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Reduced Lung Function in Smokers in a Lung Cancer Screening Cohort With Asbestos Exposure and Pleural Plaques

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Background *While low dose computed tomography (LDCT) screening for lung cancer is recommended for high-risk smokers, ages 55–74 years, information about asbestos exposure may not be routinely elicited. Asbestos exposure is associated with declining respiratory function over time; however, the effect of a history of asbestos exposure in LDCT screening cohorts is limited. We report the relationship between asbestos exposure and pulmonary function in a cohort of heavy smokers with a history of occupational asbestos exposure, hypothesizing that these subjects will have additional decreased pulmonary function. We also examined relationships between spirometric measurements and the presence of isolated pleural plaques.*

Methods *A cross-sectional study was performed using data from the NYU Lung Cancer Biomarker Center cohort to compare study subjects with a history asbestos exposure primarily in the period since 1970 when tighter federal standards were in place ($n = 359$) to those without asbestos exposure ($n = 1038$) with respect to pulmonary function, LDCT lung imaging findings, and clinical symptoms. We further classified individuals with asbestos exposure by length of exposure time to examine the effect of duration of exposure on pulmonary function. Lastly, for asbestos-exposed participants, we examined the association of spirometric measurements with the presence of absence of isolated pleural plaques.*

Results *Individuals with asbestos exposure had decreased FVC % predicted compared to those with no asbestos exposure (76% vs. 85% predicted, $P < 0.01$) and FEV_1 % predicted (64% vs. 67% predicted, $P < 0.01$). Since there was no change in FEV_1/FVC ratio, the findings are consistent with restrictive impairment. Those with $\geq$20 years of exposure had a lower mean FVC % predicted compared to those with less than 20 years of exposure (74% vs. 78% predicted, $P = 0.017$). Individuals with asbestos exposure were more likely to have pleural plaques ($P < 0.001$) on CT. Those with isolated pleural plaques had lower mean % predicted FEV_1 ($P = 0.005$) and FVC ($P = 0.001$) compared to those without pleural plaques.*

Conclusions *Occupational asbestos exposure in a cohort of heavy smokers was associated with a significant restrictive decline in pulmonary function, with longer duration of exposure associated with greater decline. The presence of isolated pleural plaques was also associated with reduced lung function.* Am. J. Ind. Med. 59:178–185, 2016.

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INTRODUCTION

Despite improved regulatory standards, asbestos-related lung diseases continue to play a significant role in occupational and environmental health. Asbestos is a naturally occurring mineral that has long been used in construction and various kinds of insulation. Individuals working in industries such as construction, shipbuilding, wiring, and boiler maintenance may have a history of asbestos exposure, predisposing them to significant diseases such as malignant mesothelioma, lung cancer, asbestosis, and other asbestos-related lung disease. Currently, those at risk for asbestos exposure in the U.S. are mainly construction and utility employees.

The natural history of asbestos-related lung diseases usually includes occupational exposure ($>$2 years, but usually $>$10 years), followed by a long latency period ($>$10 but usually $>$20 years) before onset of radiologic, physiologic, and carcinogenic changes. Thus, even though the Occupational Health and Safety Administration regulated asbestos exposure in 1970, asbestos-related diseases continue to be diagnosed [Goldyn et al., 2008]. In order to address the health needs of populations at high risk for asbestos-related diseases, it is important to understand the consequences of exposure for cancer risk and lung function decline.

The concentration of asbestos bodies in bronchoalveolar lavage fluid is positively correlated with computed tomography (CT) abnormalities and decreased pulmonary function, as would be expected given that asbestos affects the lung parenchyma as well as the pleural lining [Vathesatogkit et al., 2004]. Studies in asbestos-exposed groups show that there is an excess longitudinal decrease in forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) in workers with a history of asbestos exposure [Wang et al., 2010; Winters et al., 2012]. Additionally, studies have shown respiratory function loss to be associated with CT abnormalities in asbestos-exposed workers, and specifically that decreased FVC and total lung capacity (TLC) are associated with parenchymal fibrosis and pleural thickening [Piirila et al., 2009; Larson et al., 2012] or obstruction [Kilburn and Warshaw, 1994; Ohar et al., 2004]. Finally, it has recently been shown that cigarette smoke exposure with asbestosis has a supra-additive effect on lung cancer mortality as compared to asbestosis alone or smoking alone [Markowitz et al., 2013].

In the United States, there are many more workers at risk for low-level asbestos exposure than there are for high-level exposure, and the effect of low-level exposure combined with heavy smoking on pulmonary function, respiratory symptoms, and radiographic imaging is not well defined. In addition reduced lung function itself has been shown to be a risk factor for lung cancer in a heavy smoking cohort.

In this study, we performed a cross-sectional study of a lung cancer screening cohort, comparing the pulmonary function of individuals with a history of asbestos exposure to those without exposure. We also examined the relationship between pulmonary function and duration of asbestos exposure, and associations among asbestos exposure, clinical symptoms, and low dose CT (LDCT) findings. Finally, we examined the relationship between pulmonary function measurements and the presence of isolated pleural plaques.

MATERIALS AND METHODS

The Institutional Review Board of the NYU School of Medicine and the Bellevue Research Committee approved this research; all subjects gave informed consent. We recruited 1397 subjects over 50 years old with $\geq$20 pack-years smoking history to the NYU Lung Cancer Biomarker Center study between March 2001 and June 2013. We previously reported on lung cancer and the high prevalence of non-calcified nodules in this smoking cohort [Greenberg et al., 2012]. Subjects were recruited via mailings to NYU physicians, presentations within several NYU medical departments, a joint LDCT screening program agreement with the Utility Workers' Union and Con Edison (NYC), as well as advertisements and fliers. Exclusion criteria from the study included prior history of cancer or chemotherapy. Enrolled subjects attended clinic visits in which they filled out medical questionnaires; donated peripheral blood samples; performed spirometry, which was analyzed according to American Thoracic Society (ATS) standards [ATS, 1991]; and underwent LDCT lung imaging. Thoracic Radiology faculty provided written interpretations of the scans that described nodule characteristics (including size, density, and locale), and other abnormalities (pleural plaques, asbestosis, nonspecific fibrosis, emphysema, and bronchial wall thickening). National Health and Nutrition Examination Survey (NHANES) spirometric values were used for determining percent predicted values. Questionnaires were ATS-validated respiratory questionnaires that included demographic characteristics, tobacco use, chronological occupational history, and exposures, alcohol use, family history, and past medical history, and respiratory symptoms.

Subjects in the study were divided by history of asbestos exposure based on job description or self-reported exposure. Subjects with a history of U.S. Navy engineering work, boiler maintenance, employment as electricians or construction workers, or non-administrative work for Con-Edison (a regulated utility that provides electric service in New York City) were considered to have a history of asbestos exposure. In reviewing occupational histories, we determined that Con-Edison used union-contract boilermakers; thus, asbestos exposures among Con-Edison workers were primarily in the maintenance of underground wiring and steam-pipes. We

recorded job histories and durations. Analyses used data from the initial visit only. Variables evaluated included: age, sex, asbestos exposure history, and spirometric measurements. LDCT findings (evidence of emphysema, parenchymal fibrosis, pleural plaques, pleural thickening, noncalcified nodule characteristics, ground glass opacity as determined by a single chest radiologist at NYU Langone Medical Center), smoking history, and respiratory symptoms (cough, phlegm, wheezing, and dyspnea score).

Statistical Analysis

The data were analyzed using SPSS statistical software version 21. Analyses were performed with the asbestos exposure group based on job description and duration in that job. Student's *t*-tests and Pearson's chi-square test were used to compare the asbestos-exposed group to the non-exposed group. Stepwise logistic multivariate analysis was used to obtain three models, and dependent lung function variables were dichotomized to either FVC greater than or less than-or-equal to 80%, FEV_1 greater than or less than-or-equal to 80%, and FEV_1/FVC ratio greater than or less than-or-equal to 70%. First, to predict presence of pleural plaque (dependent variable), the independent variables $FVC < 80\%$ predicted, $FEV_1/FVC < 0.70$, age, gender, smoking status, pack-years, body mass index (BMI), emphysema, pleural thickening, and history of asbestos exposure were used. Second, two additional models of pulmonary function used $FVC < 80$ % predicted and $FEV_1/FVC < 0.70$ as dependent variables, with independent variables age, gender, smoking status, pack-years, BMI, emphysema, pleural thickening, pleural plaques, and history of asbestos exposure. Means are reported with associated standard deviation (SD) of the data used to calculate the mean.

RESULTS

Demographic Data and Baseline Characteristics

Of 1,397 individuals enrolled in the NYU Lung Cancer Biomarker Center study (Fig. 1), 359 (25.8%) had a history of asbestos exposure as defined in the Materials and Methods section. Importantly, 68 individuals had been told by their physician that they had asbestosis, and 291 were deemed to have a history of exposure based on a history of non-administrative Con-Edison work, U.S. Navy engineering, boiler maintenance, electrician work or construction work. Mean exposure duration was 22.5 ± 12.6 years. Of the asbestos-exposed group, 225 subjects had greater than or

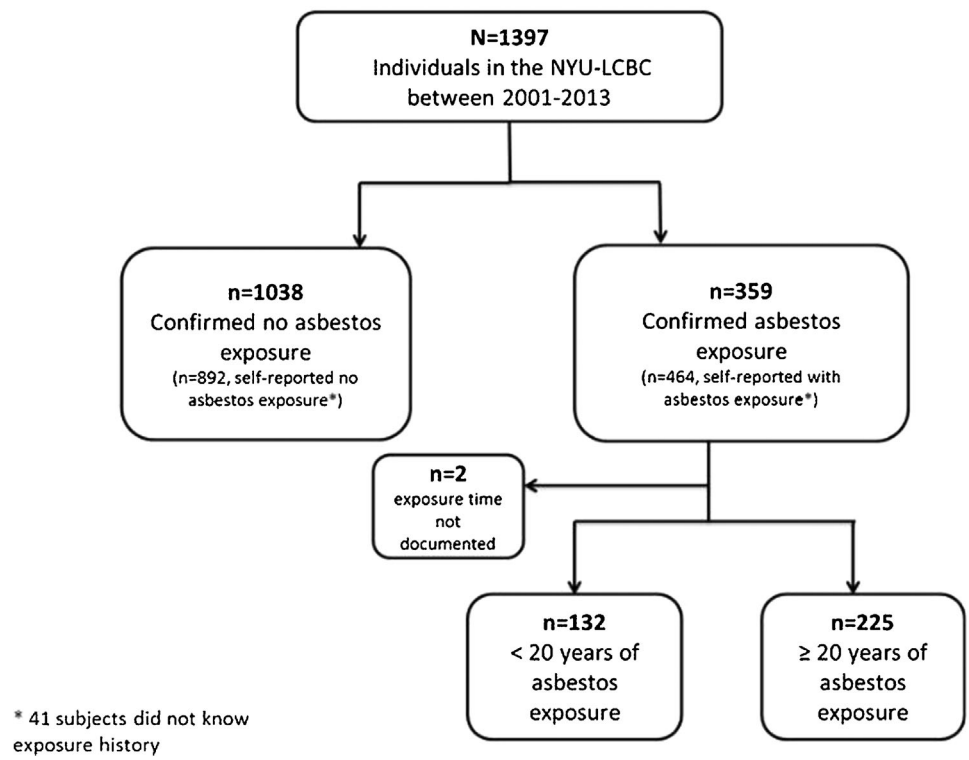

FIGURE 1. Study inclusion/exclusion criteria (Consort diagram).

equal to 20 years of exposure (mean 31.0 ± 6.3 years), and 132 subjects had less than 20 years of exposure (mean 8.0 ± 5.5 years).

The groups with and without asbestos exposure were comparable with regard to age, race, and pack-years of cigarette exposure (Table I). There were more men in the exposed group than in the non-exposed group (96% vs. 37%, $P < 0.01$). BMI was significantly higher in the asbestos exposure group than in the non-exposed group (mean 30 ± 6 vs. $27 \pm 6\,kg/m^2$, $P < 0.001$). There were fewer current smokers in the exposed group than in the non-exposed group (39.7% vs. 53.6%, $P = 0.002$), but the means of pack-years of exposure, 42 and 41, were similar. A total of 43 individuals developed lung cancer over the course of the study, with the proportions not significantly different between the exposed (11/359) and unexposed groups (32/1038).

Spirometry

First, using univariate analysis, we compared individuals with asbestos exposure to those without exposure based on job history. Subjects with a history of asbestos exposure had a significantly decreased FVC % predicted (mean $75.5 \pm 15.5\%$ vs. $84.6 \pm 17.2\%$, $P < 0.01$) and FEV_1 % predicted (mean $63.5 \pm 15.7\%$ vs. $67.0 \pm 16.1\%$, $P < 0.01$) than those with no history of exposure (Fig. 2), unadjusted. There was no significant difference in FEV_1/FVC (mean $74.3 \pm 8.2\%$ vs. $74.4 \pm 8.7\%$, $P = 0.78$) between the two groups.

To further study the effect of duration of exposure on pulmonary function, we compared those with at least 20 years of exposure (n = 223) to those with less than 20 years of exposure (n = 129). We found that individuals with $\geq$20 years of asbestos exposure had significantly decreased FVC % predicted (mean $74.0 \pm 14.2\%$ vs. $78.1 \pm 17.2\%$, $P = 0.017$) than those with <20 years of asbestos exposure (Fig. 3), unadjusted. There was no significant difference in FEV_1 % predicted (mean $62.5 \pm 14.0\%$ vs. $65.2 \pm 18.5\%$, $P = 0.12$) or FEV_1/FVC ratio (mean $74.2 \pm 8.0\%$ vs. $74.3 \pm 8.6\%$, $P = 0.88$) between these two groups.

A sub-analysis was performed of the association between the presence of isolated pleural plaques and pulmonary function in individuals with asbestos exposure. Subjects with pleural plaques detected on LDCT scan (n = 26) had a lower FVC % predicted (mean $76.4 \pm 16.5\%$ vs. $76.8 \pm 15.6\%$, $P < 0.01$) than the individuals (n = 220) with no radiographic abnormalities (no emphysema, or pleural plaques) (Fig. 4), with no difference in FEV_1 and FEV_1/FVC ratio, unadjusted. There was no significant difference in BMI ($29.4\,kg/m^2$ vs. $27.8\,kg/m^2$), smoking status, and pack-year smoking history (44.2 pack-years vs. 41.9 pack-years) between those with pleural plaques and those without pleural plaques, respectively.

As there was a higher proportion of women in the no asbestos exposure group, we performed a sub-group analysis on male subjects only. Age, race and mean pack-years were similar in both male exposed and unexposed groups. There was a greater proportion of current smokers ($P < 0.001$) and lower mean BMI ($P = 0.02$) in the exposed group. Pulmonary function analysis in the male cohort also showed a decrease in FVC % predicted ($75.0 \pm 15.0\%$ vs. $79.2 \pm 15.2\%$, $P < 0.0001$) and FEV_1 % predicted ($63.2 \pm 15.6\%$ vs. $66.0 \pm 15.4\%$, $P = 0.016$), in the asbestos-exposure group relative to the no asbestos-exposure group; there was no difference in the FEV_1/FVC ratio ($P = 0.35$) In the full sample, after adjusting for gender, pulmonary function value differences between the two exposure groups were still significantly different.

Multivariate analysis revealed that the presence of pleural plaques was significantly associated with history of

TABLE I. Baseline Characteristics of Participants With and Without Asbestos Exposure in NYU Lung Cancer Center Screening Program

	No asbestos exposure (n = 1,038)	Asbestos exposure (n = 359)	*p*-value*
Mean age ± SD	58 ± 10	57 ± 9	NS
Race (%)			NS
White	923 (89)	315 (88)	
Black	63 (6)	26 (7)	
Asian	28 (3)	5 (1)	
Hispanic	50 (5)	22 (6)	NS
Male Sex (%)	380 (37)	345 (96)	<0.001
BMI*	27.0 ± 6	29.9 ± 6	<0.001
Current Smokers (%)	557 (54)	142 (40)	0.002
Mean Pack-Years ± SD	42 ± 23	41 ± 25	NS
Exposure Duration	—	23 ± 13	
Lung Cancer (%)	32 (3)	11 (3)	NS

*BMI, body mass index; SD, standard deviation.
Statistical comparison was made between "No asbestos exposure" and "Asbestos exposure."

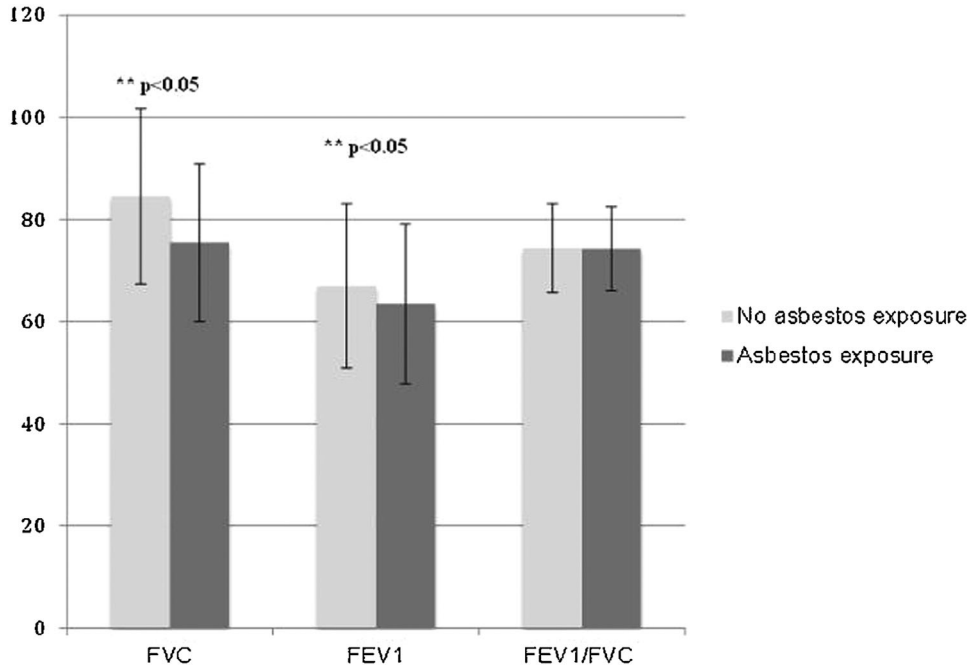

FIGURE 2. Means of spirometric measurements (expressed as % predicted for FVC and FEV_1, and as % for FEV_1/FVC) for study subjects with and without a history of asbestos exposure.

asbestos exposure (OR 20.4, 95%CI: 8.13–52.6) and subject's age (OR 1.14, 95%CI: 1.088–1.19). Multivariate analysis for FVC < 80% predicted found history of asbestos exposure (OR 1.92, 95%CI: 1.35–2.74), subject's age (OR 1.13, 95%CI: 1.105–1.28), pack years (OR 1.01, 95%CI: 1.004–1.017), male gender (OR 2.72, 95%CI: 2.001–3.703), current smoking status (OR 1.60, 95%CI: 1.177–2.0930, and BMI (OR 1.07, 95%CI: 1.04–1.10) as significant independent variables. Multivariate analysis for FEV_1/FVC < 0.70 found presence of emphysema (OR 1.77, 95%CI: 1.31–2.41),

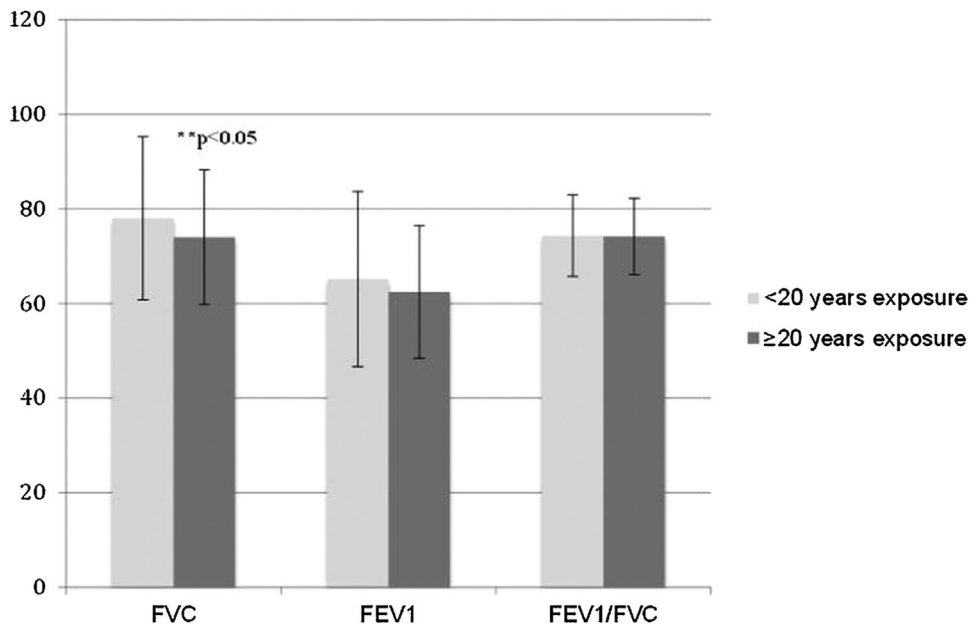

FIGURE 3. Means of spirometric measurements (expressed as % predicted for FVC and FEV_1, and as % for FEV_1/FVC) for study subjects with less than or at least 20 years of asbestos exposure.

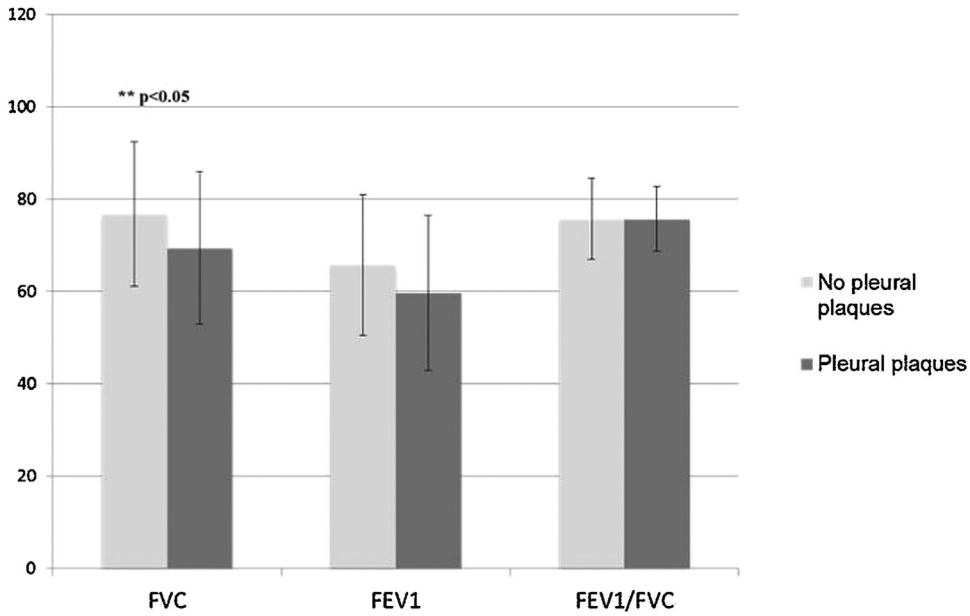

FIGURE 4. Means of spirometric measurements (expressed as % predicted for FVC and FEV_1, and as % for FEV_1/FVC) for asbestos-exposed subjects with and without pleural plaques.

subject's age (OR 1.04, 95%CI: 1.03–1.06), pack years (OR 1.01, 95%CI: 1.00–1.02), male gender (OR 1.70, 95%CI: 1.30–2.23), and BMI (OR 1.05, 95%CI: 1.02–1.07) to be significant variables.

Radiographic Changes and Respiratory Symptoms

To examine the effect of occupational asbestos exposure on lung structure we compared baseline LDCT radiographic results in exposed and non-exposed individuals. As expected, univariate analysis revealed that a history of asbestos exposure was associated with a significantly increased likelihood of pleural plaques (odds ratio (OR) 17.5, 95%CI 7.82–40.0, $P < 0.001$). Individuals with asbestos exposure were significantly less likely to have radiographic evidence of ground glass opacities (OR 0.7, 95%CI 0.5–0.99, $P = 0.04$) or emphysema (OR 0.8, 95%CI 0.6–0.98, $P = 0.10$). Non-calcified nodules >4 mm were observed in 41% of asbestos-exposed and 44% of non-exposed, and nonspecific fibrosis in 8% of asbestos-exposed and 6% of non-exposed.

We also compared respiratory symptoms in the exposed and non-exposed groups. Subjects with a history of asbestos exposure had significantly greater odds of phlegm production (OR 1.49, 95%CI 1.16–1.93, $P = 0.002$). There was no significant difference in reported symptoms of cough (28% vs. 25%, $P = 0.30$), wheezing (34% vs. 37%, $P = 0.59$) or Medical Research Council dyspnea score (1.7 vs. 1.3, $P = 0.47$).

DISCUSSION

We found that those with asbestos exposure in the NYU Lung Cancer Biomarker Center's LDCT scan screening program of heavy smokers had significant reductions in FVC and FEV_1 consistent with a restrictive effect and those with >20 years' exposure had further reductions. Asbestos-exposed individuals with isolated pleural plaques also showed a restrictive spirometric pattern relative to those without plaques.

These results were somewhat surprising since asbestos exposure has been reasonably well controlled in the U.S. over the past 30–45 years. There are, however, limited data on exposures to asbestos that may occur in maintenance and repair of steam pipes, electrical wiring, and power plants. Previous studies [Imbernon et al., 1995; Johansen and Olsen, 1998] have documented asbestos-related malignancies in electrical workers in epidemiological cohort and case-control studies. In our cohort, while both comparison groups displayed mild obstructive disease, likely attributable to the significant smoking history of >40 pack-years, those with occupational asbestos exposure had an additional restrictive lung pattern. Restrictive change in pulmonary function may be a consequence of low-level asbestos exposure, an effect that has previously been described with high-level asbestos exposure [Siracusa et al., 1988; Larson et al., 2012; Algranti et al., 2013] although some studies have demonstrated a primarily obstructive pattern [Kilburn and Warshaw, 1994; Ohar et al., 2004]. Our study indicates that a long duration of low-level asbestos exposure is associated with further

declines in pulmonary function, as others have shown for higher levels of exposure [Rom, 1992; Wang et al., 2001; Piirila et al., 2009; Wang et al., 2010].

A subgroup analysis designed to compare pulmonary function in those asbestos-exposed subjects with and without pleural plaques revealed significant decrease in FVC, and a trend for decrease in $FEV_{1,}$ in those with isolated pleural plaques. This result is consistent with multiple prior studies that demonstrate lower FEV_1 and FVC in cohorts with high levels of asbestos exposure and presence of pleural plaques [Jarvholm and Sanden, 1986; Oliver et al., 1988; Bourbeau et al., 1990; Lilis et al., 1991; Wilken et al., 2011; Kopylev et al., 2014]. Lockey and colleagues [Lockey et al., 2015] reported a relationship between cumulative fiber exposure and localized pleural thickening at lifetime exposure levels 3–10 times less than the 45-year working lifetime U.S. Occupational Safety and Health Administration standard of 4.5 fiber-year/cm^3 for commercial asbestos exposure.

The American Thoracic Society, in considering pulmonary function changes due to asbestos-related pleural plaques, concluded that studies of large cohorts showed a significant 5% reduction in FVC attributable to the plaques [ATS Statement, 2004]. Wilken and colleagues [Wilken et al., 2011] performed a systematic review and meta-analysis of 9,921 workers exposed to asbestos and found a statistically significant reduction in FVC in those without radiological changes [94.9% predicted (95%CI 92.9–96.9)], those with pleural fibrosis [87.1% predicted (95%CI 83.9–90.4)], and asbestosis [84.8% predicted (95%CI 80.8–88.8)].

Recently, a systematic review of the association between pleural plaques and changes in lung function found that the presence of pleural plaques was associated with a small, but statistically significant decline in FVC and FEV_1 in comparison to asbestos-exposed individuals without plaques [Kopylev et al., 2014]; FVC was associated with a 4.09% decrease and FEV1 was decreased by 2%. Further analysis in this study suggests that additional pleural plaque detected by high-resolution CT, compared to that detected on X-ray alone, still did not account for the observed lung function decline in those with pleural plaques. The Environmental Protection Agency (EPA) conducted an assessment of the adverse effects of Libby amphibole asbestos exposure targeting pleural plaques as an end point for their Integrated Risk Information System. The authors concluded that localized pleural thickening may be the most sensitive of the effects examined, as the radiological outcome most likely to occur after first occupational exposure, and the outcome most likely to appear at relatively low cumulative exposure levels.

There are several limitations to this study. First, asbestos exposure was assigned to the exposed group based on an occupational exposure history from questionnaires, and expert evaluation of the job description. Even though there was no way to accurately confirm or quantify exposure history, the finding of increased frequency of pleural plaques in the exposed group strongly suggests true asbestos exposure. Second, an important limitation on generalizability from this study is the nature of this cohort as a heavy-smoking cohort with reduced lung function across all subjects. However, the significantly greater reductions in lung function in the asbestos-exposed individuals suggest a contribution above that of smoking alone, attributable to concomitant asbestos exposure. Third, radiographic readings were performed by clinical radiologists; results were not verified by an independent radiologist to assess inter-rater agreement. The contribution of this study lies in its finding of additional decline in FVC and FEV_1 significantly associated with asbestos exposure, duration of exposure, and isolated pleural plaques, in a heavily smoking cohort. Asbestos exposure should routinely be queried in lung cancer CT-scan screening programs.

AUTHORS' CONTRIBUTIONS

SL, JJT, and WNR contributed to the concept, design of the study, data analysis and interpretation, and the writing of the manuscript. DAH, JSM, and HP contributed to the concept and writing and editing of the manuscript.

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DISCLOSURE BY AJIM EDITOR OF RECORD

Rodney Ehrlich declares that he has no competing or conflicts of interest in the review and publication decision regarding this article.

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