# Determinants of restrictive lung function in asbestos-induced pleural fibrosis

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*Pulmonary Disease Division, Department of Internal Medicine, Department of Radiology, and Division of Agricultural Medicine and Occupational Health, Department of Preventive Medicine, University of Iowa, Iowa City, Iowa 52242*

SCHWARTZ, DAVID A., JEFFREY R. GALVIN, CHARLES S. DAYTON, WILLIAM STANFORD, JAMES A. MERCHANT, AND GARY W. HUNNINGHAKE. *Determinants of restrictive lung function in asbestos-induced pleural fibrosis.* J. Appl. Physiol. 68(5): 1932–1937, 1990.—We evaluated whether restrictive lung function among asbestos-exposed individuals with pleural fibrosis was caused by radiographically inapparent parenchymal inflammation and/or parenchymal fibrosis. All 24 study participants were sheet metal workers who were nonsmokers with normal parenchyma on posteroanterior chest radiograph. These subjects had either normal pleura ($n$ = 7), circumscribed plaques ($n$ = 9), or diffuse pleural thickening ($n$ = 8). After controlling for age, years in the trade, and pack-years of smoking, we found that sheet metal workers with diffuse pleural thickening had a lower forced vital capacity ($P < 0.001$), total lung capacity ($P < 0.01$), and CO-diffusing capacity of the lung ($P < 0.05$) than those with normal pleura. Similarly, sheet metal workers with circumscribed plaques were found to have a reduced forced vital capacity; however, because of the small number of study subjects, this difference (regression coefficient = −11.0) was only marginally significant ($P = 0.06$). Although circumscribed plaque and diffuse pleural thickening were both associated with a lymphocytic alveolitis and a higher prevalence of parenchymal fibrosis on high-resolution computerized tomography (HRCT) scan, neither a lymphocytic alveolitis nor the finding of parenchymal fibrosis on HRCT scan influenced the relationship between pleural fibrosis and restrictive lung function. We conclude that pleural fibrosis is associated with restrictive lung function and abnormally low diffusion that appears to be independent of our measures of parenchymal injury (chest X-ray, bronchoalveolar lavage, and HRCT scan). Despite these findings, the lower CO-diffusing capacity of the lung among those with diffuse pleural thickening and the associations that were observed between pleural fibrosis and both a lymphocytic alveolitis and parenchymal fibrosis on HRCT scan suggest that parenchymal inflammation and/or early parenchymal fibrosis may, at least in part, contribute to the development of restrictive lung function among those with asbestos-induced pleural fibrosis.

alveolitis; interstitial fibrosis; asbestosis

THE ASSOCIATION between asbestos exposure and interstitial fibrosis has been firmly established (2). Individuals with asbestos-induced interstitial fibrosis (i.e., asbestosis) frequently have restrictive lung function with a reduction in the diffusing capacity of CO (5, 9, 25, 26, 34, 35). Moreover, bronchoalveolar lavage studies in persons with asbestosis have identified an active alveolitis that is characterized by an excess number and percentage of total and activated lymphocytes and neutrophils (6, 7, 12, 13, 16, 29, 30).

Although asbestos-induced pleural fibrosis is the most common chest X-ray abnormality among asbestos-exposed persons, and it has recently been shown to contribute to the development of restrictive lung function (4, 10, 17–20, 22, 23, 27, 28, 31, 36), little work has been done to characterize the mechanisms underlying the restrictive impairment. Trapping of the lung as the result of limited motion of the chest wall has been thought to be the cause of restrictive lung function in those with diffuse pleural thickening (22, 23, 28, 36). However, it is conceptually difficult to accept the hypothesis that an isolated pleural plaque can alone restrict lung function by limiting chest wall motion. Because pleural plaques in the absence of radiographic fibrosis have been found to be associated with lower diffusing capacities (27), it is possible that the restrictive lung volumes among individuals with pleural fibrosis represent a subclinical alveolitis or an early manifestation of interstitial fibrosis that is not readily apparent on the posteroanterior (PA) chest radiograph. This hypothesis is supported by the recent observation that individuals with asbestos-induced pleural fibrosis and no evidence of interstitial disease appear to have an elevated number and percentage of lymphocytes in their lavage fluid (33).

The purpose of this investigation was to examine the determinants of restrictive lung function among individuals with asbestos-induced pleural fibrosis. We were particularly interested in determining whether pleural fibrosis was associated with parenchymal changes indicative of interstitial disease that were not appreciated on the PA chest radiograph. A priori we hypothesize that subclinical alveolitis and/or interstitial fibrosis not detected by routine chest radiograph is largely responsible for the development of restrictive lung function among those with asbestos-induced pleural fibrosis.

## METHODS

*Study population.* As part of a nationwide union-sponsored screening program, 1,211 sheet metal workers had a chest radiograph and spirometric evaluation (Fig. 1). Chest radiographs were performed in the PA projection

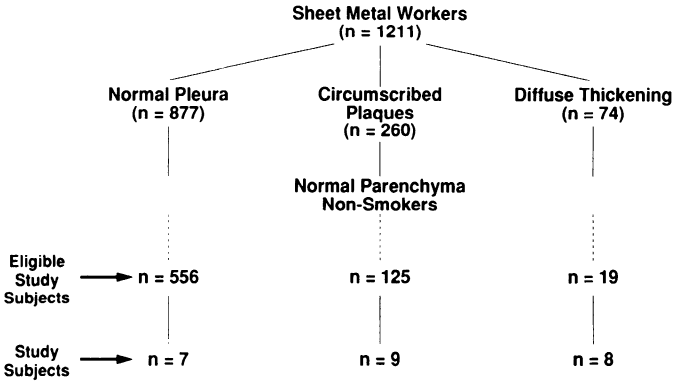


FIG. 1. Cohort of sheet metal workers and eligible study participants from which study subjects were selected.

and interpreted by one experienced reader (*JAM*) who was blinded to the clinical history and used the International Labor Organization (ILO) 1980 Classification of Radiographs of Pneumoconioses (15). Approximately 17% were found to have radiographic evidence of interstitial fibrosis and 28% had radiographic evidence of pleural fibrosis. Of those with pleural fibrosis, 78% had circumscribed plaques and 22% had diffuse pleural thickening involving the costophrenic angle. Because we wanted to determine whether pleural fibrosis was independently associated with either a subclinical alveolitis or parenchymal fibrosis that was not apparent on the chest radiograph, we limited our potential study subjects to never or former (at least 5 yr before the current study) smokers who had no evidence of interstitial fibrosis on their chest radiograph. Because of financial constraints, the study was limited to 24 subjects. These 24 study subjects were selected from the pool of eligible study subjects ($n$ = 700; see Fig. 1) so that an equivalent number of individuals represented each category of pleural involvement (normal pleura, circumscribed plaques, and diffuse pleural thickening). The investigators were blinded to the clinical measures (symptomatology and initial spirometry) at the time of subject recruitment. Study subjects were invited to participate on the basis of their proximity to Iowa City. In total, 36 eligible subjects were contacted to identify 24 who were willing to participate. The nonparticipants were equally distributed in the three categories of pleural involvement.

*Pulmonary function testing.* The pulmonary function tests consisted of standard spirometry with the use of a Medical Graphics 1070 system (St. Paul, MN) and 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. The measurements of lung function were performed with standard protocols, and the American Thoracic Society guidelines (3) were used to determine acceptability. The predicted normal values used were those of Morris et al. (24) for spirometry, Goldman and Becklake (14) for lung volumes, and Van Ganse et al. (32) for the 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 s. Lung windows and levels were optimized for viewing lung parenchyma.

The HRCT scans were independently evaluated by three readers (*DAS, JRG,* and *WS*) who graded parenchymal abnormalities according to established criteria (1, 11, 37). 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 were 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 (1, 11, 37), and for the purposes of this study it was felt that any one of these findings was indicative of asbestos-induced interstitial fibrosis. 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 by using our standard method (38). Premedications included atropine sulfate (0.8 g im), meperidine hydrochloride (75 mg im), and two inhalations of metaproterenol (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 cords. The bronchoscope (Olympus model BF 4B2; 4.9 mm diam 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 (5 20-ml aliquots).

Immediately after the lavage, the lavage fluid was strained through two layers of surgical 4 × 4-in. 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 $1 \times 10^7$ cells/ml. The cells present in 10–12 $\mu$l of the $1 \times 10^7$-ml cell 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 $\chi^2$ test with 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 (8).

We used a multivariate linear regression model (21) 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 relationships 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 improvements in the model could be achieved by the inclusion of any one of these interactive terms.

## RESULTS

Individuals with diffuse pleural thickening tended to be older and more often retired from the sheet metal trade than persons with normal pleura (Table 1). All study subjects were white, had a similar duration of work experience in the sheet metal trade, and had an equivalent smoking history.

Measures of spirometry, lung volumes, and CO-diffusing capacity of the lung ($D_{LCO}$) were reduced in sheet metal workers with diffuse pleural thickening compared with those with normal pleura (Table 2). When individuals with diffuse pleural thickening were compared with those with normal pleura, sheet metal workers with diffuse pleural thickening had a significantly lower forced expired volume in 1 s ($FEV_1$), forced vital capacity, (FVC), and total lung capacity (TLC). Large clinically meaningful mean differences were observed in the residual volume (RV) and $D_{LCO}$ between these two groups that were not statistically significant. Although the $FEV_1$/FVC was lower for individuals with diffuse pleural thickening, these differences were not statistically significant after controlling for age. Sheet metal workers with circumscribed pleural plaques tended to have a lower $FEV_1$ and FVC than those study subjects with normal pleura. However, because of the small numbers of study subjects and the relatively broad standard deviations, these differences were not statistically significant. The lung volumes and $D_{LCO}$ were virtually indistinguishable between sheet metal workers with circumscribed plaques and those with normal pleura. This univariate analysis suggests that the pattern of abnormalities among those with diffuse pleural thickening represents a restrictive defect, whereas persons with circumscribed pleural plaques tend to have modest reductions in spirometric measures of lung function and lung volumes that are similar to those with normal pleura.

When we controlled for potential confounders (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 FVC, TLC, and $D_{LCO}$ compared with those with normal pleura (Table 3). In fact, the regression analyses indicate that on average, sheet metal workers with diffuse pleural thickening have a 27% reduction in FVC, a 25% reduction in TLC, and a 22% reduction in $D_{LCO}$. Marginally significant ($P = 0.06$), although potentially clinically meaningful, reductions in FVC (11% decrement) were also observed among sheet metal workers with circumscribed pleural plaques. These data indicate that diffuse pleural thickening and also possibly circumscribed plaques are associated with reduced lung volumes. In addition, diffuse pleural thickening was found to be associated with a reduction in $D_{LCO}$.

Next we investigated whether pleural fibrosis was as-

TABLE 1. *Demographic features of study subjects by presence and type of pleural fibrosis*

| | Normal Pleura | Circumscribed Plaques | Diffuse Thickening |
|---|---|---|---|
| *n* | 7 | 9 | 8 |
| Age, yr | 55.8±8.4 | 54.9±6.8 | 68.9±7.8 |
| Years in the trade | 33.3±6.6 | 30.3±7.2 | 31.0±12.3 |
| %Retired | 14.3 | 0 | 62.5 |
| Smoking history | | | |
| % Never | 42.9 | 33.3 | 37.5 |
| % Former | 57.1 | 66.7 | 62.5 |
| Pack-years | 23.7±23.3 | 14.2±22.7 | 19.6±13.7 |

Values are means ± SD.

TABLE 2. *Comparison of spirometry, lung volumes, and diffusing capacity by presence and type of pleural fibrosis*

| | Normal Pleura | Circumscribed Plaques | Diffuse Thickening |
|---|---|---|---|
| *n* | 7 | 9 | 8 |
| $FEV_1$ | 110.4±9.1 | 100.1±17.2 | 71.5±11.6* |
| FVC | 104.9±6.7 | 96.0±11.8 | 76.8±13.5* |
| $FEV_1$/FVC | 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* |
| RV | 120.7±21.9 | 121.6±42.5 | 100.4±26.7 |
| $D_{LCO}$ | 111.6±23.2 | 111.8±16.3 | 91.9±19.8 |

Values are regression coefficients ± SD expressed as percent predicted, except $FEV_1$/FVC. *P* values were computed by comparing individuals with circumscribed plaques and those with normal pleura and by comparing sheet metal workers with diffuse pleural thickening and those with normal pleura. * $P < 0.005$.

TABLE 3. *Multivariate linear regression model for prediction of FVC, TLC, and $D_{LCO}$*

| Dependent Variables | Regression Coefficient | |
|---|---|---|
| | Plaques vs. normal | Diffuse vs. normal |
| FVC | −11.0±5.3* | −27.1±5.2† |
| TLC | −1.5±6.6 | −24.9±7.6‡ |
| $D_{LCO}$ | −7.3±8.6 | −21.8±10.0§ |

Values are regression coefficients ± SE. Regression models were controlled for age, years in the sheet metal trade, and pack-years of smoking while comparing effect of type of pleural fibrosis on percent predicted FVC, TLC, and $D_{LCO}$. * $P = 0.06$; † $P < 0.001$; ‡ $P < 0.01$; § $P < 0.05$.

TABLE 4. *Comparison of bronchoalveolar lavage and HRCT scan by presence and type of pleural fibrosis*

| | Normal Pleura | Circumscribed Plaques | Diffuse Thickening |
|---|---|---|---|
| *n* | 7 | 9 | 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* |
| % Lymphocytes | 3.9±3.8 | 7.8±6.2 | 15.5±12.1† |
| HRCT scan | | | |
| Parenchymal fibrosis | 14.3% | 55.6% | 87.5%* |

Values are means ± SD. *P* values were computed by comparing individuals with circumscribed plaques and those with normal pleura and by comparing sheet metal workers with diffuse pleural thickening and those with normal pleura. * $P < 0.01$; † $P < 0.05$.

TABLE 5. *Multivariate linear regression model comparing BAL %lymphocytes and interstitial fibrosis with measures of restricted lung function*

| Dependent Variables | Regression Coefficient | |
|---|---|---|
| | %Lymphocytes BAL | Fibrosis HRCT |
| FVC | −0.74±0.35* | −8.84±6.50 |
| TLC | −0.92±0.37* | −12.59±8.07 |
| $D_{LCO}$ | −0.74±0.46 | −13.82±9.41 |

Values are regression coefficients ± SE. Regression models were controlled for age, years in the sheet metal trade, and pack-years of smoking, while both effects of %lymphocytes in bronchoalveolar lavage (BAL) and parenchymal fibrosis identified by HRCT scan on measures of lung function were compared. * $P < 0.05$.

sociated with either an alveolitis or parenchymal fibrosis that was not readily apparent on the PA chest radiograph. The purpose for this analysis was to determine whether the presence of an alveolitis (via bronchoalveolar lavage) or parenchymal fibrosis (via HRCT scan) altered the previously described relationship between pleural fibrosis and restrictive lung function.

Sheet metal workers with diffuse pleural thickening were more likely to exhibit an increased percentage of lymphocytes in their lavage fluid and were also more likely to have parenchymal fibrosis on their HRCT scan (Table 4). Although sheet metal workers with circumscribed plaques compared with those with normal pleura had a higher percentage of lymphocytes in the lavage fluid and also an increased prevalence of parenchymal fibrosis detected on HRCT, these differences were not statistically significant. Despite the lack of significance, it remains interesting, in terms of a lymphocytic alveolitis and also HRCT-detected parenchymal fibrosis, that individuals 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 is a linear relationship between the percentage of lymphocytes in the lavage fluid and the designated pleural categories ($F = 7.50$, $P = 0.01$). Also, a significant trend to increased risk of interstitial fibrosis (designated by HRCT scan) is observed across the three categories of pleural involvement ($\chi^2$ trend = 7.68, $P = 0.02$).

When we examined the relationship between reduced lung function and both a lymphocytic alveolitis and parenchymal fibrosis (via HRCT scan), we found that after controlling for the appropriate factors (age, years in the trade, and pack-years of smoking), a lymphocytic alveolitis was associated with a lower FVC and TLC, but the presence of parenchymal fibrosis on HRCT was not related to reduction in any of these measures of lung function (Table 5).

To further understand the determinants of restrictive lung function and reduced diffusing capacity in these study subjects, we performed an additional multivariate regression analysis. While controlling for age, years in the sheet metal trade, and pack-years of smoking, we examined whether pleural fibrosis, a lymphocytic alveolitis, or parenchymal fibrosis via HRCT scan was the major determinant of reduced lung volumes and a reduced diffusing capacity. Table 6 shows that either both forms of pleural fibrosis (circumscribed plaques or diffuse pleural thickening) or diffuse pleural thickening alone was the principal determinant of declines in lung volumes and $D_{LCO}$. Moreover, once either of these factors was taken into account, the presence of an alveolitis or interstitial fibrosis (designated by HRCT scan) contributed very little to these measures of lung function.

TABLE 6. *Multivariate linear regression model assessing relative contribution of pleural fibrosis, BAL %lymphocytes, and HRCT parenchymal fibrosis on measures of lung function*

| | Regression Coefficient | | |
|---|---|---|---|
| | FVC | TLC | $D_{LCO}$ |
| | *Model I* | | |
| Pleural fibrosis | −14.04 (0.0001) | −12.77 (0.003) | −11.20 (0.03) |
| BAL %lymphocytes | −0.03 (0.90) | −0.20 (0.34) | −0.11 (0.63) |
| HRCT parenchymal fibrosis | −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) |
| BAL %lymphocytes | −0.25 (0.24) | −0.18 (0.54) | −0.52 (0.68) |
| HRCT parenchymal fibrosis | −0.08 (0.72) | 0.05 (0.88) | −1.6 (0.15) |

Values expressed as regression coefficients with *P* values in parentheses. Regression models were controlled for age, years in the sheet metal trade, and pack-years of smoking, while relationship among pleural fibrosis, bronchoalveolar lavage (BAL) %lymphocytes, and HRCT scan parenchymal fibrosis on measures of lung function was investigated. *Model I* compared those with pleural fibrosis (either circumscribed plaques or diffuse pleural thickening) and those with normal pleura. *Model II* compared those with diffuse pleural thickening and those with normal pleura.

## DISCUSSION

Our data indicate that asbestos-induced pleural fibrosis and, in particular, diffuse pleural thickening is associated with a loss of lung volume and a decrease in $D_{LCO}$. In addition, although pleural fibrosis was associated with a lymphocytic alveolitis and abnormal grades of parenchymal fibrosis (as ascertained by HRCT scans), these sensitive (but not specific) measures of parenchymal injury had very little effect on the relationship between pleural fibrosis and restrictive lung function. These findings indicate that pleural fibrosis is associated with reduced lung volumes and a diminished diffusing capacity that appears to be independent of its association with a lymphocytic alveolitis and parenchymal fibrosis.

The mechanisms accounting for the impaired lung function among those with asbestos-induced pleural fibrosis remain obscure. Although we found that a lymphocytic alveolitis and parenchymal fibrosis via HRCT scan do not appear to influence this relationship, more specific measures of parenchymal injury may demonstrate that parenchymal damage accounts for a portion of the reduced lung volumes in those with pleural fibrosis. Given the strong association that we observed between pleural fibrosis and parenchymal abnormalities (lymphocytic alveolitis and interstitial changes on HRCT scan), it is very likely that parenchymal injury, at least in part, contributes to the development of restrictive lung function. Moreover, because our study subjects received their HRCT scan in the supine position, we may have underestimated the degree and extent of parenchymal fibrosis (1) in these asbestos-exposed individuals. Perhaps inflammatory mediators or histological specimens would provide a more specific measure of parenchymal damage and be better predictors of functional impairment. Alternatively, diffuse pleural thickening and also extensive pleural plaques may impair chest wall motion and limit lung expansion. However, if this were the sole mechanism accounting for lung function impairment associated with pleural fibrosis, we should not have observed lower diffusing capacities in persons with diffuse pleural thickening compared with those with normal pleura. A lower diffusing capacity has also been reported among individuals with asbestos-induced circumscribed plaques (27). A diminished single-breath diffusing capacity indicates that either capillary blood volume or the surface area for diffusion has been compromised. In aggregate, these findings suggest that parenchymal injury is likely to be a contributing factor in the development of restrictive lung function in those with asbestos-induced pleural fibrosis.

Our studies indicate that bronchoalveolar lavage and HRCT scan may allow us to detect parenchymal injury before abnormalities on PA chest radiographs. If, in prospective studies, asbestos-exposed individuals with these abnormalities are found to be more likely to develop clinical interstitial fibrosis, then these tests may prove to be helpful in identifying persons at a "preclinical" stage of their parenchymal injury. Further work is needed to determine whether these indicators of early inflammation and fibrosis are predictive of those who are at risk of developing clinically significant asbestosis.

Although these studies provide a more detailed representation of the relationship among pleural fibrosis, parenchymal inflammation, parenchymal fibrosis, and lung function, there are still several questions to address. First, if pleural fibrosis is the major determinant of functional impairment, why was such a strong relationship observed between pleural fibrosis and a reduced $D_{LCO}$, a higher percentage of lavage lymphocytes, and a higher prevalence of parenchymal fibrosis identified on HRCT scan? Second, might the percentage of lymphocytes in the lavage fluid or the finding of parenchymal fibrosis on HRCT scan be an early or preclinical form of asbestos-induced lung injury? Third, given the marginal relationship between HRCT-designated parenchymal fibrosis and lung function impairment, what role should this radiological procedure play in the evaluation of asbestos-exposed persons? 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.

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