDCT lung cancer screening protocols—two risk factor-based guidelines and two risk model-based strategies—in the same cohort. We found that the NCCN-2 risk factor-based guideline performed better than the USPSTF-2014 guideline or either of the risk model-based strategies (PLCOm2012 and Bach) in detecting lung cancer, although this was at the expense of an increase in false-positive scans. Compared with the USPSTF-2014, PLCOm2012, and Bach, the NCCN-2 guideline screened the largest number of people and demonstrated the highest sensitivity in detecting lung cancer, but also the lowest specificity. When applied to this occupational/environmental-exposed cohort, our findings are consistent with the recent USPSTF-2020 proposal to expand the guideline by lowering age from 55 years to 50 years and smoking history from ≥30 to ≥20 pack-years, as reflected in the existing NCCN-2 guideline.

Although few, previous studies have compared the performance of LDCT lung cancer screening risk factor-based guidelines and risk model-based strategies.[29-34] In a recent validation study, the PLCOm2012 model demonstrated the highest discriminative, calibration, sensitivity, and specificity performance compared with the USPSTF-2014 guideline and the Bach model.[32,33] However, these studies did not include comparison with

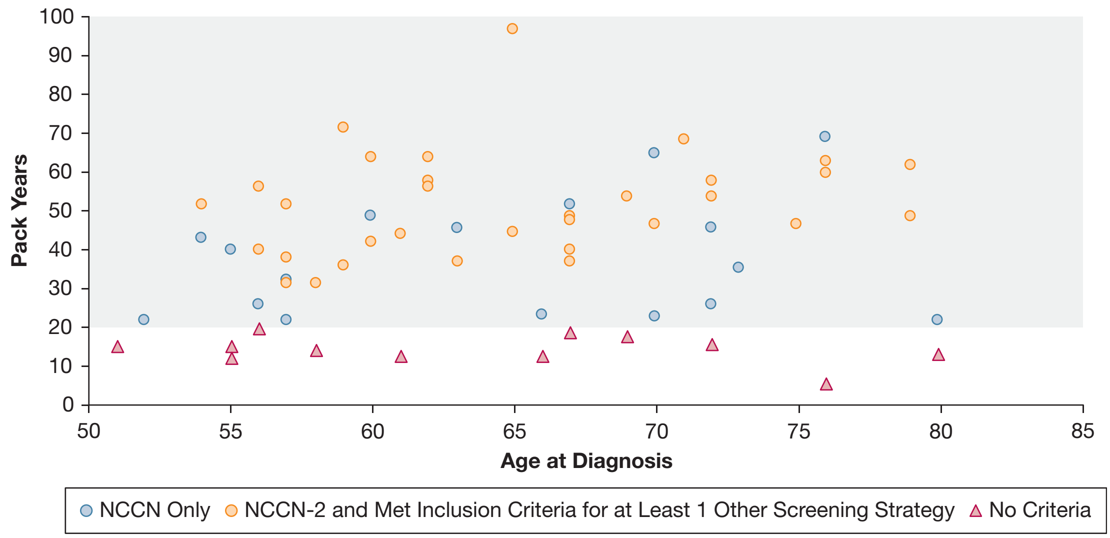

Figure 2 – - *Scatter plots of all lung cancer cases (N = 63) by age at diagnosis and pack-years. Age at diagnosis vs pack-years is plotted for all 63 lung cancers. The shaded area represents the NCCN-2 guideline criteria. The blue dots represent cancers captured by NCCN only. The orange dots represent cancers captured by NCCN-2 as well as at least one of the other guideline or models, USPSTF-2014, PLCOm2012, or Bach model. The red triangles represent cancers not captured by any of the guidelines or models. Nearly half of the 50 cancers identified by NCCN-2 were not identified by the other three screening protocols; the USPSTF-2014 did not identify 22 (three <55-years old, 13 quit smoking >15 years ago, and six smoked <30 pack-years); the PLCOm2012 did not identify 18 (13 quit smoking >15 years ago and seven smoked <30 pack-years); and the Bach model did not identify 21 (13 quit smoking >15 years ago and seven smoked <30 pack-years). NCCN = National Comprehensive Cancer Network Group; PLCOm2012 = Prostate Lung Colorectal and Ovarian Cancer. Screening; USPSTF-2014 = United States Preventive Services Task Force.*

the NCCN-2 guideline. Similarly, our investigation found the PLCOm2012 model has a somewhat higher sensitivity than the USPSTF-2014 guideline and Bach model, possibly because of the greater heterogeneity of their risk factor profiles,[35,36] but the sensitivity of the PLCOm2012 model was lower than that of the NCCN-2 guideline, which had the highest sensitivity of all four guidelines or models studied.

Even lowering smoking history eligibility to ≥20 pack-years (ie, consistent with NCCN-2 and the USPSTF-2020 proposal) still missed 19.0% (12/63) of the lung cancers in our study population. In contrast to the USPSTF-2014 guideline or the USPSTF-2020 proposal, the NCCN-2 guideline includes former smokers who quit >15 years ago, if they smoked ≥20 pack-years and have occupational exposure(s). In our study, excluding former smokers with a ≥20 pack-year history who quit >15 years ago would have missed 20.6% (13/63) of the lung cancers. A similar finding was reported in an occupational cohort of nuclear weapons workers in which one third of those with lung cancer detected using the NCCN-2 criteria had quit smoking >15 years earlier.[37] Cessation of tobacco smoking decreases the risk for lung cancer but does not eliminate it and must be considered in those with other risk factors, such as occupational exposure.[38,39]

The occupational exposure in this population and the population itself is unique, limiting generalizability of these findings. Although the lack of a difference in LDCT screening results between firefighters and EMS, or between levels of potential carcinogenic WTC exposure, may be evidence that the intensity of occupational exposure did not impact lung cancer risk significantly in this cohort, it also may be attributed to our inability to account for mitigating factors such as personal protective equipment, self-selection bias toward the healthy worker effect, and small numbers limiting our power to detect differences.

Strengths of this study are numerous. Performance comparisons between risk factor-based guidelines and risk model-based strategies for LDCT lung cancer screening within the same cohort allowed us to determine which screening guideline/model proved most accurate in detecting early lung cancers. Risk reduction in CT scan follow-up was achieved by using a single, experienced pulmonologist consistently adhering to a validated diagnostic protocol (eg, Fleischner Society) for the diagnosis of suspicious nodules.[25,26,40,41] We believe the absence of serious complications from these procedures resulted from strict adherence to this validated diagnostic protocol and the exclusive use of academic, tertiary-care medical centers for all procedures.[42-44] Additional strengths of our study include a novel study population with a strong ability to track cancer diagnoses, treatment, and management. The high level of compliance (73% of participants obtaining follow-up scans) demonstrates that LDCT screening was accepted and feasible in a labor management-endorsed, occupational health program as opposed to the usual academic or tertiary-care decision-making process tested in the NLST.[3]

Generalizability of our findings is limited by the unique exposure (WTC) and the study population (firefighters and EMS), its male predominance, the healthy worker effect, higher socioeconomic status, and the no-cost aspect of the WTC Health Program for those undergoing screening, evaluation, and treatment. Related to exposure, another limitation was substituting WTC exposure for asbestos in the Bach model without the ability to grade an individual's WTC exposure based on specific chemical or carcinogen exposures at the WTC site or throughout their career.[8,45] Unfortunately, these data do not exist. Despite limited information on occupational risk, we were able to identify an occupational group in whom LDCT screening was able to detect early, localized lung cancers. Other limitations related to study design include the potential impact of volunteer/participation bias, inability to provide formal comparisons among screening protocols because individuals in each guideline/model overlapped, the potential for over-diagnosis (ie, cancers that are not life-threatening),[46] and lack of statistical power to analyze the impact of screening on mortality rates.

Although we found that the NCCN-2 guideline detected a greater number of lung cancers in this occupational cohort, caution is needed when applying our findings, because our study was designed only to determine the accuracy of these risk factor guidelines and risk model-based strategies. The NCCN-2 risk-factor guideline was more accurate in detecting lung cancer than the USPSTF-2014 risk-factor guideline or the risk model-based strategies (PLCOm2012 or Bach). Because false-positive proportions were similar for all four screening protocols, using the more expansive NCCN-2 criteria will result in a higher number of participants screened and therefore will yield a higher number of false-positives. The balance between benefit and risk or harm between these four screening protocols cannot be accounted for in our study, designed to determine accuracy. This is especially true for our study because negative consequences from resulting diagnostic procedures were minimized by strict adherence to widely accepted diagnostic protocols[25,26] applied consistently by a single experienced pulmonologist—a situation uncommon in everyday clinical practice.

Interpretation

In this unique cohort, our study provides evidence for an expanded risk factor-based approach using the NCCN-2 guideline to provide a higher screening yield of early-stage lung cancers than found using the current USPSTF-2014 risk factor-based guideline, the PLCOm2012 model, or the Bach model. In an occupationally exposed cohort, screening only individuals with a smoking history $\geq$30 pack-years and who currently smoke or have quit within the past 15 years exemplifies an eligibility threshold that may fail to account for the increased risk attributable to the synergistic effects of occupational carcinogenic exposures and smoking.[47-52] Our findings are consistent with the recent USPSTF-2020 proposal, currently under review, to expand LDCT lung cancer screening eligibility by lowering smoking history to $\geq$20 pack-years and age to 50 years.[6] Future LDCT lung cancer screening studies should address the impact of risk factor-based and risk model-based strategies in those with multiple risks (occupational/environmental exposures, comorbidities, and family history) and lower smoking exposures ($<$20 pack-years, cessation $>$15 years). To maximize the balance between benefits and risks or harms, studies should include strict use of widely accepted diagnostic and treatment protocols coupled with adequately powered analysis of side effects and mortality rates. Until such time, regardless of setting (occupational, community, academic, or tertiary-care), LDCT screening protocols should be applied with careful protocol-driven, shared decision-making and appreciation of how risk-benefit assessments are impacted by exposure uncertainties, comorbid disease, life expectancy,[53] and the diagnostic or treatment expertise within the community.

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