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Prevalence of Pulmonary Nodules Detected by Computed Tomography in World Trade Center Rescue and Recovery Workers

To the Editor:

The collapse of the World Trade Center (WTC) after the terrorist attacks of September 11, 2001, exposed a large number of rescue and disaster recovery workers (hereafter "WTC responders") to potentially toxic inhalable particulates (1, 2). Lower respiratory symptoms and functional (3–5) and imaging (6–8) abnormalities have been common among WTC responders. Although early studies have not revealed an increased risk of lung cancer (9–12), the WTC Health Program covers lung cancer screening. Workers in the WTC responder cohorts (>50,000) had substantial tobacco and relevant pre-WTC (7) and WTC-related occupational exposures, and as they age, many are becoming eligible for lung cancer screening with low-dose computed tomography (LDCT) (13).

Because the presence of lung nodules and other abnormalities may impact the cost–benefit balance of lung cancer screening (13, 14), we analyzed chest imaging data of a large group of WTC responders, hypothesizing that *1*) WTC responders would have increased prevalence of noncalcified nodules (NCNs), and *2*) this prevalence would be related to WTC-related and other pre-WTC occupational exposures.

Methods

We used previously described WTC responder data from the WTC Chest Computed Tomography Imaging Archive (www.clinicaltrials.gov identifier NCT03295279) (7) and the WTC General Responder Cohort Data Center (4, 15). Responders were evaluated at the Mount Sinai WTC Pulmonary Evaluation Unit in New York City, and they underwent computed tomographic (CT) imaging of the chest between 2003 and 2012. For subjects with multiple scans, we selected the earliest. The Mount Sinai Institutional Review Board approved this study (HS12-00925).

Research radiologists reinterpreted deidentified chest CT scans using a standardized protocol (16, 17). Radiologists identified all nodules, recording their consistency, location, size at largest diameter, and presence of calcification. Radiologists also recorded systematically all other pulmonary findings, including pleural thickening.

The primary outcome in this study was the presence of NCNs. We used the nodule measurements to classify their severity according to the Lung CT Screening Reporting and Data System (Lung-RADS) criteria (14) into Lung-RADS 1, 2, or 3–4 categories.

As measures of WTC exposure, we used two separate dichotomous variables, namely arrival at the WTC site within 48 hours of the attack and WTC exposure duration (with 60 d as a cutoff) (3, 7, 8).

Multivariable analyses included these covariates: age at CT scan, sex, race/ethnicity, educational attainment, income, smoking status and intensity (pack-years) at baseline screening visit (18), and pre-WTC occupational exposures. As a measure of pre-WTC (7) respiratory exposure to asbestos, we used the presence of pleural thickening.

We then combined individual-level data of subjects meeting National Lung Screening Trial (NLST) inclusion criteria in our WTC cohort with individual-level data of 26,722 NLST participants randomized to LDCT from the first round of screening (13), and we created a 1:5 sample matched on age (in 5-yr increments), sex, smoking status, and pack-year quantity. Our outcome of interest was NLST "positivity" (NCN ⩾4 mm or suspicious for cancer), and WTC exposure was our main predictor.

Statistical analysis. We first estimated the prevalence of lung nodules and tabulated characteristics (including incidental findings) by Lung-RADS categories. Next, we fit ordinal regression models of nodule severity according to Lung-RADS classification (outcome) to assess the association of our primary WTC- and pre–WTC-related occupational exposures of interest.

Last, in the matched combined WTC-NLST sample, we compared the prevalence of nodules that met NLST positivity criteria on baseline scans using the chi-square test. We then fit a logistic regression model with NLST positivity as the outcome, adjusting for age, pack-years of smoking, and smoking status. This analysis had 75% power to detect a minimum 1.6-fold increase in positive scans associated with WTC exposure.

We employed multiple imputation to account for missingness (<5% for any variable) in our models (19). All analyses were performed using SAS version 9.3 software (SAS Institute).

Results

Of 1,617 subjects with chest CT scans performed a median of 8.7 (interquartile range, 7.1–10.1) years after September 11, 2001, 967

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Table 1. Baseline characteristics of study group (*N* = 1,617), stratified by lung CT screening reporting and data system findings

Characteristic	Lung–RADS		
	1	2	3–4*
n (%)	650 (40)	889 (55)	78 (5)
Number of nodules, median (IQR)	0	1 (1–2)	2 (1–4)
Any noncalcified solid nodule	0 (0)	757 (85)	78 (100)
Age at CT, yr, median (IQR)	49 (43–54)	50 (44–57)	53 (45–60)
Race/ethnicity			
Non-Latino white	340 (53)	469 (53)	49 (63)
Non-Latino black	67 (10)	73 (8)	9 (11)
Latino	224 (35)	313 (35)	18 (23)
Non-Latino other	14 (2)	27 (3)	2 (3)
Missing	5 (<1)	7 (<1)	0 (0)
Female sex	109 (17)	143 (16)	8 (10)
Education level			
Less than high school	84 (13)	123 (14)	9 (11)
High school graduate	164 (25)	234 (26)	29 (37)
Some college	192 (30)	241 (27)	19 (24)
College graduate	143 (22)	198 (22)	14 (18)
Unknown	67 (10)	93 (11)	7 (9)
Annual income			
<$30,000	119 (18)	182 (20)	10 (13)
$30,000–$60,000	173 (27)	211 (24)	26 (33)
$60,000–$80,000	89 (14)	110 (12)	12 (15)
>$80,000	125 (19)	187 (21)	19 (24)
Missing	144 (22)	199 (22)	11 (14)
Smoking status			
Current	120 (19)	172 (19)	25 (32)
Former	157 (24)	262 (30)	21 (27)
Never	373 (57)	454 (51)	32 (41)
Smoking pack-years†,‡, median (IQR)	11.6 (4–25)	11.3 (4–25)	19.3 (8–35)
COPD§	9 (1.4)	18 (2)	1 (1)
Significant pre-WTC exposures	350 (54)	457 (51)	48 (61)
Pre-WTC asbestos exposure	157 (24)	204 (23)	19 (24)
Pleural thickening	123 (19)	280 (32)	19 (24)
Pre-WTC silica exposure	79 (12)	111 (13)	15 (19)
WTC exposure level			
Low	78 (12)	107 (12)	17 (22)
Intermediate	427 (66)	615 (69)	46 (59)
High	127 (20)	147 (17)	15 (19)
Missing	18 (3)	20 (2)	0 (0)
WTC arrival within 48 h	343 (53)	429 (48)	39 (50)
WTC exposure duration			
≤60 d	263 (41)	353 (40)	36 (46)
>60 d	379 (58)	529 (60)	42 (54)
Missing	8 (1)	7 (<1)	0 (0)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CT = computed tomography; IQR = interquartile range; Lung-RADS = Lung CT Screening Reporting and Data System; WTC = World Trade Center.
*Lung-RADS subcategory classification of participant findings: Lung-RADS 3 (*n* = 51), Lung-RADS 4A (*n* = 16), Lung-RADS 4B (*n* = 11).
†Pack-year information missing for 86 subjects.
‡Among ever smokers.
§Based on evidence at least twice of post-bronchodilator ratio of forced expiratory volume in 1 second to forced vital capacity less than 0.7.

(60%; 95% confidence interval [CI], 57–62%) had at least one pulmonary nodule (Table 1), with 52% (95% CI, 49–54%) having at least one noncalcified solid nodule. Moreover, 889 (55%; 95% CI, 53–57%) of the 1,617 subjects had Lung-RADS level 2 findings, and 78 (5%; 95% CI, 4–6%) had Lung-RADS levels 3–4 findings, respectively (Table 1). Compared with subjects with lower Lung-RADS findings, subjects with higher Lung-RADS findings were more likely to be older and to be current smokers, and there was a trend toward greater pack-years of smoking among current or former smokers with Lung-RADS levels 3–4 findings.

Overall, subjects with Lung-RADS 3–4 findings were more likely to have multiple pulmonary nodules (median, 2) than those with Lung-RADS 2 and 1 findings ($P < 0.001$) (Table 1). In the unadjusted ordinal regression analysis, age, pack-years of smoking, former smoking, and a concurrent CT finding of pleural thickening were significantly associated with increasing severity of Lung-RADS findings. In multivariable analyses (Table 2), pleural thickening, but not WTC-related exposures, was significantly associated with severity of Lung-RADS findings.

Last, our comparison of NLST nodule positivity between WTC responders who met NLST inclusion criteria at the time of their earliest chest CT scan and their matched NLST first-round participants revealed no unadjusted (32.5% vs. 24.9%; $P = 0.2$) or adjusted (adjusted odds ratio, 1.5; 95% CI, 0.9–2.5) difference.

Discussion

The prevalence of pulmonary nodules in this WTC responder cohort is similar to that reported in lung cancer screening cohorts. In these WTC responders, age and pleural thickening were significantly associated with severity of Lung-RADS findings. Aside from pleural thickening, consistent with pre-WTC (7) asbestos exposure, neither WTC nor pre-WTC occupational exposure variables were associated with nodular lung disease. Our findings, if replicated, could be supportive of the recommendation to "relax" lung cancer screening eligibility criteria in consideration of occupational and environmental exposures (20, 21), which may be highly relevant in the WTC and other occupationally exposed populations (7). With LDCT-based lung cancer screening for heavy smokers now a standard of care in the United States (21), and with a sizable proportion of smokers among the WTC responder population, many may be referred for screening as the cohort ages. Estimating the influence of WTC-related and WTC-unrelated occupational exposures on the basis of the presence of NCNs is an additional factor to consider when assessing the benefits associated with lung cancer screening in this group (22).

The strengths of our study included the relatively large number of participants with imaging interpretations collected in a research setting, systematically ascertained smoking and occupational exposure data, and individual-level comparisons with a large screening trial. Notable limitations included the small size of our sample of patients meeting NLST inclusion criteria. In addition, because our study included only an initial imaging encounter for WTC responders, it did not determine the incidence of lung nodules or their longitudinal progression.

Table 2. Ordinal logistic regression models of Lung-RADS stages in WTC responders by occupational exposure predictors

Characteristic	Unadjusted Odds Ratio	*P* Value	Adjusted Odds Ratio*	*P* Value
WTC exposure duration				
<60 d	Reference		Reference	
⩾60 d	0.99 (0.81–1.21)	0.92	0.98 (0.80–1.20)	0.98
WTC arrival <48 h	0.85 (0.70–1.03)	0.11	0.87 (0.71–1.07)	0.13
Pleural thickening	1.73 (1.38–2.16)	<0.0001	1.71 (1.36–2.15)	<0.001

Definition of abbreviations: CT = computed tomography; Lung-RADS = Lung CT Screening Reporting and Data System; WTC = World Trade Center.
*Adjusted for WTC occupational exposure, pleural thickening (as a marker of pre-WTC occupational exposure to asbestos fibers), age, sex, race/ethnicity, smoking status, and pack-year smoking quantity. Interaction of the two WTC exposure variables, and of these with pleural thickening, were not significant. Models with two alternate pre-WTC occupational exposure variables, yielded essentially identical results (data not presented).

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Ethnically Diverse Normative Data for Diffusing Capacity and Lung Volumes: Another Research Priority

To the Editor:

We read with interest the recent ATS Workshop Report on Identifying Clinical and Research Priorities in Sickle Cell Lung Disease (SCD) (1). We congratulate the authors for this comprehensive assessment of research priorities in SCD.

A number of the highlighted research questions centered around lung function. We wish to point out that these questions could be challenging to address because of the lack of robust normative data for lung volumes and diffusing capacity from African Americans.

The Global Lung Function Initiative (GLI) has collected respiratory function outcomes from researchers and health care professionals from around the world. To date, the GLI Network hasproduced reference equations for spirometry from 74,000 subjects across the lifespan and from a variety of ethnic and national backgrounds, using modern and robust statistical techniques (2).

GLI has also collected data for Transfer Factor for Carbon Monoxide and generated normative values from 12,660 measurements from asymptomatic, lifetime nonsmokers from 14different countries (3). Unfortunately, 85% of the submitted data were from white subjects. Similarly, the majority of plethysmography data submitted to GLI for the development of normative data for lung volumes were from white subjects (S. Stanojevic, personal communication).

As SCD predominantly affects African Americans in the United States, this complicates interpretation of lung function data, as patients are compared with normative data obtained from white subjects. One recent study in children found lower DL_{CO} and alveolar volume in African Americans compared with white subjects (4). We suggest that obtaining normative data from diverse ethnic groups will be important for lung function assessment in patients with SCD, as well as nonwhite patients undergoing pulmonary toxic chemotherapy, and should be high on the list of research priorities.

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