The Clinical Relevance of Asbestos-Induced Pleural Fibrosis[a]

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Asbestos-induced pleural fibrosis is the most common radiographic abnormality among asbestos-exposed persons and is thought to independently contribute to the development of restrictive lung volumes[1-5] and a reduced diffusing capacity.[2,6,7] Circumscribed pleural plaques and diffuse pleural thickening account for more than 90% of asbestos-induced pleural abnormalities,[8,9] and their prevalence is expected to increase for the next 15 to 20 years.[10,11] Several studies have reported that pleural plaques and diffuse pleural thickening appear to independently contribute to the development of restrictive lung function. After controlling for age, cigarette smoking, and duration of employment, pleural plaques, in the absence of interstitial fibrosis, were found to be associated with a reduction in both vital capacity[1-5] and the diffusing capacity of carbon monoxide.[2,6,7]

To assess the clinical significance of asbestos-induced pleural fibrosis, we evaluated the relationship between radiographic evidence of pleural fibrosis and spirometric values in 1,211 sheet-metal workers.[4] Of those with pleural fibrosis, 260 had circumscribed plaques and 74 had diffuse pleural thickening. Factors that were found to be associated with the presence and type of pleural fibrosis included age, number of years in the trade, pack–years of cigarette smoking, and the presence and degree of interstitial fibrosis. Among persons with normal-appearing parenchyma and also among those with interstitial fibrosis, we observed a consistent decline in the percent predicted forced vital capacity that was significantly associated with the type of pleural fibrosis present (FIG. 1). Moreover, the percent predicted forced vital capacity of those with diffuse pleural thickening and normal parenchyma was similar to those with asbestosis and normal pleura. After controlling for potential confounders (age, years in the trade, pack–years of smoking, and ILO profusion category), linear regression models demonstrated that both circumscribed plaques and diffuse pleural thickening were independently associated with decrements in forced vital capacity.[4] Furthermore, our data indicate that the effect of diffuse pleural thickening on forced vital capacity was approximately twice as great as that seen with circumscribed pleural plaques. However, little work has been done to characterize the mechanisms underlying the restrictive impairment.

Trapping of the lung due to limited motion of the chest wall has been thought to be the cause of restrictive lung function in those with diffuse pleural thickening.

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However, circumscribed pleural plaques have also been shown to be associated with both restrictive lung function and a lower diffusing capacity. Thus, we have hypothesized that restrictive lung function among individuals with pleural fibrosis results from parenchymal injury, which is not readily apparent on the routine chest radiograph. The purpose of this investigation was to examine the determinants of restrictive lung function among workers with asbestos-induced pleural fibrosis. We were particularly interested in determining whether pleural fibrosis was associated with parenchymal changes indicative of underlying interstitial lung disease, which were not appreciated on the routine chest radiograph. *A priori*, we hypothesized that a subclinical alveolitis and/or interstitial fibrosis not detected on the routine chest X-ray was largely responsible for the development of restrictive lung function among those with asbestos-induced pleural fibrosis. A detailed report of this investigation has been previously published.[7]

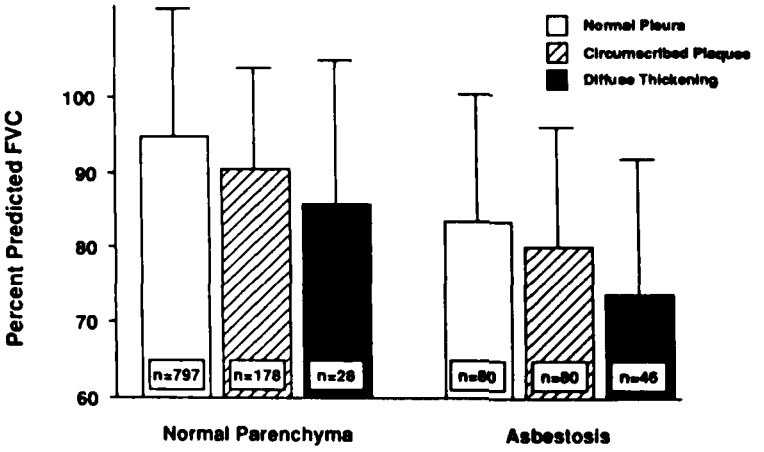

FIGURE 1. The percentage of predicted forced vital capacity (FVC) stratified by parenchymal fibrosis (normal = profusion ≤ 0/1; asbestosis = profusion ≥ 1/0) and pleural fibrosis (normal pleura, circumscribed plaques, and diffuse pleural thickening). A significant clinical and statistical decline was observed between categories of pleural fibrosis for those with normal parenchyma (ANOVA $F = 8.62$, $p = 0.0002$) and those with asbestosis (ANOVA $F = 4.88$, $p = 0.009$). (From Schwartz *et al.*[4] Reprinted by permission.)

METHODS

For the purpose of this study, we defined circumscribed plaques using the standard criteria,[12] but in our definition of diffuse pleural thickening we required obliteration of the costophrenic angle on the involved side. This modification of the International Labor Organization (ILO) classification system was added to decrease the high degree of intrareader variability that has previously been reported in distinguishing circumscribed pleural plaques from diffuse pleural thickening.[13]

Since we were interested in determining whether pleural fibrosis was independently associated with either a subclinical alveolitis or interstitial fibrosis that was

not apparent on the chest radiograph, we limited out potential study subjects to those who had never smoked or former smokers who had normal-appearing parenchyma on their chest radiograph. Study subjects were selected from the pool of eligible sheet-metal workers, in such a way that a comparable number of persons represented each category of pleural involvement. The investigators were blinded to the initial spirometric measures at the time of subject recruitment. In total, 24 sheet-metal workers were included in the study: 7 with normal pleura, 9 with circumscribed plaques, and 8 with diffuse pleural thickening.

Pulmonary Function Testing

The pulmonary function tests consisted of standard spirometry with the use of a Medical Graphics 1070 system (St. Paul, MN) and measurement of lung volumes via body plethysmography Medical Graphics 1085 system (St. Paul, MN). A single breath-diffusing capacity was measured by using the Medical Graphics 1070 system. Measurements of lung function were performed in accordance with standard protocols, using the American Thoracic Society guidelines[14] to determine acceptability. The predicted normal values used were those of Morris *et al.*[15] for spirometry, Goldman and Becklake[16] for lung volumes, and Van Ganse *et al.*[17] for diffusing capacity.

High-Resolution Chest CT scan

High-resolution CT scans (HRCT, scans of lung parenchyma) were obtained by using an Imatron C-100 ultrafast scanner. Images were obtained at full inspiration with the subjects supine. A high spatial frequency algorithm was used to reconstruct the image data and the smallest possible scanning circle was employed to maximize the resolution. The scanning time was 0.6 seconds. Lung windows and levels were optimized for viewing lung parenchyma.

The HRCT scans were independently evaluated by three readers who graded parenchymal abnormalities according to established criteria.[18–20] Although these readers could not be blinded to the presence of pleural fibrosis, they were blinded to the actual category of pleural involvement when they were interpreting the HRCT scan. The HRCT scan was read as being consistent with interstitial fibrosis if all three readers agreed that at least one of the following four abnormalities was present: subpleural curvilinear lines, parenchymal bands, thickened interstitial short lines, or honeycombing. These findings have been found to be associated with asbestos-induced interstitial fibrosis,[18–20] and, for the purposes of this study, any one of these findings was thought to be indicative of asbestos-induced interstitial abnormalities. Increased densities seen only in the dependent areas of the lung were disregarded.

Bronchoalveolar Lavage and Cell Analysis

Bronchoscopic examination and lavage were performed on all study subjects using our standard method.[21] Premedications included atropine sulfate (0.8 mg im), meperidine hydrochloride (75 mg im), and two inhalations of metraproterenol (total 1.3 mg) from a hand-held pressurized canister. The upper airway was anesthetized with Dyclone gargle and aerosolized 4% lidocaine. Lidocaine was also

applied topically to the pyriform sinuses and vocal chords. The bronchoscope (Olympus model BF 4B2; 4.9 mm diameter at the tip) was advanced into the airways, and the tip was maintained in the wedged position in a subsegmental bronchus throughout the lavage procedure. In all cases two lavages were performed, and in most instances, subsegments of the right middle lobe and lingula were lavaged. Each lavage consisted of 100 ml of saline solution (five, 20-ml aliquots).

Immediately after the lavage, the lavage fluid was strained through two layers of surgical 4 × 4-inch gauze into 50-ml conical tubes. The tubes were centrifuged for 5 min at 200 *g*, and the residual pellet of cells was resuspended and washed twice in Hanks' balanced salt solution (without Ca^{2+} or Mg^{2+}). After the second wash, a small aliquot of the sample was removed for a cell count with the use of a hemocytometer. The cells were then washed once more and resuspended in RPMI 1640 medium so that the final concentration was 1×10^7 cells/ml. The cells present in 10–12 μl of the 1×10^7 cells/ml suspension were spun onto a glass slide with the use of a filter card and a cytocentrifuge (Cytospin-2; Shanden Southern, Sewickley, PA). Three drops of fetal calf serum were added to the cell suspension to help the cells stick to the slide. After drying for 2 min, staining of the cells was accomplished by using a Diff Quick Stain Set (Harleco, Gibbstown, NJ). The cells were counted and classified only after the cytocentrifuge preparation was felt to be satisfactory by the following criteria: negligible staining artifact, uniform dispersal of cells without clumping, essentially no disruption of cells, and $< 3\%$ airway epithelial cells.

Statistical Analysis

Univariate comparisons were made to determine whether demographic or clinical variables were associated with the presence or type of pleural fibrosis. A χ^2 test with the Yates correction factor was employed to test differences in the prevalence of categorical variables between sheet-metal workers with normal pleura and those with either circumscribed plaques or diffuse pleural thickening, whereas a Student's *t* test was used to examine difference in continuous variables.[22]

We used a multivariate linear regression model[23] to determine whether the presence of an alveolitis (via lavage) or parenchymal fibrosis (via HRCT scan) altered the relationship between pleural fibrosis and lung function. A linear model was generated that incorporated all potential confounders and determined the relative strength of the relationship between reduced lung volumes and pleural fibrosis, alveolitis, and HRCT-designated parenchymal fibrosis. After a linear model was established, all possible interactions were tested in a stepwise manner to determine whether significant improvement in the model could be achieved by the inclusion of any one of these interactive terms.

RESULTS

In our study population, individuals with diffuse pleural thickening tended to be older and more often retired from the sheet-metal trade than were subjects in either of the other study groups. All study subjects were white, had a similar duration of work experience in the sheet-metal trade, and between each category of pleural findings, the smoking history was quite similar.[7]

TABLE 1. Comparison[a] of Spirometry, Lung Volumes, and Diffusing Capacity by Presence and Type of Pleural Fibrosis

	Normal Pleura (n = 7)	Circumscribed Plaques (n = 9)	Diffuse Thickening (n = 8)
FEV_1	110.4 ± 9.1	100.1 ± 17.2	71.5 ± 11.6[b]
FVC	104.9 ± 6.7	96.0 ± 11.8	76.8 ± 13.5[b]
FEV_1/FVC ratio	76.1 ± 6.4	75.1 ± 7.9	65.5 ± 11.4
TLC	121.9 ± 12.5	116.7 ± 13.9	95.1 ± 17.0[b]
RV	120.7 ± 21.9	121.6 ± 42.5	100.4 ± 26.7
DLCO	111.6 ± 23.2	111.8 ± 16.3	91.9 ± 19.8

[a] p values were computed by comparing persons with circumscribed plaques with those with normal pleura and by comparing sheet-metal workers with diffuse pleural thickening with those with normal pleura. All values are expressed as the mean ± standard deviaiton. All measures of lung function are expressed as a percent of predicted values, except for the FEV_1/FVC ratio.

[b] $p < 0.005$.

Sheet-metal workers with circumscribed pleural plaques tended to have a lower forced expiratory volume and forced vital capacity than did study subjects with normal pleura (TABLE 1). However, these differences were not statistically significant, and the lung volumes and diffusing capacity were virtually indistinguishable between sheet-metal workers with circumscribed plaques and those with normal pleura (TABLE 1). Both flows (as measured by spirometry) and lung volumes (as measured by body plethysmography) were reduced in sheet-metal workers with diffuse pleural thickening when compared with those with normal pleura (TABLE 1). Sheet-metal workers with diffuse pleural thickening had a significantly lower forced expiratory volume, forced vital capacity, and total lung capacity. Large mean differences were also observed in the residual volume and diffusing capacity between these two groups, although these differences were not statistically significant.

When we controlled for potential confounders, including age, years in the trade, and pack–years of smoking, we found that sheet-metal workers with diffuse pleural thickening had significant and clinically meaningful reductions in the forced vital capacity, total lung capacity, and diffusing capacity of carbon monoxide when compared to those with normal pleura (TABLE 2). The regression coefficients indicate that after controlling for age, years in the trade, and pack–years of smoking, sheet-metal workers with diffuse pleural thickening had on average a

TABLE 2. Multivariate Linear Regression Model[a] for Prediction of FVC, TLC, and DLCO

Dependent Variables	Regression Coefficient (Standard Error)	
	Plaques vs. Normal	Diffuse vs. Normal
FVC	−11.0 (5.3) (p = 0.06)	−27.1 (5.2) ($p < 0.001$)
TLC	− 1.5 (6.6)	−24.9 (7.6) ($p < 0.01$)
DLCO	− 7.3 (8.6)	−21.8 (10.0) ($p < 0.05$)

[a] Regression models controlled for age, years in the sheet-metal trade, and pack–years of smoking while comparing the effect of the type of pleural fibrosis on percent predicted FVC, TLC, and DLCO.

27% reduction in the forced vital capacity, a 25% reduction in the total lung capacity, and a 22% reduction in the diffusing capacity of carbon monoxide. Marginally significant and potentially clinically meaningful reductions in forced vital capacity were also observed among sheet-metal workers with circumscribed pleural plaques. These analyses indicate that diffuse pleural thickening and also possibly circumscribed plaques appear to be independently associated with reduced lung volumes. In addition, diffuse pleural thickening was associated with a reduction in the diffusing capacity of carbon monoxide.

Next, we investigated whether asbestos-induced pleural fibrosis was associated with parenchymal injury that was not readily apparent on the routine chest radiograph. The purpose for this analysis was to determine whether the presence of an alveolitis or interstitial changes on HRCT scan altered the previously described relationship between pleural fibrosis and restrictive lung function. Sheet-metal workers with diffuse pleural thickening, when compared to those with normal pleura, were more likely to exhibit an increased percentage of lymphocytes in their lavage fluid and were also more likely to show interstitial changes on high-resolution CT scan (TABLE 3). Although sheet-metal workers with circumscribed plaques had a higher percentage of lymphocytes in the lavage fluid and also an increased prevalence of interstitial changes detected on high-resolution CT scan, these changes were not significantly different from those in persons with normal pleura. Despite the lack of significance, it remains interesting, in terms of both lymphocytic alveolitis and the interstitial changes detected by high-resolution CT, that persons with circumscribed pleural plaques fell between those with normal pleura and those with diffuse pleural thickening. In fact, an analysis of variance demonstrates that there was a linear relationship between the percentage of lymphocytes in the lavage fluid and the designated pleural categories. Also, a significant trend to increased risk for interstitial abnormalities (via HRCT) was observed across the three categories of pleural involvement.

To further understand the determinants of restrictive lung function and a reduced diffusing capacity among these study subjects, we examined whether pleural fibrosis, a lymphocytic alveolitis, or interstitial changes via high-resolution CT scan was the principal determinant of reduced lung volumes and a reduced diffusing capacity. In these multivariate analyses (TABLE 4), we control for age, years in the sheet-metal trade, and pack–years of smoking. In Model I, we examine the effect of asbestos-induced pleural fibrosis (circumscribed plaques and diffuse pleural thickening), bronchoalveolar lavage lymphocytes, and intersti-

TABLE 3. Comparison[a] of Bronchoalveolar Lavage and High-Resolution CT Scan by Presence and Type of Pleural Fibrosis

	Normal Pleura ($n = 7$)	Circumscribed Plaques ($n = 9$)	Diffuse Thickening ($n = 8$)
	Bronchoalveolar Lavage		
Cell count	9.1 ± 7.6	8.6 ± 5.7	9.2 ± 3.9
% Macrophages	95.7 ± 3.8	91.4 ± 5.9	82.7 ± 11.3 ($p < 0.01$)
% Lymphocytes	3.9 ± 3.8	7.8 ± 6.2	15.5 ± 12.1 ($p < 0.05$)
	High-Resolution CT Scan		
Parenchymal abnormalities	14.3%	55.6%	87.5% ($p < 0.01$)

[a] Values were computed by comparing individuals with circumscribed plaques to those with normal pleura and by comparing sheet-metal workers with diffuse pleural thickening to those with normal pleura. Values are either expressed as the mean ± standard deviation or the percentage of persons within each designated pleural category.

TABLE 4. Multivariate Linear Regression Model[a] to Assess the Relative Contribution of Pleural Fibrosis, Lymphocytosis (on Bronchoalveolar Lavage), and Parenchymal Abnormalities (on HRCT) on Measures of Lung Function

	Regression Coefficient (p Value)		
	FVC	TLC	DLCO
Model I			
Pleural fibrosis	−14.04 (0.0001)	−12.77 (0.003)	−11.20 (0.03)
Lymphocytes (% seen on bronchoalveolar lavage)	−0.03 (0.90)	−0.20 (0.34)	−0.11 (0.63)
Parenchymal abnormalities (seen on HRCT)	−0.11 (0.58)	−0.14 (0.53)	−0.24 (0.33)
Model II			
Diffuse thickening	−27.13 (0.0003)	−24.92 (0.008)	−21.81 (0.05)
Lymphocytes (% seen on bronchoalveolar lavage)	−0.25 (0.24)	−0.18 (0.54)	−0.52 (0.68)
Parenchymal abnormalities (seen on HRCT)	−0.08 (0.72)	0.05 (0.88)	−1.6 (0.15)

[a] Regression models controlled for age, years in the sheet-metal trade, and pack–years of smoking while investigating the relation between pleural fibrosis, lymphocytes (% of BAL), and parenchymal abnormalities (seen on HRCT scan) on measures of lung function (expressed as percent predicted). Model I compared those with pleural fibrosis (either circumscribed plaques or diffuse pleural thickening) to those with normal pleura. Model II compared those with diffuse pleural thickening to those with normal pleura.

tial changes detected by HRCT scan on three measures of lung function—forced vital capacity (FVC), total lung capacity (TLC), and the differing capacity of carbon monoxide (DLCO). The regression coefficients indicate that circumscribed pleural plaques and diffuse pleural thickening together are responsible for a 14% decline in the forced vital capacity, a 13% decline in the total lung capacity, and an 11% decline in the diffusing capacity of carbon monoxide. Model I also indicates that the percentage of lymphocytes obtained on lavage and interstitial changes on high-resolution chest CT scan have no additional effect on this relationship. Model II demonstrates that these findings are more persuasive for asbestos-induced diffuse pleural thickening. These analyses indicate that asbestos-induced pleural fibrosis and diffuse pleural thickening, in particular, are the principal determinants of declines in lung volumes and the diffusing capacity of carbon monoxide. Moreover, once either pleural fibrosis or diffuse pleural thickening are taken into account, the presence of a lymphocytic alveolitis or interstitial changes identified by high-resolution CT scan contribute very little to these decrements in lung function.

DISCUSSION

Our data indicate that asbestos-induced pleural fibrosis and, in particular, diffuse pleural thickening are associated with a loss of lung volume and a decrease in the diffusing capacity of carbon monoxide. In addition, although pleural fibrosis is associated with a lymphocytic alveolitis and interstitial fibrosis, these sensitive measures of parenchymal injury have very little effect on the relationship between pleural fibrosis and restrictive lung function. These findings indicate that pleural

fibrosis is associated with reduced lung volume and a diminished diffusing capacity that appears to be independent of its association with a lymphocytic alveolitis and interstitial fibrosis. Our findings lead us to conclude that asbestos-induced pleural disease contributes to the development of restrictive lung function and identifies a group of exposed individuals who are at excess risk of asbestosis.

Although these studies provide a more detailed representation of the relationship between pleural fibrosis, parenchymal fibrosis, and lung function, two provocative questions deserve further consideration. First, if pleural fibrosis is the major determinant of functional impairment, why was such a strong relationship observed between pleural fibrosis and a lower diffusing capacity of carbon monoxide, a higher percentage of lymphocytes obtained by lavage, and a higher prevalence of interstitial abnormalities identified on high-resolution CT scan? Second, might the higher percentage of lymphocytes in the lavage fluid or the finding of parenchymal changes on HRCT scan be an early or preclinical sign of asbestos-induced lung disease? Answers to these questions in controlled prospective studies may allow clinicians to stage, determine prognosis, and possibly alter the course of asbestos-induced interstitial lung disease.

SUMMARY

Asbestos-induced pleural fibrosis is the most common radiographic abnormality among asbestos-exposed persons. Circumscribed pleural plaques and diffuse pleural thickening account for more than 90% of the asbestos-induced chest wall abnormalities, and their prevalence is expected to increase for the next 15 to 20 years. Several investigators have recently found that pleural plaques and diffuse pleural thickening independently contribute to the development of restrictive lung function. The work presented in this paper indicates that asbestos-induced pleural fibrosis is also associated with evidence of interstitial lung abnormalities, even among those with normal parenchyma on chest X-ray film. These parenchymal abnormalities include an increased percentage of lymphocytes on bronchoalveolar lavage and an increase in the interstitial changes observed on high-resolution chest computerized tomography (HRCT) scan. However, neither a lymphocytic alveolitis nor an interstitial parenchymal fibrosis influenced the relationship between pleural fibrosis and restrictive lung function. We conclude that asbestos-induced pleural disease contributes to the development of restrictive lung function and identify a group of exposed individuals who are at excess risk of asbestosis.

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