Continued Progression of Asbestos-Related Respiratory Disease after More Than 15 Years of Non-Exposure

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ABSTRACT: **Background:** Most studies on asbestos-related diseases describe the associations between exposure and disease and the factors influencing that association. It is recognized that there is a long latency period between exposure and disease, but the health status of affected individuals after long-term non-exposure is uncertain.

Objectives: To describe the changes in pulmonary function tests (PFTs) and computed tomographic imaging of the thorax over a 15 year period after cessation of exposure to asbestos in a cohort of Israeli power plant workers.

Methods: Israeli power plant workers whose PFTs and thoracic CT imaging between 1993 and 1998 revealed asbestos-related disease underwent a second clinical, functional and imaging evaluation up to 15 years later. The two sets of results were compared.

Results: Of the original cohort of 59 males, 35 were still alive and 18 of them agreed to take part in the current study. The mean length of their exposure was 30 ± 10.06 years (range 7–43 years). Comparison of the initial and follow-up examination findings revealed a significant increase in calcification of the pleural plaques (from 37% to 66%, $P = 0.008$) and a deterioration in PFT results ($P = 0.04$). Of the 24 men who died, malignant disease was the cause of death in 53%, mostly in sites other than the respiratory system.

Conclusions: PFTs declined and CT findings worsened in subjects who were formerly exposed to asbestos and had not been exposed to it for over a decade. Continued monitoring of individuals exposed to asbestos, even decades after the cessation of exposure, is recommended.

IMAJ 2012; 14: 560-565

KEY WORDS: asbestos, pleural diseases, pulmonary function test (PFT), occupational lung disease, power plant workers

The term "asbestos" is used to describe a group of fibrous minerals that may induce pulmonary damage after their inhalation. It is a good thermal and electrical isolator made of durable, strong and flexible material. Asbestos was extensively used in a variety of commercial settings, among them insulation, brake pads and lining, household products, floor tiles, electric wiring, paints and cements. Inhalation of asbestos fibers is associated with a wide spectrum of pleuropulmonary disorders, including asbestosis, pleural fibrosis (plaques or diffuse thickening), non-malignant pleural effusion, rounded atelectasis, airflow obstruction and a number of malignancies [1]. The major malignancies associated with asbestos are cancer of the lung (with a complex relationship to cigarette smoking) and mesothelioma (pleural or peritoneal), with additional risk also reported for other sites. One of the most important implications of non-malignant asbestos-related disease is the close correlation between the presence of non-malignant disease and the risk of malignancy [1].

Asbestosis, the interstitial pneumonitis and fibrosis caused by inhalation of asbestos fibers, usually becomes evident only after an appreciably extended latent period. The duration and intensity of exposure influence the prevalence of parenchymal pulmonary fibrosis. Asbestosis is usually associated with dyspnea, bibasilar rales, and changes in pulmonary function. It may remain static or progress, but regression is rare [1].

Bilateral non-symmetric pleural plaques are indicators of exposure to asbestos. They are lesions of the parietal pleura, sharply circumscribed with either a smooth or a rounded knobby surface, and range in color from white to pale yellow. The origin of pleural plaques is not clear, and their presence is associated with impairment of pulmonary function tests [1].

Subjects with suspected asbestos-related disease should undergo a thorough evaluation, which includes exposure assessment, physical examination, PFT and thoracic imaging (conventional chest X-ray or computed tomography as required). PFT should include spirometry, all lung volumes, and carbon monoxide diffusing capacity. As with other interstitial lung diseases, the classic finding in asbestosis is a restrictive impairment. Mixed restrictive and obstructive impairment is frequently seen, and isolated obstructive impairment is unusual. In addition to diminished lung volumes, the carbon monoxide diffusing capacity is commonly reduced due to diminished alveolar-capillary gas diffusion, as well as ventilation-perfusion mismatching. Although a low diffusing capacity for carbon monoxide is often reported as the most sensitive indicator of early asbestosis, it is also a relatively non-specific finding.

PFT = pulmonary function test

The initial radiographic presentation of asbestos-related diseases may show pleural or parenchymal pathology. Asbestosis typically appears as small irregular parenchymal opacities in the lower lobes bilaterally. Over time, the distribution and density or "profusion" of opacities may spread through the middle and upper lung zones, followed by reticular changes. While pleural plaques and effusions are frequently documented on plain chest X-rays, it is well recognized that CT is superior to chest films in identifying parenchymal lesions, rounded atelectasis, and pleural plaques [2]. On the other hand, only 50–80% of cases of documented pleural disease demonstrated by autopsy are detected by chest films, conventional CT, or high resolution CT [3].

The diagnosis of non-malignant asbestos-related disease rests, as it did in 1986, on the following essential criteria: a compatible structural lesion, evidence of exposure, and exclusion of other plausible conditions, with an additional requirement for impairment assessment if the other three criteria suggest asbestos-related disease [4]. The diagnosis of malignant asbestos-related diseases is based on tissue diagnosis, as in most other cancers.

As the detrimental effects of asbestos on human health became evident, legislature and regulations were implemented to control its use. The last decades of the 20th century saw a decrease in exposure to asbestos; however, the incidence of its long-term complications has risen due to a characteristic latency period of 10–30 years between exposure and the manifestations of asbestos-related diseases. The long-term natural history of these diseases is well studied, but comparisons of objective pulmonological test results over time are scarce.

The aim of this study was to describe the changes in PFTs and CT imaging of the thorax over a 15 year period after cessation of exposure to asbestos in a cohort of Israeli power plant workers. We also examined the causes of death in the non-survivors of the original cohort.

PATIENTS AND METHODS

From 1993 to 1998, 59 men between the age of 41 and 78 with a history of asbestos exposure and respiratory complaints were examined by a pulmonologist. They also underwent PFTs and thoracic CT imaging as part of the workup of their respiratory complaints. They were all diagnosed as suffering from asbestos-related disease; patients with pleural effusion were excluded. The subjects who agreed to participate in the current (2007) follow-up study underwent a medical interview and physical examination, as well as repeated PFTs and thoracic CTs. The current data were compared with their first examinations. The cause of death was documented for the non-survivors of the original cohort.

All subjects underwent plethysmography, dynamic spirometry, and DLCO testing using standard protocols according to American Thoracic Society specifications [5]. All measurements were interpreted by a specialist in pulmonary diseases. PFT results were interpreted as being either normal or abnormal, and the type of impairment was defined as obstructive, restrictive, or combined in the latter. They also underwent CT scans, which were interpreted by a radiologist who compared the recent results to the initial ones and noted whether there had been any change or progression of pleural or parenchymal disease in each individual subject.

STATISTICAL ANALYSIS

All statistical analyses were performed using the SPSS statistical package for Windows (SPSS Inc., Chicago, IL, USA). The paired *t*-test assessed all continuous variables used to characterize pulmonary function (e.g., forced expiratory volume in one second, forced vital capacity, total lung capacity, DLCO, etc.). The chi-square test was used for all dichotomous variables. Some variables were the presence of deterioration or aggravation of the findings in PFT or CT; the McNemar paired test was used for these dichotomous variables, which determine the change in the severity of the findings. The Kaplan-Meier analysis was applied to describe the survival of the subjects, using different variables. The comparison between the survival curves was done using the Log-rank test. The Cox proportional hazard models were used to compare the survival of the groups in each variable. The level of significance for all analyses was two-tailed ($P < 0.05$).

The study was approved by the Institutional ethics committee. All subjects received information on the study and gave their written informed consent. All procedures were done according to the research ethics of the Declaration of Helsinki.

RESULTS

There were 59 men in the original cohort. Their characteristics are listed in Table 1. The mean age in the first examination was 66 ± 6.5 years (range 41–78 years), the mean length of exposure to asbestos was 29.9 ± 9.7 years (range 3–43); 44% of the subjects had a history of smoking and 13% had a prior lung disorder (3% asthma, 10% chronic obstructive pulmonary disease). There were 35 survivors of the original cohort. One subject was lost to follow-up. A total of 18 males consented to participate in the current study; none of them showed any signs of clinical deterioration.

In the first examination 54 of the 59 study patients had a PFT; 18 of them (33%) had normal PFT findings, 16 (30%) had obstructive impairment, 14 (26%) restrictive impairment, and 6 (11%) mixed obstructive and restric-

DLCO = diffusing capacity for carbon monoxide

Table 1. Characteristics of subjects, n (%)

Age at first examination (mean 66 ± 6.5 yrs)	
‹ 60	7 (12)
61–70	35 (59)
› 71	17 (29)
Years exposed (mean 29.9 ± 9.7 yrs)	
‹ 20	10 (17)
21-30	20 (34)
31-40	22 (37)
› 41	5 (9)
Unknown	2 (3)
Main occupation/site	
Power plant	27 (46)
Pipe filter	5 (8)
Welder	5 (8)
Boilers	4 (7)
Turbines	3 (5)
Electrician	2 (3)
Mechanic	2 (3)
Brake lining	1 (2)
Insulation	1 (2)
Construction	1 (2)
Others	8 (14)
Smoking history	
Never smoked	27 (46)
Ever Smoked	26 (44)
Unknown	6 (10)
Prior lung disease	
None	51 (87)
Asthma	2 (3)
COPD	6 (10)

COPD = chronic obstructive pulmonary disease

tive impairment. In the second examination only 18% of the subjects had normal PFT findings; 62% had obstructive impairment, 13% restrictive impairment and 7% mixed obstructive/restrictive impairment. Taken together, these results showed an overall deterioration in PFTs ($P = 0.04$) [Figure 1A]. There was a trend towards an increase in obstructive impairment ($P = 0.08$) [Figure 1A].

The imaging studies in the first examination showed that 95% of all 59 subjects had pleural plaques, 37% of which were calcified. Pulmonary fibrosis was found in 37% of the subjects in the original cohort. Comparison of the initial and follow-up imaging examinations revealed the same prevalence of pleural plaques and pulmonary fibrosis but a significant increase in calcified plaques (from 37% to 66%, $P = 0.008$) [Figure 1B]. None of the subjects developed pleural effusion, and there was no association between duration of exposure and PFT impairment or imaging abnormalities.

Twenty-three patients of the original cohort (39%) were deceased at the time of the current study. Cancer (53%) and lung diseases (35%) were the leading causes of death. The primary neoplasm in death from cancer was as follows: lung in 23%, colon 12%, esophageal 6%, pancreas 6%, and brain 6%. Among the subjects who died due to lung disease, 23%

Figure 1. [A] Pattern of pulmonary function tests (PFTs) in the initial and follow-up examinations. The histogram demonstrates that PFTs deteriorated significantly ($P = 0.04$) over time despite non-exposure to asbestos. There is a trend of increment of the obstructive impairment ($P = 0.08$)
[B] Chest imaging studies in the initial and follow-up study. The histogram demonstrates worsening of pleural changes, even without significant parenchymal involvement

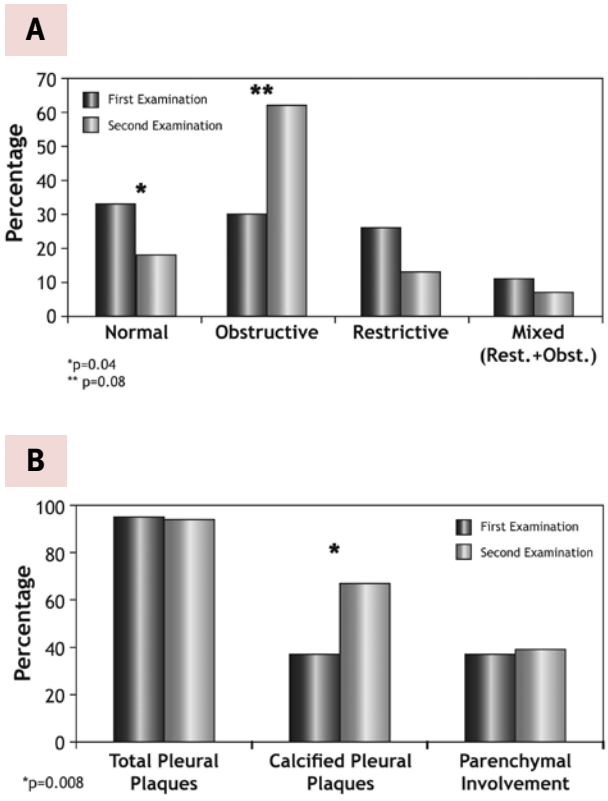


Figure 2. Cause of death in the 24 non-survivors among the original 59 subjects. ILD = interstitial lung disease, IHD = ischemic heart disease

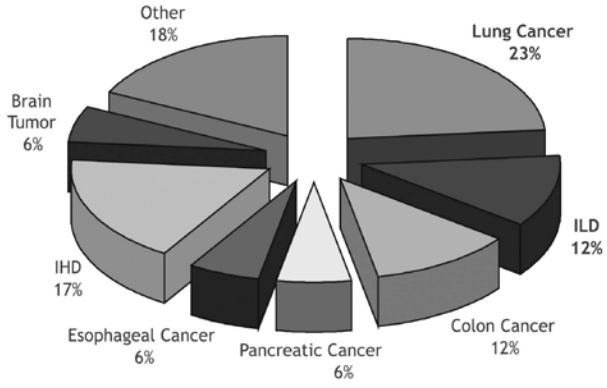
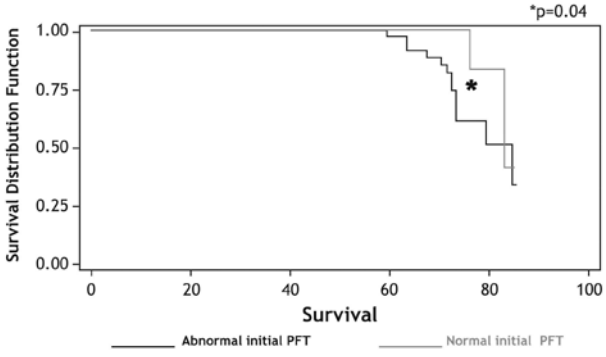


Figure 3. Kaplan-Maier curve in subjects with normal vs. abnormal pulmonary function tests in the initial examination (n=59)



died from lung cancer and 12% from interstitial lung disease [Figure 2]. As expected, survival rates were lower ($P = 0.04$) in subjects with abnormal initial PFTs [Figure 3]. The presence of pleural or parenchymal disease and the duration of exposure did not influence the survival rates in our cohort.

DISCUSSION

Asbestos-related diseases continue to represent a significant respiratory problem despite improvement in the workplace and decrease in its use following legislation. Asbestos has been the largest single cause of occupational cancer in the United States and a significant cause of disease and disability from non-malignant disease. The management of asbestos-related diseases remains challenging since there is no specific treatment [6]. The associations between exposure and disease and the factors influencing that association have been studied in depth. In the present study we looked at the progression of asbestos-related diseases more than 15 years after the individuals were no longer exposed to the material.

Pleural plaques are one of the common non-malignant complications of chronic exposure to asbestos. Progression of pleural plaques is defined as the increase in number or area of the plaques, or the appearance of calcification [7]. Most of the published studies reported that the prevalence of pleural plaques is closely related to cumulative exposure or duration of exposure [1,8]. In contrast to those data, our findings indicated no significant correlation between the duration of exposure and the prevalence of pleural plaques, possibly because the intensity of exposure varied considerably.

Time since first exposure (TSFE) has recently been strongly correlated to the frequency of pleural plaques. Paris et al. [9] conducted a screening program of non-malignant asbestos-related diseases by CT scans among 1011 asbestos-exposed volunteers in France and reported that TSFE was the key predictive variable for pleural plaques. Another screening program on 5545 subjects showed the same correlation [10]. This long-term progression of pleural plaques after the exposure had long ceased was, however, extrapolated from the results of screening evaluations at a single time point, and not from a comparison of the results of a cohort at two remote reference points. In an old cohort of 384 men in a Wittenoom mine in Western Australia, de Klerk et al. [11] concluded that the relative rate of progression decreases slowly with time, and that the pleural disease does not progress more than 15 years after its onset. Our results refuted their conclusion: by comparing imaging results after an interval of 15 years of non-exposure, we showed that the pleural disease continues to worsen. We found that calcification of the pleural plaques continues to progress more than 15 years after exposure has ceased, as evidenced by an almost doubling of their prevalence (from 37% to 66%, $P = 0.008$) in the follow-up examination. While calcification of the plaques may suggest a benign alteration, it should be borne in mind that the presence of pleural plaques is associated with a greater risk of mesothelioma and lung cancer [12,13], thus supporting the need to follow subjects with pleural plaques. Moreover, calcification of the pleural plaques was found to be associated with the progression and deterioration of the parenchymal disease [7].

Parenchymal disease due to asbestos exposure can remain static or progress after cessation of exposure. None of our study patients had any evidence of an increment in pulmonary fibrosis at the long-term follow-up, but the prevalence of abnormal PFTs was significantly higher in the follow-up examinations, indicating a major deterioration of lung function, which may be related to early subclinical fibrosis or airway obstruction. There are many confounding factors that may influence the PFT results in our cohort, blurring the connection between the past occupational exposure and the deterioration of the PFTs. However, considering the fact that the imaging studies were progressive (i.e., the disease was still dynamic), one may relate the deterioration of the PFT to the asbestos exposure. As with other interstitial lung diseases, the classic finding in asbestosis is a restrictive impairment, or mixed restrictive and obstructive impairment [1]. Our results did not show a restrictive or mixed pattern of deterioration, but there was a trend towards a high prevalence of obstructive impairment not associated with smoking status. These results may be explained by the fact that there was no radiographic progression of the parenchymal disease, which is known to be the parameter most responsible for the restrictive impairment. In addition, it is well recognized that asbestos exposure independently contributes to the accelerated decline

TSFE = time since first exposure

in airflow over time, whether or not exposure ceases [1,14]. This decline is thought to be due to small airway disease, consistent with the known pathology of bronchiolitis in early asbestosis [15]. Another potential reason for the PFT deterioration is the progression of the pleural plaques. Opinions on this issue are divided in the literature. Some studies of large cohorts have shown a significant reduction in lung function attributable to the plaques, even when interstitial fibrosis is absent radiographically [16-18], while longitudinal studies failed to show a more rapid decrement in pulmonary function in subjects with pleural plaques [19].

The impact of asbestos exposure on health is well documented, with the two leading causes of death being asbestosis and lung cancer [20]. Over one-half of the non-survivors in our original cohort died from malignant disease and 12% due to interstitial lung disease. We found that abnormal PFTs at the initial examination indicated poor prognosis and correlated with an increased risk for death. One may hypothesize that an abnormal PFT precedes a pathologic process, which leads to a more aggressive disease.

The yearly number of asbestos-related cancer deaths in workers is estimated to be 100,000–140,000 worldwide [21]. Several types of cancer are linked to asbestos exposure. The association with malignant mesothelioma, and with lung, laryngeal and ovarian cancer is well established, while the evidence for an association between asbestos and colorectal, pharynx and stomach cancer is limited and controversial [22,23]. Nevertheless, we found that 53% of the deceased subjects in our cohort died of malignant disease, primarily lung cancer, but also of gastrointestinal neoplasm (e.g., colon, esophageal and pancreas). This high percentage of cancer deaths in our study strengthens the association between asbestos exposure and cancer in sites other than the respiratory system. The incidence of mesothelioma in Israel [24] and worldwide is still increasing and is estimated to peak within the next 10 years [25]. There was no case of mesothelioma in our cohort, most probably due to the small number of subjects.

There are some potential limitations of the present study. First, economic interests could pose a confounding element in this setting. Because Israeli workers are entitled to financial compensation and early retirement in the case of asbestos-related disease, including pleural plaques, we used only objective measurements (PFT and CT scans) and not self-reporting to obviate this potential bias. Second, the small number of compliant subjects in our cohort, and the low percentage of subjects who agreed to participate in the current study, may influence the results and lessen the power of the study to detect other factors affecting the progression of the disease. Third, it is possible that we did not find any correlation between the duration of exposure and the functional or radiographic deterioration because exposure assessments were based exclusively on patients' assertions and medical files, and the accuracy of the exposure parameters may be questionable.

In summary, asbestos remains a significant cause of morbidity and mortality in exposed workers for as long as decades after non-exposure. We showed deterioration of pulmonary function and worsening of pleural changes, even without significant parenchymal involvement. We also showed a higher mortality rate and a higher prevalence of cancer deaths in exposed persons compared to the general population. The results suggested that deterioration in PFT results may be a poor prognostic factor. Given the long latency between asbestos exposure and disease, together with the new data we provided on progression after years of non-exposure, we recommend that continuous monitoring and screening of ever-exposed subjects be considered.

Acknowledgment

The authors thank Mrs. Esther Eshkol for her writing assistance.

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Capsule

Iatrogenic Creutzfeldt-Jakob disease, final assessment

The book on iatrogenic Creutzfeldt-Jakob disease (CJD) in humans is almost closed. This form of CJD transmission via medical misadventures was first detected in 1974. Today, only occasional CJD cases with exceptionally long incubation periods still appear. The main sources of the largest outbreaks were tissues from human cadavers with unsuspected CJD that were used for dura mater grafts and growth hormone extracts. A few additional cases resulted from neurosurgical instrument contamination, corneal grafts, gonadotropic hormone, and secondary infections from blood transfusions. Although the definitive answer to the problem of iatrogenic CJD is still not available (a laboratory test to identify potential donors who harbor the infectious agent), certain other measures have worked well: applying special sterilization of penetrating surgical instruments, reducing the infectious potential of donor blood and tissue, and excluding donors known to have higher than normal risk for CJD.

Emerg Infect Dis 2012; 18: 901
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Capsule

Restoring voluntary control of locomotion after paralyzing spinal cord injury

Half the human spinal cord injuries lead to chronic paralysis. van den Brand et al. have introduced an electrochemical neuroprosthesis and a robotic postural interface designed to encourage supraspinally mediated movements in rats with paralyzing lesions. Despite the interruption of direct supraspinal pathways, the cortex regained the capacity to transform contextual information into task-specific commands to execute refined locomotion. This recovery relied on the extensive remodeling of cortical projections, including the formation of brainstem and intraspinal relays that restored qualitative control over electrochemically enabled lumbosacral circuitries. Automated treadmill-restricted training, which did not engage cortical neurons, failed to promote translesional plasticity and recovery. By encouraging active participation under functional states, our training paradigm triggered a cortex-dependent recovery that may improve function after similar injuries in humans.

Science 2012; 36: 1182
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Don't be yourself. Be someone a little nicer

Mignon McLaughlin (1913-1983), American journalist and author