Progression of pleural and parenchymal disease on chest radiographs of workers exposed to amosite asbestos

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Abstract

Objectives—To determine predictors of progression of pleural and parenchymal disease on the chest radiographs of workers exposed to a short term, intense exposure of amosite asbestos.

Methods—The first and last of a series of chest radiographs of 887 workers exposed to amosite was interpreted and coded according to International Labour Organisation (ILO) standards by two physicians. Significant predictors of disease progression were found by a linear stepwise regression analysis from among such variables as smoking history, latency (time since first exposure), duration and intensity of exposure, and cytology.

Results—Although most radiographs remained normal, some showed progression of disease with about twice as many patients with abnormalities on the last film. Various combinations of age, intensity of exposure, and time between films were significant predictors of pleural and parenchymal disease and progression of such disease. No predominance of one sided disease was noted. Cytology and smoking were unreliable predictors of disease. Most disease progression was minor, usually of less than two scoring categories.

Conclusion—An intense, yet short, exposure to amosite asbestos can produce pleural and parenchymal changes on chest radiographs. The number of those affected roughly doubled over a period spanning 10 to 20 years after exposure. Age and intensity of exposure are the most important predictors of disease.

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For a period of 18 years (1954-72), tons of amosite, or brown asbestos, were shipped from the Transvaal asbestos mines in South Africa to a manufacturing plant in Owentown just north of Tyler, Texas. Amosite was chosen, rather than the more common and easily accessible chrysotile, because of unique physical characteristics that allow it to be moulded and formed, like a clay material, for insulation of pipes and vessels. The workers at the Tyler plant were exposed to amosite fibre counts of three to 18 times more than current Occupa-

tional Safety and Health Administration (OSHA) standards. The exposure was relatively pure given the isolated rural location of the plant and lack of local industry. It was also brief with an average time of employment of a worker of only 12.7 months. The plant was eventually closed in 1972 after strict institution of OSHA guidelines on air standards.

Beginning in 1972, the Texas asbestos workers project was initiated with funding from the National Cancer Institute. The University of Texas Health Center has followed up a population of more than 900 exposed people for a period of >20 years with repeated chest radiographs, sputum analysis, lung function tests, and other laboratory studies. Therapeutic intervention with β carotene and vitamin A was examined double blind in an attempt to investigate the possible suppression of development of malignancy in these patients at high risk of lung cancer.^{1,2}

The exposure to pure fibre, short time of exposure, high level of exposure, and the long term follow up make this cohort unique.

Methods

The earliest chest radiograph of good quality from each patient's radiograph file was placed on a motorised view box for interpretation and scoring by each reader who used the International Labour Organisation (ILO) standard films. A second film, the latest available, was read at least one week later with most of the second films read two to three months later. Over 2000 films were read so bias introduced by memory of the earlier film was minimised. The initial film was not a pre-employment chest radiograph but rather marked the beginning of the Texas asbestos workers project pleural disease study. JRS is a board certified radiologist and has been certified as a B reader by National Institute for Occupational Safety and Health (NIOSH) since 1986 (recertified 1990, 1994). GH is an experienced pulmonary physician, intensively involved in asbestos research, and experienced in reading radiographs of workers exposed to asbestos. Progression of disease was based solely on the change in ILO classification with no collaborative interpretation taking place. A potential bias could have resulted as the researchers could not be blinded to the age of the film, because the initial films exhibited wear and tear and were thicker with rounded corners. Pleural thickening of >5 mm was required as a minimum marker for pleural disease. This

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Table 1 Cohort description

	Value (SD)
Workers in study (n)	887
Male workers (n(%))	879 (99.1)
Female workers (n(%))	8 (0.9)
White workers (n(%))	611 (68.9)
Black workers (n(%))	276 (31.1)
Current or ex-smokers (%)	84.2
Age at first exposure (y) (mean(SD))	28.1 (9.5)
Duration of exposure (months) (mean(SD))	8.0 (14.9)
Intensity of exposure (fibre-months) (mean(SD))*	638.9 (1460)
Time from first exposure to first x ray film (y) (mean(SD))	21.6 (8.1)
Mean age at first chest x ray film (y)	49.6 (12.7)
Mean time between first and last chest x ray film (y)	10.1 (5.9)

* Calculated from measured fibre/ml at known task sites and the months worked at each site.

stricter requirement was chosen to increase the specificity of pleural changes and eliminate pleural disease not related to asbestos. A pleural index, modified from the method of Bourbeau *et al* was instituted both to increase objectivity and to simplify statistical analysis.³ Categories of thickening, noted as A, B, and C, on the ILO form, were assigned a number of 1, 2, or 3 respectively. This number was multiplied by the length of abnormal pleura, again according to the ILO scoring, to arrive at the pleural index, which combines the thickness and length abnormalities into one measure. For the combined reader pleural index, the lowest score of the two readers was selected. Similarly a parenchymal scoring system was devised to allow regression analysis. Each subcategory of profusion was assigned a score beginning with 0/0 scored as 1 and ending with 3/3 scored as 10. A combined reader profusion score was determined by the higher profusion score from the right or left for each reader and then selecting the lower of the two readers' scores.

Duration of exposure, type of job within the factory, smoking history, and the time since first exposure were known for each worker (table 1). Sputum samples for cytological examination were collected throughout the study for pathological examination. An estimate of cumulative exposure designated fibre-months of exposure was derived from employment records as well as information reported by the workers about their duration and types of jobs within the plant and OSHA measurement of airborne fibre counts at these job sites. There was a very wide range of exposure intensity for the workers (see SDs, table I). Thus fibre-month expresses the severity of exposure or a combination of duration and intensity. Although several regression models were considered, both ordinary linear and logistic stepwise multivariate regression analyses were used to identify significant correlations of disease and progression of disease. Both interactive and higher terms were used in the regression but none were found to be significant. Both categorical and continuous variables were used. Two subgroups, those workers with a profusion score 1/2 and those with a change ≥ 2 categories were analysed separately.

Table 2 Change in ILO profusion score*

	<i>Second film score</i>										
	0	2	3	4	5	6	7	8	9	Total	
First film score:											
0	738	17	13	9	3	4	1	—	—	785	
2	3	2	1	1	1	—	—	—	—	8	
3	1	—	2	—	—	—	—	—	—	3	
4	—	—	—	2	—	2	—	—	1	5	
6	—	—	—	—	—	—	1	—	—	1	
Total	742	19	16	12	4	6	2	—	1	802	

* Score of 3 corresponds to ILO profusion of 1/0.

Results

The average time span between films was 10.2 years. The first film was taken, on average, 11.4 years after the time of first occupational exposure to asbestos, and the second film was taken 21.6 years after the time of first exposure.

PARENCHYMAL CHANGES

Both readers detected small amounts of parenchymal disease, defined as $>0/1$, on the first film—4.2% (JRS) and 0.6% (GH). By the time of the second film, those figures were 9% and 8.5%, respectively. The parenchymal changes were almost exclusively small opacities. Table 2 shows the changes in parenchymal scores from the first to the last film. Most patients (738 out of 805) were normal on both films. Of those with progressive disease most represented incident cases—that is, cases showing new disease that had had a normal first film—and cases with minor progression of one category—for example, 0/0 to 1/0—(see first row of table 2). Figures 1 and 2 show examples of progression of parenchymal disease. Thus, roughly twice as much parenchymal disease developed in this 10 year time span beginning about 10 years after a very brief and intense exposure to amosite.

To investigate discrepancies in interpretation and scoring, the first and last films of each patient were examined simply to see if the first film had been interpreted as abnormal and the second film as normal. The two readers interpreted a total of 14 cases in such a way. Consensus reinterpretation of all these cases showed an even split between films showing acute disease that resolved, poor inspiration, and reader misinterpretation. Overall variation between observers was analysed with a Cohen's κ of 0.42 measured for first film profusion scoring and 0.52 for the second film indicating significant agreement ($P < 0.0001$).

To find if a select group of workers with considerable progression in parenchymal disease was different from the overall population, an analysis was applied to all cases with a change in parenchymal profusion score of ≥ 2 . Only 8% of workers showed this severity of change. A second subcategory of workers with severe parenchymal disease (score $\geq 1/2$) was also analysed. JRS found 64 cases (7.2%) of workers advancing by profusion scores of ≥ 2 , whereas GH detected 60 cases (6.8%). Only 23 workers (2.5%) were identified with an ILO category of $>1/2$; three of these were seen on the first film as well as on the second film. Both readers easily identified these 23 cases with no disagreement.

Figure 1 (A) First chest radiograph interpreted as normal. (B) Close up of right lower lung field.

PLEURAL CHANGES

An increase in pleural abnormalities was also found, with one reader recording an increase from 11.6% to 25% from first to last film and the other reader noting an increase from 18.7% to 34.9%. This would be slightly less than the doubling noted for parenchymal changes over the same 10 year time span. Table 3 shows the change in combined pleural index from the first to the last film. The combined pleural index is the lowest pleural score of the two

readers, after the maximum of the right and left score had been chosen for each case for each reader.

Again most workers (610) were normal on both films with most abnormal films representing new disease on the second film (table 3). Examination of each case that showed less severe pleural disease on the second film showed that the discrepancy arose from three areas: (a) subpleural lipomatosis scored as pleural plaque disease on the first film (64%);

Figure 2 (A) Last chest radiograph, extensive parenchymal disease, 18 years later. (B) Close up.

Table 3 Combined pleural index, change from first to second film

	Second film pleural index											Total
	0	1	2	3	4	5	6	7	8	10	11	
First film index:												
0	610	20	37	4	57	1	2	1	3	—	2	737
1	5	2	1	1	2	—	—	—	—	—	—	11
2	7	1	8	—	7	1	1	1	—	—	1	27
3	1	—	—	—	—	—	—	—	—	—	—	1
4	8	—	3	—	9	—	2	1	1	1	—	25
5	—	—	—	—	—	—	—	—	—	1	—	1
8	—	—	—	—	1	—	—	—	—	—	—	1
10	1	—	—	—	—	—	—	—	—	—	—	1
Total	632	23	49	5	76	2	5	3	4	2	3	804

Table 4 Right and left pleural disease compared using median of pleural index score

	Pleural index score			
	First film		Second film	
	Right	Left	Right	Left
Radiologist:				
JRS	4	5	6	6
GH	1	1	2	2

(b) over measurement of pleural disease on the first films 30%; and (c) reader misinterpretation (6%). The first column of table 3 shows an example of this. These discrepancies were confirmed mostly by consensus reading but by oblique films and computed tomography in some. A total of 23 cases fell into this category. Kappa values for variation of pleural readings between observers were 0.3 on both the first and second film. Both of these values represent significant agreement between readers ($P < 0.0001$) after adjusting for agreement by chance.

Table 5 Regression analysis

Dependent variable	Type of regression†	Reader‡	Significance (P value)*					
			Age	Fibre-month	Duration§	Latency¶	Smoking	Sputum cytology**
Pleural index on first film	O	B	> 0.0001	NS	NS	NS	NS	0.06
		S	> 0.0001	NS	NS	NS	NS	0.18
		H	> 0.0001	NS	NS	NS	NS	0.008
Pleural index on second film	O	B	> 0.0001	0.0001	0.0075	0.067	NS	NS
		S	0.0017	0.0002	0.038	0.028	NS	NS
		H	> 0.0001	0.0006	0.061	0.072	NS	NS
Change in pleural index between films	O	B	NS	0.0003	0.016	NS	NS	NS
		S	NS	NS	NS	NS	NS	NS
		H	NS	0.011	NS	NS	NS	NS
Any pleural disease first film	L	B	NS	0.003	0.03	NS	NS	NS
		S	> 0.0001	NS	NS	0.089	NS	0.063
		H	> 0.0001	0.051	0.08	NS	NS	0.0054
Any pleural disease second film	L	B	NS	0.040	0.0034	0.012	NS	NS
		S	0.0026	0.0001	NS	0.0007	NS	NS
		H	> 0.0001	> 0.0001	NS	NS	0.029	0.044
Profusion score first film	O	B	0.001	NS	NS	NS	NS	NS
		S	0.0003	NS	NS	NS	NS	NS
		H	0.0012	NS	NS	NS	NS	NS
Profusion score second film	O	B	> 0.0001	0.0001	NS	NS	NS	NS
		S	> 0.0001	> 0.0001	NS	NS	NS	NS
		H	> 0.0001	0.0003	NS	NS	NS	NS
Profusion score > 1/2 first film	L	B	NS	NS	NS	NS	NS	NS
		S	NS	NS	NS	NS	NS	NS
		H	NS	NS	NS	NS	NS	NS
Profusion score > 1/2 second score	L	B	0.0015	0.0073	NS	NS	NS	NS
		S	0.010	0.0070	NS	0.037	NS	NS
		H	0.0001	0.0007	NS	NS	NS	NS
Change of profusion score > 2 from first film to second	L	B	0.0002	NS	0.0001	0.014	0.056	NS
		S	> 0.0001	> 0.0001	NS	0.0022	NS	NS
		H	> 0.0001	NS	0.0002	0.016	0.039	NS

* $P > 0.1$ coded as NS (not significant); † O = ordinary linear regression, L = logistic regression; ‡ B = both readers combined, S = Shepherd, H = Hillerdal; § Duration of employment in months; ¶ Time since first employment in months; || Ever-smoked v never smoked; ** Moderate atypia of Greater.

Pleural calcification serves as a highly recognisable and therefore, perhaps less subjective, marker on chest radiographs of pleural disease secondary to asbestos exposure. A few patients did show such calcification on the initial film (1.1% by JRS and 0.6% by GH). This increased the cases involved to 5.1% as judged by JRS and 4.6% by GH on the second film. This would roughly represent a fourfold increase. As some investigators⁴ have detected a difference in right to left pleural disease, a separate analysis was performed to detect pleural disease predominating on one side of the chest. Table 4 shows this for both readers. No significant left or right predominance was found.

REGRESSION ANALYSIS

Finally, a linear stepwise regression analysis was performed to correlate pleural and parenchymal changes on the first and last film with the age of the worker at the time of the film, the time since the first exposure (latency), the duration of asbestos exposure, an estimate of the fibre-months (cumulative exposure reflecting both intensity and duration), atypical sputum cytology, and smoking. We used the pleural index and parenchymal score as dependent variables (table 5). Regression analysis for those clearly showing a rapid progression of disease (>2 categories) and for those with severe disease (score >1/2) found the same independent predictors of disease as for all workers with only latency representing an additional predictor for both subcategories. Table 5 also shows an analysis of the results of the individual interpreters.

Discussion

This cohort of asbestos workers is unique in many ways. The workers were recruited locally from a mainly rural area, where there was little chance of having been exposed to asbestos earlier and they were exposed to only one type of asbestos—namely, amosite. The exposure was short term, but severe, and the exposure levels well documented. The group has been followed up with chest radiographs, spirometry, and cytological examinations. Also, most of the workers have remained in the area after closure of the factory, making follow up almost complete. Most malignant or other disease in the cohort has been treated locally, often at the same hospital (University of Texas Health Centre) where the Texas asbestos workers project was conducted.

Amosite is produced in South Africa (hence its name, which is short for asbestos mines of South Africa) and exported all over the world. It has been extensively used, but in most instances it has been mixed with other fibre types. Therefore, cohorts with only exposure to amosite are rare. The only earlier description of such a cohort is that by Ehrlich *et al* from a New Jersey factory.⁵ Interestingly, that factory was forced to close due to concern about environmental safety of the workers and the manufacturing process was then moved to Tyler, where the local circumstances were more favourable for this type of factory in those days (the 1950s and 1960s).

This study documented a doubling in parenchymal disease over about 10 years between films with only slightly less progression for pleural disease. Significant agreement between readers was calculated despite most films showing very little radiographic change. Regression analysis (table 5) found that the age of the worker at the time of film and fibre-months were the only significant predictors of parenchymal disease on the second film. No significant factors were discovered on the first film for parenchymal disease.

Have others also documented continued progression of such disease? The workers exposed to amosite from the study of Ehrlich *et al*⁶ showed increased radiographic disease with time. In that study a much greater percentage of workers (20%), showed parenchymal abnormality on the first film which was taken, on average, 25 years after exposure, versus about 9% of Tyler workers with disease 22 years after first exposure. Cumulative exposure was the only significant independent factor for parenchymal disease in the New Jersey study, whereas age was a second independent predictor of such disease in Tyler. The exposure levels were similar between the two factories and were more accurately measured in Tyler. In the New Jersey study, exposure was simply estimated from the Tyler exposure levels. The workers in the New Jersey factory worked for a mean of only six months, compared with the 12.7 months in Tyler. Progression in the profusion score (in New Jersey) was more than a twofold to threefold increase in number of patients with disease (versus the two fold increase in Tyler). Similarly, Cookson *et al*⁸

documented parenchymal disease worsening over a 30 year period in 384 crocidolite miners in Western Australia. Total exposure and time from the first exposure (highly colinear with age) were significant determinants of progression of parenchymal disease in these miners. There is good reason to think that even more disease will be found in the Tyler group when followed up further. Thus, parenchymal disease and progression of such disease are highly dependent on age, time since exposure, and on cumulative exposure, no matter how short. Most of the progression was of two categories or less.

Although smoking was a significant factor for one reader only, it has been found in other studies to be a predictor of the presence of parenchymal opacities in asbestos workers (see the meta-analysis of Blanc⁷). Barnhart *et al*⁸ found increased risk of parenchymal opacities in patients who smoked and were exposed to asbestos. Others⁹ have shown that smoking is not an independent predictor of parenchymal disease. It is noteworthy that it is usually the lower categories (0/1, 1/0, 1/1) which are found to be increased in smokers. These are also the categories which are most difficult to differentiate and to score objectively. For example, Rossiter¹⁰ noted a wide variation (28%–71% read as normal) in reader interpretation for these categories. No correlation between sputum cytology and pleural or parenchymal disease could be found in our study.

Pleural plaques result from the migration of asbestos fibres from the lung through the visceral pleura into the pleural space. The fibres are deposited into the parietal pleura where they are engulfed into macrophages inciting a persistent low grade fibroblastic response.¹¹ The background incidence of pleural plaques has been estimated to be from 0.003% in Western Australian adults to 1.8% in laboratory personnel in the United States.¹² By comparison, Hillerdal¹³ reported that a minimum of 2.7% and more probably about 3.4% of inhabitants of the relatively lightly industrialised county in Sweden had pleural plaques. However, most of this recruited population, especially the men, were found to have a history of exposure. An unusually long latency period to develop pleural plaques (33 years) was documented for this group with light exposure. These estimates may serve as the most accurate baseline for pleural disease in the general population, including both exposed and unexposed people with perhaps 0.003%, the Australian figure, representing a completely unexposed population.

About twice as many patients' radiographs showed pleural disease by the time of the second film, 10 years after the first film and 20 years after the time of first exposure. Progression of pleural plaques, both thickness and extent, might be expected given the continued inflammatory response to the inciting fibres and activation of fibroblasts. de Klerk *et al*¹⁴ also found, in analysing 384 South African crocidolite miners, that cumulative exposure and age were associated with progressive pleural thickening. In that study most of the change

occurred with increased thickness of small plaques and the progression occurred between five and 15 years after first exposure. No progression was noted after year 15. Our analysis shows progression between years 10 and 21, roughly during the same period. An even more pronounced increase was found in the extent of pleural calcification from first to last film.

The study of Ehrlich *et al*⁶ confirms progression of pleural disease in 51%–71% of the New Jersey amosite cases with about 15%–21% of this increase representing new disease, incident or attack cases, in patients with no pleural plaques on the first film. Among our patients with pleural disease on the second film 22% were free from pleural disease on their first film representing virtually the same attack rate. This new set of incident cases could represent patients with pleural disease not initially detectable on the plain radiograph. For example, Hillerdal and Lindren¹⁵ estimated, with a necropsy series, that only 10%–15% of plaques at necropsy are visible on recent chest radiographs. The specificity of the diagnosis of plaques decreases dramatically if lesions <5 mm are included. Reader misinterpretation can be a considerable problem, however, given well documented reliability within an observer. Rossiter's study, for example, found a variance of 20%–50% in the perceived presence of pleural disease.¹⁰ It is very likely that this variance was minimised by requiring a minimum of 5 mm thickening for inclusion in this study.

The regression analysis (table 5) calculated on the first film for each reader showed a significant correlation for the presence of pleural disease only with age. On the second film, age, fibre-months of exposure, and duration of exposure are all significant, virtually the same as in the study by de Klerk *et al*.¹⁴ Age is most likely a surrogate for time elapsed since exposure, but due to the high collinearity it is not possible to statistically separate the two measures. No correlation was found for smoking or latency. When the changes from first to last film in the combined pleural indices were analysed, the time between films, fibre-months, and the duration of exposure was significant. As in other studies,^{5–16} there was no relation between progression of pleural thickening and smoking. Orlowski *et al*¹⁷ also found a correlation of presence of pleural disease with age as well as latency. Lilis *et al*¹⁸ in a study of 17 800 asbestos insulation workers found a correlation

of the pleural index only with latency and not with duration or smoking. The study of Ehrlich *et al*⁶ found that only latency closely correlated with pleural abnormality and that there was no exposure threshold for pleural plaques. In fact an average of 37% of workers with <1 month of employment had pleural disease. Given this short exposure (12.7 months) the correlation with fibre-months in this study more than likely highlights the severity of the fibre burden rather than the duration of the assault.

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