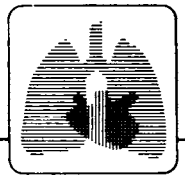

# reviews

## New Developments in Asbestos-Induced Pleural Disease*

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Between 1940 and 1979, 27.5 million individuals in the United States were exposed to asbestos while at work.[1] Among exposed workers, almost 19 million have had cumulative exposures that are considered to be potentially hazardous.[1] These asbestos-exposed workers have developed or are at risk of developing pulmonary fibrosis, lung cancer, mesothelioma, and gastrointestinal malignancies.[1-4] Although pleural fibrosis is a characteristic feature of asbestos exposure and occurs much more commonly than any of the other asbestos-induced diseases, the clinical features and pathogenesis of pleural fibrosis are not widely appreciated and have not been adequately studied. Given the large number of asbestos-exposed individuals who are likely to have, or over the next 20 years develop this problem, it is important to carefully evaluate the diagnostic accuracy of the current International Labour Organization classification system, assess the physiologic consequences of pleural fibrosis, and determine the relationship between the pathogenesis of pleural fibrosis and other manifestations of asbestos-induced lung disease.

### *Prevalence*

The nonmalignant forms of asbestos-induced pleural abnormalities include pleural effusions, pleural plaques, diffuse pleural thickening, and rounded atelectasis.[5] Circumscribed pleural plaques and diffuse pleural thickening account for over 90 percent of asbestos-induced pleural abnormalities[5-9] and their prevalence is expected to increase for at least the next 15 to 20 years.[1,2] Collectively termed pleural fibrosis, circumscribed pleural plaques, and diffuse pleural thickening represent the most common roentgenographic manifestation of asbestos exposure.[5-9] The development of pleural fibrosis is dependent on the cumulative dose of asbestos exposure[10-13] and the elapsed time since first exposure to asbestos.[13-15] Given these variables, between 20 and 60 percent of workers exposed to high concentrations of asbestos have been found to have roentgenographic evidence of pleural fibrosis.[13,15-20] Environmental exposure to asbestos, by virtue of either household contact[21,22] or endemic exposure to asbestiform minerals,[23-27] has resulted in a prevalence of pleural fibrosis ranging from 2 to 17 percent. Autopsy studies[28-43] have documented that pleural plaques are a common finding. Of 7,085 routine autopsies reported in 16 separate studies[28-43] investigating the prevalence of pleural plaques in the general population, pleural plaques were identified in 857 or 12.2 percent (range = 0.5 to 39.3 percent) of the autopsies. Moreover, autopsy studies[28,29] and recent studies utilizing CT scans[44-47] indicate that the standard chest roentgenogram is able to identify between 50 and 80 percent of the pleural plaques that are actually present.

### *Pathogenesis*

Although circumscribed pleural plaques and diffuse pleural thickening are considered under the broad category of asbestos-induced pleural fibrosis, these processes are distinct entities that are likely to involve different clinical and pathogenic components. Only recently has the International Classification of Pneumoconioses (ILO 1980) recognized this distinction and expanded their classification of chest wall abnormalities to separate circumscribed pleural plaques and diffuse pleural thickening.[48]

Circumscribed pleural plaques develop slowly with a latency period of approximately 15 years. These lesions exclusively involve the parietal pleura, are often bilateral and symmetric, and occur most commonly between the fifth and eighth ribs in the posterior/lateral portion of the chest while sparing the apices and costophrenic angles.[5-9,48-51] Diffuse pleural thickening has a similar prolonged latency; however, its development is closely associated with previous

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pleural effusions.[14,51] Diffuse pleural thickening primarily involves the visceral pleura, commonly extends into the costophrenic angle, and is usually unilateral.[5-9,14,48-51] While circumscribed pleural plaques remain as discrete lesions of the parietal pleura, diffuse pleural thickening often results in adhesions and fusion of the visceral and parietal pleura.[5-9,52]

Although the pathogenesis of asbestos-induced pleural fibrosis is still unclear, studies investigating the alveolar clearance of asbestos fibers indicate that the pulmonary lymphatics may play a primary role in seeding both the parietal and visceral pleura with microfibrils.[53,54] Capillaries appear to play a minor role in this process; however, Kanazawa et al[55] have demonstrated that intravenous injections of asbestos will concentrate in the "milky spots" within the mesothelial layer of serosal cavities. Using radioactive-labelled anthophyllite, Morgan et al[56] have observed a movement of the fibers to the mediastinal lymph nodes and subvisceral pleural foci. Short chrysotile microfibrils have been shown to migrate from alveoli to the interstitium,[57] pleural cavity,[58] and regional lymph nodes.[55,59] In humans, Sebastian et al[60] have shown that inhaled asbestos fibers accumulate in the periphery of the lung[60] and that short chrysotile microfibrils are the dominant fiber type in pleural plaques.[61] Asbestos fibers or their fragments have been observed in the parietal pleura,[8,53,62-66] the pleural cavity,[67] pleural mesotheliomas,[62] mediastinal lymph nodes,[68] spleen,[62,69] liver,[62] gastric wall,[62,69] and in a variety of abdominal tumors.[69-71] Findings from one study[68] indicate that asbestos fibers are actually concentrated in the mediastinal lymph nodes. Asbestos fibers not removed by the conducting airways appear to be cleared from the alveoli primarily by the lung lymphatics.[53,54] Fibers that gain access to the parenchymal lymphatic plexus would tend to accumulate in the mediastinal lymph nodes while fibers in the pleural lymphatic plexus would migrate peripherally and collect in subvisceral pleural foci.[8,53,54]

Any hypothesis addressing the pathogenesis of circumscribed pleural plaques must account for several peculiar characteristics of these lesions. These dense collections of collagenous connective tissue are located primarily in the posterior and lateral aspect of the chest, usually bilateral and symmetric in shape, are orientated parallel to the ribs, do not have associated pleural adhesions, and spare the apices and costophrenic angle.[64,72] Although microscopic fragments of asbestos fibers have been observed within the circumscribed pleural plaque,[53,73,74] it remains unclear whether these short microfibrils are directly responsible for initiating a localized inflammatory response. Kiviluoto[73] and Meurman[30] have proposed that circumscribed pleural plaques form as a direct result of local inflammation of the parietal pleura from asbestos fibers which protrude from the visceral pleura. Since supportive pathologic material (such as fibers protruding from the visceral pleura or adhesions between the visceral pleura and circumscribed plaques) has not been presented and asbestos fibers are too short to be anchored in the visceral pleura and span the pleural cavity, this theory has not gained wide acceptance. Since animal[56] and human[60] studies have shown that asbestos fibers migrate peripherally in the lung parenchyma, and others have occasionally demonstrated fibers in the pleural effusions of asbestos workers,[67] a transpleural route has been proposed[72] for microfibrils to reach the parietal pleura. Once in the pleural cavity, asbestos fibers may gain access to the parietal pleura through preformed stomas connecting the pleural cavity and the lymphatics in the parietal pleura.[75] The transpleural migration of fibers might account for the predilection of pleural plaques to form in the gravity-dependent (posterior and basilar) portion of the chest cavity. However, no studies have confirmed the relationship between inflammation and obliteration of the parietal stomas and the development of pleural plaques. Furthermore, the transpleural route fails to address several important characteristics of these lesions, such as bilaterality, symmetric shape, orientation parallel to the ribs, and sparing of the apices and costophrenic angle. Alternatively, since asbestos fibers are cleared by the parenchymal lymphatic plexus and accumulate in the mediastinal lymph nodes,[68] microfibrils may reach the parietal pleura through retrograde lymphatic drainage involving flow from the mediastinal nodes to the retrosternal and intercostal lymphatics.[76] Given the peculiar characteristics of circumscribed pleural plaques (bilateral, symmetric, and orientated parallel to the ribs), the data presented thus far suggest that microfibrils embolize to the parietal pleura by either the parenchymal lymphatic plexus or via the costal vascular supply. Once present in the parietal pleura, the fiber itself or agents carried by the fiber appear to be responsible for initiating and promoting the inflammatory response. This hypothesis provides a mechanism to account for the finding of fibers in other anatomic sites, but also causes one to consider why plaques occur in the parietal pleura and not at these other sites of fiber deposition.

The pathogenesis of diffuse pleural thickening remains even less well understood. However, its locale and strong association with interstitial fibrosis suggest that it may be a direct extension of parenchymal fibrosis to the visceral pleura. Both diffuse pleural thickening and parenchymal fibrosis are localized in the lung periphery and result in inflammation and fibrosis of the superficial or pleural lymphatic plexus.[8,53,54,77] This fits well with the peripheral migration of asbestos fibers that are observed in animal

inhalation studies[53,56] and also in humans.[60] Moreover, the strong association with interstitial fibrosis[77] suggests that the development of diffuse pleural fibrosis requires exposure to high concentrations of asbestos fibers and may involve pathogenic mechanisms that are similar to asbestos-induced interstitial fibrosis. Alternatively, a localized visceral pleural inflammatory reaction to an asbestos-related hemorrhagic pleural effusion may result in diffuse and extensive fibrosis of the visceral pleura.[14,51] This would be analogous to the development of a fibrothorax as a complication of an empyema or a hemothorax.[78] An additional hypothesis that may account for the development of diffuse pleural thickening involves the interaction of specific inflammatory cells and mediators of inflammation within the pleural cavity. Recently, Sahn and Antony[79] have demonstrated that neutrophils and macrophages in the pleural space may help contain and limit the amount of pleural fibrosis following exposure to asbestos. These findings are potentially important because they indicate that inflammatory responses to asbestos in the pleural cavity may parallel those observed in the lung parenchyma.

Bronchoalveolar lavage studies in persons with asbestosis have identified an active alveolitis which is characterized by an excess number and percentage of total and activated lymphocytes and neutrophils.[80-86] However, the alveolar macrophage appears to be a pivotal cell in the development of asbestos-induced interstitial fibrosis since it dominates the inflammatory response in the lower respiratory tract,[80-86] is rapidly recruited to the lung following asbestos deposition,[87] plays a primary role in the initial processing of the asbestos fiber, and may function as a modulator of the chronic inflammatory response. Animal inhalation studies[88-90] and pathologic specimens from patients with asbestosis[91] demonstrate that the asbestos fibers are initially deposited at the bifurcation of the alveolar ducts and within hours are phagocytized by alveolar macrophages and epithelial cells. The inflammatory process that is initially dominated by alveolar macrophages appears to precede the development of peribronchiolar fibrosis.[92,93] Bronchoalveolar lavage studies in animals exposed to asbestos[94-97] and in patients with asbestosis[80-86,98] indicate that in these settings, alveolar macrophages spontaneously release increased amounts of neutrophil chemotactic factors,[85,97] oxygen free radicals,[84,94] fibronectin,[84] macrophage-derived growth factor,[84] a factor exhibiting interleukin-like activity,[95] and leukotriene $B_4$.[98] *In vitro* studies demonstrate a dose-dependent increase in macrophage production of leukotriene $B_4$, tumor necrosis factor, and lipid peroxidation products following exposure to asbestos.[99,100] Although the pathologic significance of these cytokines is still unclear, these factors may prove to be useful in following the activity of asbestos-induced lung diseases.

*Roentgenographic Manifestations*

In 1950, the ILO established a system to classify roentgenographic changes associated with pneumoconioses. This classification system was originally intended as an epidemiologic tool to conduct surveys among workers at risk of pneumoconioses.[101] Over the past 30 years, there has been a growing tendency to use the ILO classification of chest roentgenograms as definitive diagnostic criteria.[49] Although we have some information on how these criteria function when applied as a screening tool, we have a great deal to learn regarding its utility as a diagnostic tool.[19,102]

In 1980, the ILO modified the classification system to incorporate a semiquantitative method of categorizing pleural involvement.[48] However, the definition of circumscribed plaques and diffuse pleural thickening is ambiguous in the ILO 1980 classification. The ILO criteria document indicates that these two chest wall abnormalities can usually, but not always, be distinguished. Although standard roentgenograms are provided which include an example of these pleural lesions, the ILO criteria document[48] does very little to describe the distinguishing features of pleural plaques and diffuse pleural thickening. In fact, some authorities believe that the ILO 1980 standard roentgenograms mistakenly identify a circumscribed plaque as diffuse pleural thickening. This confusion has led to unclear comparisons between studies and has created an obvious need to improve this section of the 1980 ILO classification.

Recently, more extensive pleural thickening and involvement of the costophrenic angle has been found to be associated with a higher likelihood of having previous occupational exposure to asbestos.[103] Bourbeau and Ernst[104] found unacceptably low rates of agreement between (and within) ILO trained readers regarding the presence and type of pleural abnormality. In fact, in regard to the type of abnormality (circumscribed plaque vs diffuse pleural thickening), the intrareader discordance ranged from 17 to 27 percent and the interreader discordance ranged from 19 to 28 percent.[104] Moreover, autopsy studies[28,29] and studies using CT scans[44-47] indicate that the chest roentgenogram is neither a sensitive nor specific method of identifying asbestos-induced pleural fibrosis. These studies suggest that modifications in the 1980 ILO criteria for pleural fibrosis are needed to improve the overall utility of this classification system. In addition, the specific role of the chest CT scan needs to be further clarified in identifying and defining pleural fibrosis.

*Pulmonary Function*

Several investigations have found that pleural

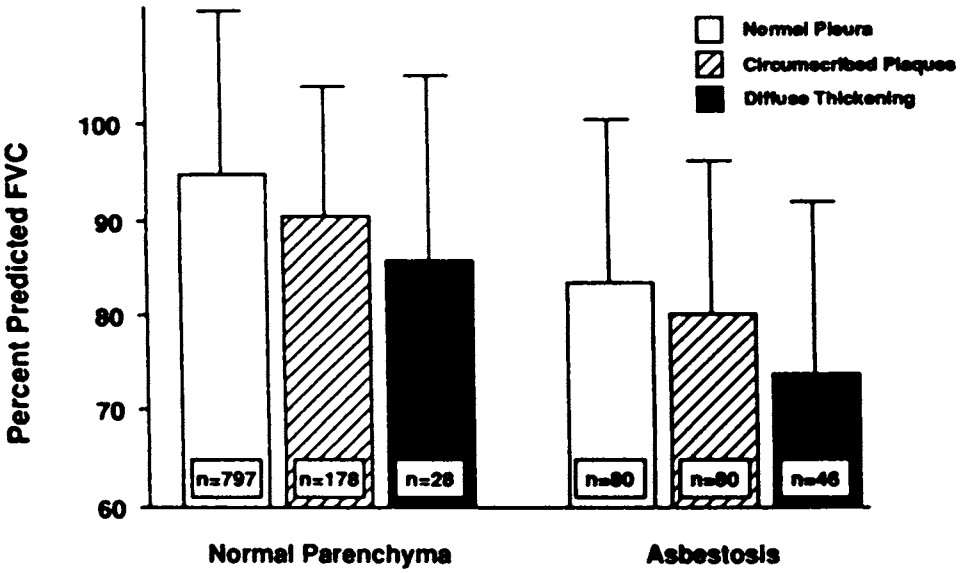


FIGURE 1. The percent predicted forced vital capacity (FVC) stratified by parenchymal fibrosis (normal = profusion 0/1; asbestosis = profusion ≥1/0) and pleural fibrosis (normal pleural, circumscribed plaques, and diffuse pleural thickening). A significant clinical and statistical decline was observed between categories of pleural fibrosis for those with normal parenchyma (ANOVA $F = 8.62$, $p = 0.0002$) and those with asbestosis (ANOVA $F = 4.88$, $p = 0.009$). (With permission from Schwartz et al.[90])

plaques[17-19,105-110] and diffuse pleural thickening[19,52,111-113] 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 vital capacity[17,18,105] and also in the diffusing capacity of carbon monoxide.[18,106] While diffuse pleural thickening has been reported to reduce lung volumes,[19,52,111-113] concerns regarding selection of study subjects and potential confounding by interstitial fibrosis and cigarette smoking have compromised the general acceptance of this association. Nonetheless, after controlling for the degree of interstitial fibrosis, Rosenstock et al[19] were able to demonstrate that diffuse pleural thickening was associated with decrements in vital capacity. These studies indicate that asbestos-induced pleural fibrosis appears to be independently associated with restrictive lung function.

To further quantify the physiologic significance of asbestos-induced pleural fibrosis, we evaluated the relationship between roentgenographic evidence of pleural fibrosis and spirometric values in 1,211 sheet metal workers.[20] Of those with pleural fibrosis (N = 334), 260 (78 percent) had circumscribed plaques and 74 (22 percent) had diffuse pleural thickening. Among persons with normal appearing parenchyma and also among those with interstitial fibrosis, we observed a consistent decline in the percent predicted FVC that was significantly associated with the type of pleural fibrosis (Fig 1). Moreover, the percent predicted FVC 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 ($p = 0.02$) and diffuse pleural thickening ($p = 0.005$) were independently associated with decrements in FVC. Furthermore, our data indicate that the effect of diffuse pleural thickening on decrements in FVC is approximately twice as great as that seen with circumscribed pleural plaques.

### *Determinants of Restrictive Lung Function in Pleural Fibrosis*

Although asbestos-induced pleural fibrosis is the most common roentgenographic abnormality among asbestos-exposed persons and has recently been shown to contribute to the development of restrictive lung function,[17-19,52,105-113] little work has been done to characterize the mechanisms underlying the restrictive impairment. Pleural fibrosis may either limit lung expansion and increase the work of breathing or lead to altered proprioceptive information resulting in abnormal ventilatory patterns.[114] Alternatively, pleural fibrosis may simply be a marker of prior asbestos exposure, placing an individual at higher risk of parenchymal fibrosis which is not appreciated on the routine chest radiogram.[19,46,114,115] Since pleural plaques arise from the parietal pleura and diffuse pleural thickening primarily involves the visceral pleura, it is very likely that more than one of these mechanisms account for the development of restrictive lung function.

Limited expansion of the lung has been thought to be responsible for the development of restrictive lung function among those with diffuse pleural thickening.[52,111-113] In studies[113-116] that have evaluated the exercise performance in workers with asbestos-induced diffuse pleural thickening and no evidence of parenchymal fibrosis, an increased $V_D$ (dead space) to $V_T$ (tidal volume) ratio and a high ventilatory equiva-

lent ($\dot{V}E/\dot{V}O_2$) was observed with exertion. Since Picado et al[113] selected patients with normal lung compliance, the abnormal response to exercise was attributed to reduced compliance of the visceral pleura. However, these findings on cardiopulmonary exercise testing (high ventilatory equivalents and an increasing VD/VT with exercise) are more characteristic of interstitial fibrosis than chest wall deficits.[117] Diaphragmatic fatigue assessed by electromyographic techniques did not appear to contribute to the abnormal exercise pattern.[113] Thus, although these investigators[113] concluded that compliance of the chest wall/pleura contributed to the development of restrictive lung function in those with pleural fibrosis, the exact determinant(s) of this functional deficit are not at all clear. Moreover, since individuals with circumscribed pleural plaques (usually with limited chest wall involvement) also develop restrictive lung function[17-20,105-110] and abnormal diffusion of carbon monoxide,[18,106] it remains difficult to accept chest wall compliance as the sole mechanism accounting for this functional abnormality.

Several pieces of evidence suggest that parenchymal inflammation and/or fibrosis are the principle determinants of restrictive lung function in persons with asbestos-induced pleural fibrosis who have normal appearing parenchyma on the chest radiogram. First, pulmonary function tests indicate that, in addition to reduced lung volumes, asbestos-induced pleural fibrosis is associated with lower diffusing capacities for carbon monoxide[18,106,112] and diminished lung compliance.[108] Second, autopsy studies[28,29] and studies using high resolution CT scans[46,47] demonstrate that the chest roentgenogram appears to underestimate the presence of parenchymal fibrosis. These studies[28,29,46,47] indicate that as many as 10 percent of individuals with anatomically defined interstitial fibrosis have normal routine chest roentgenograms. This implies that asbestos-exposed persons with pleural fibrosis may have interstitial fibrosis that is not readily apparent on the chest roentgenogram but may be responsible for the development of restrictive lung function. Third, Wallace et al[118] have recently shown that individuals with asbestos-induced pleural fibrosis and no evidence of interstitial lung disease on the chest roentgenogram have an elevated number and percentage of lymphocytes in their bronchoalveolar lavage fluid when compared to similarly exposed persons with normal chest films. These data suggest that parenchymal inflammation and/or fibrosis not appreciated on the chest x-ray film is more likely to be present among persons with pleural fibrosis than similarly exposed individuals with normal pleura.

Findings from our center[119] suggest that although parenchymal inflammation and fibrosis contribute to the loss of lung function in persons with asbestos-induced pleural fibrosis, other mechanisms may contribute to the impaired lung function. Among nonsmokers with normal parenchyma on chest x-ray film, we have found that pleural plaques and diffuse pleural thickening are associated with a lymphocytic alveolitis (Fig 2) and structural features of interstitial fibrosis on the high resolution CT scan (Fig 3). Despite this association, in a multivariate analysis, we found that neither a lymphocytic alveolitis nor the finding of parenchymal fibrosis on high resolution CT scan influenced the relation between pleural fibrosis and restrictive lung function.[119] Although the mechanisms

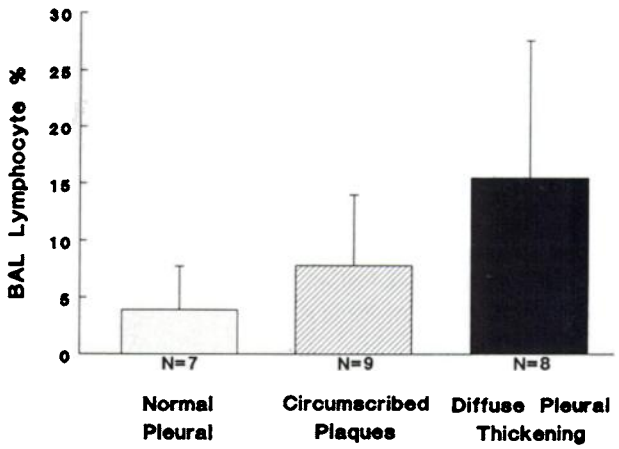


FIGURE 2. For nonsmoking asbestos workers (N = 24) with normal parenchyma on chest roentgenogram, the relationship between pleural fibrosis and bronchoalveolar lymphocytes is illustrated. Workers with diffuse pleural thickening have a lymphocytic alveolitis when compared to those with normal pleura ($p = 0.04$) and a significant trend to increase the percentage of BAL lymphocytes is observed across the categories of pleural disease (ANOVA $F = 7.50$, $P = 0.01$). (With permission from Schwartz et al.[119])

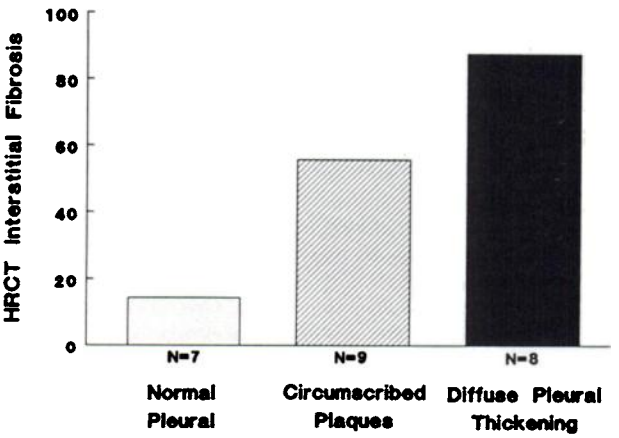


FIGURE 3. For nonsmoking-asbestos workers (N = 24) with normal parenchyma on chest roentgenogram, the relationship between pleural fibrosis and interstitial fibrosis on high resolution chest CT (HRCT) scan is illustrated. Workers with circumscribed plaques or diffuse pleural thickening are more likely to demonstrate these changes on HRCT than those with normal pleura. A significant trend to increase the prevalence of these abnormalities on HRCT is observed across the categories of pleural disease ($\chi^2$ trend = 7.70, $p = 0.02$). (With permission from Schwartz et al.[119])

accounting for impaired lung function among those with asbestos-induced pleural fibrosis remain obscure, the strong relationship between pleural fibrosis and both a lymphocytic alveolitis and parenchymal fibrosis on high resolution CT scan suggests that parenchymal fibrosis is responsible for a portion of the reduced lung volume in those with pleural fibrosis. This is further supported by the reduced diffusing capacity observed in those with diffuse pleural thickeninig that we and others[18,106,112,119] have observed.

## Conclusions

In summary, previous studies indicate that pleural fibrosis is the most common asbestos-induced abnormality, is being underdiagnosed, and is associated with restrictive lung function that appears to be independent of its association with parenchymal fibrosis. However, little work has been done to investigate the accuracy of the current criteria for pleural fibrosis established by the ILO, the anatomic and functional validity of these criteria, and the determinants of restrictive lung function in persons with asbestos-induced pleural fibrosis. Further studies are needed to advance our understanding of impairment associated with pleural fibrosis. Results from these studies will have clear implications for clinical assessment and management of workers with asbestos-induced pleural disease.

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