Longitudinal Changes in Lung Function among Asbestos-exposed Workers

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To prospectively identify the determinants of persistent or accelerated loss of lung function among workers occupationally exposed to asbestos and assess the relative contribution of cigarette smoking, asbestos-induced pleural fibrosis, and specific findings from bronchoalveolar lavage and high resolution CT scans, we examined the determinants of lung function changes in 117 subjects occupationally exposed to asbestos for at least 1 yr in a high exposure setting. A minimum of 20 yr was required between the first exposure to asbestos and entry into the study. Baseline studies included an independent assessment of dyspnea, lung volumes, diffusing capacity of carbon monoxide (D_{LCO}), a chest radiograph, a high resolution CT (HRCT) scan, and bronchoalveolar lavage (BAL). Subjects were observed for an average of 2 yr (range, 0.5 to 4.0 yr), and lung function was measured on at least two separate occasions (mean, 4.1 separate tests). During the period of observation, there was an average 1.5% decrease in the TLC and a 2.5% decrease in the D_{LCO}. In this longitudinal data set, after controlling for age, height, pack-years of cigarette smoking, and follow-up time, persistently lower measures of TLC were independently related to moderate to severe dyspnea ($p = 0.005$), diffuse pleural thickening ($p = 0.007$), and higher concentrations of fibronectin in BAL fluid ($p = 0.01$). Interstitial lung disease either on the chest radiograph or HRCT scan was not independently associated with persistently lower measures of TLC during the period of observation. However, none of the clinical variables we examined were associated with an accelerated decline in TLC. After controlling for age, height, and follow-up time, persistently lower measures of D_{LCO} were independently related to moderate to severe dyspnea ($p = 0.006$), increased pack-years of cigarette smoking ($p = 0.00001$), honeycombing on HRCT scan ($p = 0.0009$), and higher concentrations of lymphocytes ($p = 0.0008$), neutrophils ($p = 0.0005$), eosinophils ($p = 0.03$), and fibronectin ($p = 0.02$) in the BAL fluid. Importantly, higher concentrations of neutrophils and eosinophils in the BAL fluid were significantly associated with an accelerated decline in gas exchange during the period of observation. These results indicate that among asbestos-exposed subjects, prognostically important risk factors include symptoms of dyspnea, cigarette smoking, diffuse pleural thickening, honeycombing on HRCT scan, and higher concentrations of inflammatory cells and fibronectin in the BAL fluid. **Schwartz DA, Davis CS, Merchant JA, Bunn WB, Galvin JR, Van Fossen DS, Dayton CS, Hunninghake GW. Longitudinal changes in lung function among asbestos-exposed workers. Am J Respir Crit Care Med 1994;150:1243–9.**

Asbestosis and asbestos-induced pleural fibrosis are traditionally thought to be slowly progressive disorders. Radiographic evidence of disease progression appears to be associated with advanced age (1–3), increased evidence of asbestos-induced lung disease on the chest radiograph (1, 4–7), more extensive occupational exposure to asbestos (2, 5, 8–10), and cigarette smoking (1, 7, 9). Progressive restrictive physiology has been reported to be associated with cumulative asbestos exposure (8, 11–13), cigarette smoking (11), and either the presence of asbestosis (8) or of diffuse pleural thickening (4, 8) on the chest radiograph. Excess declines in diffusing capacity have been associated with higher concentrations of neutrophils in bronchoalveolar lavage (BAL) fluid (14). Risk factors such as advanced age, more extensive occupational exposure to asbestos, cigarette smoking, and specific radiographic abnormalities, which are found to be associated with disease progression, are particularly important when one considers that, among those with asbestosis, as much as 20% of the attributable mortality appears to be caused by progressive, interstitial fibrosis (15). Beyond the inherent clinical utility of these prognostic factors, specific risk factors may be particularly useful in identifying populations that may warrant aggressive therapeutic trials to diminish the risk of disease progression.

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TABLE 1

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF STUDY SUBJECTS*

Age, yr	60.6 ± 8.7
Male	100%
White	99%
Asbestos exposure	
Duration, yr	31.7 ± 11.3
Latency, yr	38.3 ± 10.0
Years since last exposure	10.5 ± 10.2
Primary occupation	
Sheet metal worker	39%
Plumber or pipefitter	22%
Insulator	8%
Machinist	8%
Welder	4%
Electrician	4%
Miscellaneous	15%
Smoking history	
Never	21%
Former	62%
Current	16%
Pack-years of smoking	29.3 ± 24.5
Length of follow-up	
6 months	17%
1 yr	19%
2 yr	21%
3 yr	38%
4 yr	5%
Number of pulmonary function tests	4.1 ± 1.8

* Values are expressed as the means ± SD for continuous variables and as percentages of all study subjects for categorical variables.

Cigarette smoking appears to enhance the development of interstitial fibrosis in workers exposed to asbestos (16–21). In addition, other forms of interstitial fibrosis such as idiopathic pulmonary fibrosis (IPF) (22, 23), histocytosis X (24), and rheumatoid-arthritis-associated interstitial lung disease (25) are epidemiologically associated with cigarette smoking. Recently, we observed that cigarette smoking influences the BAL cellularity in patients with either asbestos-induced lung disease (26) or IPF (27). These findings suggest that cigarette smoking may play a role in the pathogenesis of interstitial lung disease and may be a particularly important prognostic factor in asbestos-induced lung disease.

The purpose of this investigation was to prospectively identify the determinants of persistent or accelerated loss of lung function among workers occupationally exposed to asbestos. We were particularly interested in investigating whether findings from either BAL or the high resolution CT scan were associated with persistent or accelerated loss of lung function and whether cigarette smoking or pleural fibrosis provided additional prognostic information.

METHODS

Study Population

The subjects for this investigation were identified as part of an ongoing NHLBI-supported SCOR Program in interstitial occupational lung disease at our institution. Subjects for this study were primarily identified through the Sheet Metal Worker's 1986 screening program (28); however, many subjects were also enrolled through the Occupational Medicine Clinic at the University of Iowa. All study subjects had been occupationally exposed to asbestos for at least 1 yr in a high exposure setting (i.e., direct contact with asbestos), and a minimum of 20 yr was required between the first exposure to asbestos and entry into the study. In fact, the mean duration of occupational exposure to asbestos was 32 yr, and the mean time from first exposure to asbestos and entry into the study was 38 yr (Table 1). Although subjects with asbestos-induced parenchymal fibrosis (i.e., asbestosis) and asbestos-induced pleural disease were preferentially invited to participate in this study, asbestos-exposed subjects without obvious lung disease were also included in the study population.

In total, 117 subjects were included in this study. The study population consisted of an older population of Caucasian men who on average had extensive exposure to asbestos (Table 1). A large percentage of the subjects were either former or current cigarette smokers. The mean duration of follow-up was 2 yr, with a range of 0.5 to 4.0 yr (Table 1). Each study subject had at least one follow-up measure of pulmonary function, with an average of 4.1 measures of lung function and a range of 2 to 6 repeated measures. Study subjects were initially evaluated with a full complement of diagnostic tests and then had follow-up pulmonary function tests performed at 6 mo, 1 yr, and yearly thereafter. Test results from the initial visit were used to determine how baseline characteristics affect the slope of lung function change over follow-up time. None of these study subjects was treated with immunosuppressive therapy for their asbestos-induced lung disease.

Dyspnea Assessment

Prior to the study subject's knowledge of the other test results, dyspnea was assessed by one of the investigators (C. Dayton) who was also blinded to the test results. The dyspnea level was assigned according to the recommendations of the American Medical Association (29) and the American Thoracic Society (30). This classification system includes the following five levels of dyspnea. Class I dyspnea is dyspnea that is expected given the circumstances of the activity (i.e., dyspnea with extreme exertion). Class II dyspnea is characterized by inability to keep pace with others when walking up stairs or slight inclines. Class III dyspnea is characterized by an inability to keep pace on the level with others of the same age and body build. Class IV dyspnea occurs during such activities as climbing one flight of stairs or walking 100 yards on the level. Class V dyspnea occurs at rest and while performing activities of daily living.

Chest Radiographs

Chest radiographs were performed on 115 subjects in the posteroanterior projection and independently interpreted by three experienced readers (DAS, JAM, and JRG) who used the International Labor Organization (ILO) 1980 Classification of Radiographs and Pneumoconiosis (31). Each ILO reader was blinded to the exposure history, clinical data, and the opinions of the other readers when interpreting the radiographs. Two of the three readers agreed on the major category of parenchymal profusion (0, 1, 2, and 3) on 98% of the films. Rates of three-way agreement on the presence of either pleural plaques or diffuse pleural thickening were lower, with 69% agreement on circumscribed plaques and 85% agreement on diffuse pleural thickening. Agreement between at least two of the three readers was required to identify either a parenchymal or a pleural abnormality. In the two cases in which all three readers disagreed on the degree of parenchymal profusion, the median reading was chosen.

For the purpose of this study, we defined asbestosis as an ILO profusion of 1/0 or greater (31). The ILO classification system (31) was used to identify the presence of pleural fibrosis and to define the type (circumscribed plaques versus diffuse pleural thickening) of the pleural abnormality. However, we defined diffuse pleural thickening as requiring obliteration of the costophrenic angle on the involved side. All pleural fibrosis that was not accompanied by obliteration of the costophrenic angle was considered to be circumscribed plaque. We have used this modification of the ILO classification system (28, 32) to decrease intrareader and interreader variability (33) in distinguishing circumscribed plaques from diffuse pleural thickening. A summary of the composite chest radiograph readings is provided in Table 2. Approximately 27% of the study population had a normal chest radiograph, whereas 34% had evidence of asbestosis (ILO profusion $\geq$ 1/0) and 57% had evidence of asbestos-induced pleural fibrosis (Table 2).

High Resolution Computed Tomography Chest Scan

High resolution computed tomography (HRCT) scans of lung parenchyma were obtained on 109 study subjects using an Imatron C-100 ultrafast scanner. Images were obtained at full inspiration with the subjects prone. 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 values were

TABLE 2

PREVALENCE OF ASBESTOS-INDUCED LUNG DISEASE AS ASSESSED BY RADIOGRAPHIC STUDIES

	n (%)
Chest radiographs	
Normal	31 (27%)
Asbestosis (ILO ≥ 1/0)	19 (17%)
Pleural fibrosis	46 (40%)
Asbestosis and pleural fibrosis	19 (17%)
High resolution CT scan	
Normal	44 (40%)
Interstitial changes	29 (27%)
Pleural fibrosis	8 (7%)
Interstitial changes and pleural fibrosis	28 (26%)
Type of interstitial changes on HRCT	
Nodular lesions	34 (29%)
Ground glass	18 (15%)
Subpleural curvilinear lines	15 (13%)
Short peripheral lines	21 (18%)
Honeycombing	7 (6%)
Parenchymal bands	30 (26%)
≥ 2 Interstitial changes	36 (31%)

optimized for viewing the lung parenchyma. Three-millimeter images were obtained every 2 cm from the apex to the base of the lungs.

The HRCT scans were evaluated by two readers (DAS and JRG) who graded parenchymal abnormalities according to established criteria (34–36). The readers were blinded to the clinical characteristics of the study subjects. The HRCT scan was read as identifying interstitial changes if both readers agreed that at least one of the following six abnormalities were present: small nodular densities, subpleural curvilinear lines, parenchymal bands, thickened interstitial short lines, ground glass infiltrates, or honeycombing. These findings have been found to be associated with asbestos-induced interstitial changes (34–36), and for the purposes of this study, any one of these findings were indicative of asbestos-induced interstitial changes. Increased densities seen only in the dependent areas of the lung were disregarded. Pleural fibrosis was simply identified as either being present or absent. In total, 57 (53%) subjects had interstitial changes, and 36 (33%) had pleural fibrosis identified on HRCT scan (Table 2). In comparison with the chest radiograph, the HRCT scan tended to underestimate the prevalence of pleural fibrosis because only three HRCT slices (aortic arch, main carina, and the slice above the diaphragm) were scored for the presence of pleural disease.

Pulmonary Function Testing

The pulmonary function tests consisted of standard spirometry that was obtained with the use of a Medical Graphics 1070 system (Medical Graphics, St. Paul, MN) and lung volumes via body plethysmography using the Medical Graphics 1085 system. A single breath diffusing capacity (D_{LCO}) was measured using the Medical Graphics 1070 system. The measurements of lung function were performed with standard protocols, and the American Thoracic Society guidelines (37) were used to determine acceptability. The predicted normal values used were those of Morris and coworkers (38) for spirometry, Goldman and Becklake (39) for lung volumes, and Van Ganse and associates (40) for diffusing capacity. Full pulmonary function tests were obtained at each visit (initial visit, 6 mo, 1 yr, and then yearly).

Bronchoalveolar Lavage

Bronchoscopic examination and lavage were performed on all study subjects using our standard method (41). Premedications included atropine sulfate (0.8 mg given intramuscularly), meperidine hydrochloride (75 mg given intramuscularly), and two inhalations of metaproterenol (total, 1.3 mg) from a handheld pressurized canister. The upper airway was anesthetized with Dyclone gargle and aerosolized with 4% lidocaine. Lidocaine was also applied topically to the pyriform sinuses and vocal cords. A bronchoscope, with a 4.9-mm diameter at the tip (Olympus model BF 4B2; Olympus Corp. of America, New Hyde Park, NY), 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 (five 20-ml aliquots).

Immediately after the lavage, the lavage fluid was strained through two layers of surgical gauze 4 x 4 inches into 50-ml conical tubes. The tubes were centrifuged for 5 min at 200 x *g*, and the residual pellet of cells was resuspended and washed twice in Hank's balanced salt solution (with 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 to 12 μl of the 1×10^7 suspension were centrifuged onto a glass slide with the use of the filter card and a cytocentrifuge (Cytospin 2; Shanden Southern, Sewickley, PA). After drying for 2 min, staining of the cells was accomplished by using a Diff-Quik stain set (Harleco, Gibbstown, NJ). The cells were counted and classified only after the cytocentrifuge preparation was thought 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. Cell counts and differential were performed blinded to the clinical characteristics of the study subjects.

Protein Assays

The concentration of fibronectin in the BAL fluid was determined using a well-described ELISA (42) with a rabbit antihuman fibronectin antibody (Dakopatts, Glostrup, Denmark) and human fibronectin prepared from pooled human plasma (Cappel, West Chester, PA). Albumin concentration was measured using immunodiffusion plates with antisera and albumin standards (Calbiochem-Behring, La Jolla, CA).

Statistical Analysis

The primary objective of this investigation was to identify the determinants of lung function changes in workers occupationally exposed to asbestos. We were specifically interested in evaluating the prognostic importance of initial clinical variables on the persistent or accelerated loss of lung function during the period of observation. Because asbestosis and asbestos-induced pleural fibrosis are primarily characterized by reduced lung volumes and abnormal gas exchange (28, 32, 43, 44), a priori, we decided to focus our analysis on the TLC and the D_{LCO}.

The generalized estimating equations (GEE) approach (45, 46) was used to develop regression models assessing the relationship between each of the two outcome variables (TLC and D_{LCO}) and a set of confounders and covariates of potential interest. This regression methodology for correlated observations permits unequal numbers (and spacings) of follow-up measurements across subjects, as well as both subject-specific (time-independent) and observation-specific (time-dependent) covariates. Because the GEE approach models the occasion-specific distribution of the response variable as a function of a set of explanatory variables, the regression coefficients estimate the marginal relationship between the response and covariates. An important practical advantage of the semiparametric GEE methodology is that it is not necessary to completely specify the joint distribution of a subject's repeated observations. Instead, it is only necessary to specify the relationship between the mean and the variance and a hypothesized "working" correlation structure. The resulting estimating equations have consistent solutions even when the time dependence is misspecified. In addition, robust estimators of the variances and covariances of the estimated parameters are used.

Because the outcome variables are continuous and approximately normally distributed, the identity link function and constant variance function were used. Thus, the mean TLC (D_{LCO}) was modeled as a linear function of follow-up time and other covariates. Dichotomous explanatory variables were coded as 0 (absent) or 1 (present), and categorical covariates with $k > 2$ levels such as smoking history were coded using k-1 indicator (0, 1) variables. Because both the number and the precise spacing of the repeated measurements varied across subjects, it is not possible to assume a general, unstructured "working" correlation matrix (since the estimated correlation matrix is not guaranteed to be positive-definite). Instead, the independence and exchangeable (equal correlation between all pairs of time points) correlation structures were used. Because the two

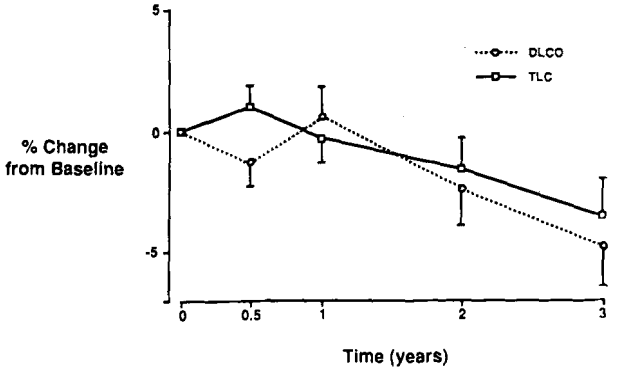

Figure 1. The percent change from baseline in D_{LCO} and TLC during the period of observation in all study subjects. n = 117.

approaches yielded similar results, only the results from the independence "working" correlation model are reported.

The regression procedure was as follows. First, for both TLC and D_{LCO}, we determined whether our potential confounders (age, height, and pack-years of cigarette smoking) interacted with follow-up time. Although TLC did not have time-dependent interactive covariates, height interacted positively with follow-up time in relation to longitudinal changes in D_{LCO}. The interaction between height and follow-up time simply indicates that taller subjects had accelerated declines in TLC during the period of observation. Moreover, the most effective means of controlling for this phenomenon is to include the interactive term in the multivariate analysis. Next, we included the confounders or covariates (age, height, pack-years of cigarette smoking, and follow-up time) and the interactive covariate term (height × follow-up time) in a model that evaluated the relationship between changes in either TLC or D_{LCO} during the follow-up period and a variety of clinical characteristics. All of the clinical characteristics that were found to be significantly related to changes in the outcome variable of interest were then tested to determine whether an interaction was observed between that characteristic and the follow-up time. Significant terms were then included in a regression model, and backward elimination was used to determine which clinical characteristics were independently associated with changes in TLC or D_{LCO} while controlling for age, height, and pack-years of cigarette smoking. After eliminating nonsignificant covariates, two- and three-way interactions of the remaining independent variables were tested. Interaction terms were included only if the interaction was significantly ($p \leq 0.05$) related to changes in lung function.

The goal of the above procedure was to obtain a parsimonious model describing the relationship between the outcome variable and a set of potential explanatory variables. Such an exploratory analysis examining the effects of multiple covariates is complicated by intercorrelations among the independent variables. In particular, the estimated regression coefficient for an independent variable depends on which variables are included and which are excluded. This problem cannot be eliminated in an observational study. Our procedure was to first examine interactions between potential confounders and follow-up time and then to separately examine individual clinical characteristics prior to the backward elimination of nonsignificant terms.

RESULTS

During the period of observation, there was an average 1.5% decrease in the TLC and a 2.5% decrease in the D_{LCO}. However, the range of lung function changes were quite broad, and Figure 1 indicates that, on average, there was a persistent decline in lung function during the period of observation. Although our subjects tended to have, on average, relatively normal lung function (Table 3), the range was also quite broad, and many study subjects had initial values well outside of what would be considered normal. Similarly, 44% of the study population did not experience unusual dyspnea with exertion. However, approximately 25% of the subjects had Class III (unable to keep pace with their peers) or worse dyspnea (Table 3). For the purposes of all subsequent analyses, subjects with dyspnea Class III or worse were considered to have moderate to severe dyspnea, and these subjects were compared with subjects with either Class I or Class II dyspnea.

TABLE 3

INITIAL PULMONARY FUNCTION AND DYSPNEA CLASSIFICATION FOR ALL STUDY SUBJECTS

	Mean ± SD	Range	n (%)
Pulmonary function*			
FEV_1	90.8 ± 20.1	39.5–134.8	
FVC	90.0 ± 16.4	43.8–131.5	
FEV_1/FVC ratio	71.3 ± 9.2	47.5–88.3	
RV	121.8 ± 37.1	21.4–234.1	
TLC	113.9 ± 18.5	60.3–162.4	
D_{LCO}	127.8 ± 26.0	48.2–186.9	
Dyspnea class			
I			51 (44%)
II			37 (32%)
III			7 (6%)
IV			15 (13%)
V			6 (5%)

* All measures of lung function are expressed as the percent predicted except for the FEV_1/FVC ratio, which is expressed in absolute terms.

After controlling for potential confounders, in this longitudinal data set, lower values for TLC were significantly associated with moderate to severe dyspnea, asbestosis on the chest radiograph, interstitial changes on the HRCT scan, diffuse pleural thickening on the chest radiograph, pleural fibrosis on the HRCT scan, and an increased concentration of macrophages, eosinophils, fibronectin, and albumin in the BAL fluid (Table 4). Interestingly, cigarette smoking (either status or pack-years) was not significantly related to TLC during the period of observation. None of these variables was found to interact with follow-up time in subsequent analyses. Thus, the specific variables that were significantly associated with a lower TLC throughout the period of observation did not affect the slope of TLC over time. Importantly, the model resulting from backward elimination indicated that after controlling for age, height, pack-years of cigarette smoking, and follow-up time, lower values for TLC during the period of observation were independently related to moderate to severe dyspnea, diffuse pleural thickening, and higher concentrations of fibronectin in the BAL fluid (Table 5). These findings demonstrate that the presence of dyspnea is associated with a 560-ml lower TLC, the presence of diffuse pleural thickening is associated with a 600-ml lower TLC, and for every nanogram of fibronectin in each milliliter of BAL fluid, the TLC is 2 ml lower. However, no interactions were observed between these variables and follow-up time, indicating that the rate of decline of TLC was not affected by these factors. Importantly, dyspnea, diffuse pleural thickening, and higher concentrations of fibronectin in the BAL fluid identify subjects with lower baseline values for TLC, and these differences appear to persist throughout the period of observation.

After controlling for potential confounders, lower values for D_{LCO} were found to be significantly associated with moderate to severe dyspnea, cigarette smoking, specific interstitial changes (honeycombing) on the HRCT scan, higher concentrations of all cells in the BAL fluid, and an increased concentration of protein (fibronectin and albumin) in BAL fluid (Table 6). Interestingly, parenchymal and pleural abnormalities on the chest radiograph were not associated with significantly lower values for D_{LCO}. In subsequent analyses, the concentration of both neutrophils and eosinophils were found to interact with follow-up time, indicating that higher concentrations of these cells in the BAL fluid significantly accelerated the rate of decline in D_{LCO}. The final model involv-

TABLE 4

RELATIONSHIP BETWEEN LONGITUDINAL CHANGES IN TLC (LITERS) AND CLINICAL PARAMETERS*

Clinical Parameter	Coefficient (SE)	p Value
Presence of dyspnea	−0.46 (0.19)	0.01
Cigarette smoking		
Former	0.45 (0.23)	0.06
Current	0.21 (0.35)	0.54
Pack-years	0.007 (0.004)	0.10
Asbestos exposure, yr	0.007 (0.01)	0.48
Chest radiograph		
Asbestosis	−0.44 (0.19)	0.02
Pleural plaques	−0.26 (0.18)	0.15
Diffuse thickening	−0.76 (0.22)	0.0006
HRCT scan		
Small nodular densities	−0.35 (0.20)	0.07
Curvilinear lines	0.11 (0.25)	0.64
Parenchymal bands	−0.02 (0.23)	0.94
Short peripheral lines	−0.70 (0.26)	0.006
Ground glass	−0.12 (0.28)	0.65
Honeycombing	−0.75 (0.25)	0.003
⩾ 2 Interstitial changes	−0.47 (0.21)	0.03
Pleural fibrosis	−0.54 (0.18)	0.004
BAL cellularity, cells × 10^4/ml		
Macrophages	−0.001 (0.0003)	0.003
Lymphocytes	−0.006 (0.003)	0.10
Neutrophils	−0.008 (0.006)	0.20
Eosinophils	−0.03 (0.005)	0.00001
BAL Proteins, ng/ml		
Fibronectin	−0.03 (0.0006)	0.00001
Albumin	−0.006 (0.002)	0.0009

* All multivariate models controlled for age, height, pack-years of cigarette smoking, and follow-up time except for the models that explored the relationship between cigarette smoking and longitudinal changes in TLC, which did not control for pack-years of cigarette smoking.

TABLE 6

RELATIONSHIP BETWEEN LONGITUDINAL CHANGES IN D_{LCO} (mL/mm Hg/min) AND CLINICAL PARAMETERS*

Clinical Parameter	Coefficient (SE)	p Value
Presence of dyspnea	−3.61 (1.03)	0.005
Cigarette smoking		
Former	−3.97 (1.49)	0.008
Current	−7.06 (1.88)	0.0002
Pack-years	−0.10 (0.02)	0.0001
Asbestos exposure, yr	−0.24 (0.15)	0.18
Chest radiograph		
Asbestosis	−2.08 (1.38)	0.13
Pleural plaques	1.25 (1.08)	0.25
Diffuse thickening	−1.81 (1.34)	0.18
HRCT scan		
Small nodular densities	0.18 (1.16)	0.88
Curvilinear lines	2.33 (1.29)	0.07
Parenchymal bands	0.33 (1.23)	0.79
Short peripheral lines	2.18 (1.23)	0.07
Ground glass	2.09 (1.30)	0.11
Honeycombing	−7.57 (2.61)	0.004
⩾ 2 Interstitial changes	1.76 (1.23)	0.15
Pleural fibrosis	−0.53 (1.28)	0.68
BAL cellularity, cells × 10^4/ml		
Macrophages	−0.004 (0.002)	0.03
Lymphocytes	−0.05 (0.025)	0.03
Neutrophils	−0.09 (0.039)	0.02
Eosinophils	−0.25 (0.097)	0.01
BAL Proteins, ng/ml		
Fibronectin	−0.02 (0.004)	0.00001
Albumin	−0.05 (0.02)	0.02

* All multivariate models controlled for age, height, pack-years of cigarette smoking, follow-up time, and the interaction between follow-up time and height. In exploring the relationship between cigarette smoking and longitudinal changes in D_{LCO}, we did not control for pack-years of smoking.

ing these significant variables indicated that after controlling for age, height, follow-up time, and the interaction between follow-up time and height, lower values for D_{LCO} during the period of observation were independently related to moderate to severe dyspnea, more pack-years of cigarette smoking, honeycombing on the HRCT scan, and higher concentrations of lymphocytes, neutrophils, eosinophils, and fibronectin in the BAL fluid (Table 7). Importantly, this multivariate model also demonstrates that higher concentrations of neutrophils and eosinophils are associated with an accelerated decline in D_{LCO} during the period of observation.

DISCUSSION

Our results indicate that among asbestos-exposed subjects, moderate to severe dyspnea and higher concentrations of fibronectin in the BAL fluid are associated with persistently lower values of lung volume and gas exchange. In addition, diffuse pleural thickening is associated with persistently lower lung volume, and more pack-years of cigarette smoking and higher concentrations of cells (lymphocytes, neutrophils, and eosinophils) are associated with reductions in gas exchange. Although these features identified subjects with lower baseline values for lung volume and gas exchange that persisted throughout the period of observation, only higher concentrations of neutrophils and eosinophils significantly accelerated the rate of decline in D_{LCO}. These results suggest that clinical symptoms can be used for prognostic purposes among asbestos-exposed subjects and that specific radiographic abnormalities and excess cells and fibronectin in the BAL fluid appear to provide additional prognostic information. Moreover, cigarette smoking represents an independent risk factor for persistent abnormalities in gas exchange.

Dyspnea, a symptom inherently plagued by recall bias, was found to be associated with persistently lower measures of lung volume and gas exchange throughout the period of follow-up. We have recently observed that among asbestos-exposed subjects dyspnea appears to be a valid symptom, and it was found to be associated with decreased lung volumes, diminished gas exchange, diminished exercise tolerance, and the presence of pleural or parenchymal radiographic abnormalities. Other studies

TABLE 5

MULTIVARIATE MODEL IDENTIFYING THE INDEPENDENT DETERMINANTS OF LONGITUDINAL CHANGES IN TLC (LITERS)*

Variable	Coefficient (SE)	p Value
Dyspnea	−0.56 (0.20)	0.005
Diffuse pleural thickening	−0.60 (0.22)	0.007
BAL fibronectin, ng/ml	−0.002 (0.0007)	0.01

* Multivariate model controlled for age, height, pack-years of cigarette smoking, and follow-up time.

TABLE 7

MULTIVARIATE MODEL* IDENTIFYING THE INDEPENDENT DETERMINANTS OF LONGITUDINAL CHANGES IN D_{LCO} (ml/mm Hg/min)*

Variable	Coefficient (SE)	p Value
Dyspnea	−2.47 (0.90)	0.006
Pack-years of smoking	−0.11 (0.02)	0.00001
Honeycombing on HRCT scan	−5.80 (1.75)	0.0009
BAL cellularity, cells × 10^4/ml		
Lymphocytes	−0.09 (0.03)	0.0008
Neutrophils × follow-up time	−0.04 (0.01)	0.0005
Eosinophils × follow-up time	−1.44 (0.69)	0.03
BAL fibronectin, ng/ml	−0.01 (0.004)	0.02

* Multivariate models controlled for age, height, follow-up time, and the interaction between follow-up time and height.

support these observations, indicating that asbestos-exposed workers with dyspnea will have significantly lower lung volumes (47) and are more likely to have radiographic abnormalities indicative of asbestos-induced lung disease (48–51). These findings suggest that a simple assessment of dyspnea may be particularly helpful in managing workers exposed to asbestos and identifying those with a worse prognosis. Additional studies are needed to identify the specific prognostic utility of dyspnea and to critically evaluate other complementary measures of functional capacity in this high risk population.

Specific findings in the BAL fluid appear to identify subjects at excess risk of disease progression. Higher concentrations of neutrophils and eosinophils were associated with more accelerated declines in gas exchange. These findings are supported by analogous studies in patients with IPF, which have shown that excess neutrophils (52–55) and eosinophils (52, 55, 56) in the BAL fluid are associated with a higher likelihood of disease progression and a failure to respond to systemic immunosuppression. However, our finding that higher concentrations of lymphocytes in the BAL fluid are associated with lower values for D_{LCO} does not appear to support the generally held belief that BAL lymphocytes suggest a more reversible interstitial process (53–55). A likely interpretation that potentially explains these divergent findings is that higher concentrations of lymphocytes are indicative of an early, potentially reversible, but active, interstitial process that is more responsive to immunosuppression (53–55). However, if patients with a lymphocytic alveolitis are not treated, they may be more likely to progress. Unlike the prior studies of patients with IPF, none of our study subjects were treated with immunosuppressive therapy for their asbestos-induced lung disease. Thus, there was no possibility of detecting a response to immunosuppression in this study population. Interestingly, our results also indicate that higher concentrations of fibronectin in the BAL fluid are associated with persistently reduced measures of lung volume and gas exchange throughout the period of observation. Importantly, among workers exposed to asbestos, higher concentrations of BAL fibronectin have been associated with the presence of interstitial lung disease (57) and restrictive lung function (58). In aggregate, these findings suggest that the concentration of cells and specific proteins in the BAL fluid may be particularly important in staging the activity of the interstitial process and determining the overall prognosis.

Our results indicate that cigarette smoking is associated with persistently reduced measures of gas exchange (D_{LCO}) among subjects exposed to asbestos. This is particularly interesting since cigarette smoking profoundly alters the concentration of BAL cells among those with either asbestosis (26) or IPF (27), and it appears to increase the risk of developing pulmonary fibrosis among workers exposed to asbestos (16–21). Importantly, cigarette smoking has been shown to profoundly alter the constituents and function of alveolar lining cells (59–63) and enhance the permeability of the airway epithelia (64). Given the results from this investigation, one could hypothesize that cigarette smoking augments the inflammatory process in pulmonary fibrosis, and it may contribute to the progression of interstitial fibrosis. Alternatively, two independent processes (asbestosis and emphysema) may both be contributing to the persistently lower measures of gas exchange. The absence of a relationship between cigarette smoking and changes in lung volume may reflect the opposing effects that interstitial fibrosis and emphysema have on this measure of lung function in patients with asbestosis (65). The results of this study, which demonstrate that longitudinal measures of gas exchange are persistently lower in smokers, and prior studies, which show an independent biologic effect of smoking (26), raise the provocative hypothesis that cigarette smoking is a risk factor for the development and progression of fibrosis, as well as of emphysema, of the lung. Further studies are clearly needed to test this hypothesis.

Our results demonstrate that pleural fibrosis, and, in particular, diffuse pleural thickening, is independently associated with persistently lower measures of lung volume. This supports the observations of previous investigators (4, 8) and further demonstrates the physiologic importance of these radiographic abnormalities. Asbestos-induced pleural fibrosis has been independently associated with excess dyspnea (48, 49) and lower lung volumes (22, 32). The results of this study indicate that asbestos-induced pleural fibrosis has long-term consequences in relation to the persistently lower measures of lung volume. In contrast, asbestosis on the chest radiograph and interstitial changes on HRCT were not significantly related to lower measures of TLC during the period of observation. This suggests that pleural fibrosis, rather than asbestosis, may be particularly important in identifying those workers who are more likely to have persistently lower measures of lung volume.

In summary, we have identified several clinical factors that are associated with persistently lower measures of lung volume and gas exchange in a population of workers occupationally exposed to asbestos. The clinical factors that we have found to have prognostic importance include symptoms of dyspnea, cigarette smoking, diffuse pleural thickening on the chest radiograph, honeycombing on the HRCT scan, and higher concentrations of lymphocytes, neutrophils, eosinophils, and fibronectin in the BAL fluid. Although further studies are needed to confirm these risk factors, consideration should be given to using these risk factors to identify high risk patients who could be approached with innovative disease-modifying drug regimens.

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