

Asbestosis as a precursor of asbestos related lung cancer: results of a prospective mortality study

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Abstract

A prospective mortality study of 839 men employed in the manufacture of asbestos cement products in 1969 examined lung cancer risk in relation to lung fibrosis seen on chest x ray film, controlling for age, smoking, and exposure to asbestos. Twenty or more years after hire, no excess of lung cancer was found among workers without radiographically detectable lung fibrosis, even among long term workers (≥ 21.5 years); nor was there a trend in risk by level of cumulative exposure to asbestos among such workers. By contrast, employees with small opacities ($\geq 1/0$; ILO classification) experienced a significantly raised risk of lung cancer (nine observed deaths v 2.1 expected), even though their exposures to asbestos were similar to the exposures of long term workers without opacities. In this population, excess risk of lung cancer was restricted to workers with x ray film evidence of asbestosis, a finding consistent with the view that asbestos is a lung carcinogen because of its fibrogenicity.

Epidemiological studies of asbestos workers have shown a dose relation with both asbestosis and risk of lung cancer (see, for example, references ¹⁻³), but few have considered the possible role of asbestosis itself in risk of lung cancer. It has been repeatedly documented that persons with asbestosis are at excess risk of developing lung cancer.⁴⁻⁷ What has been uncertain is whether this risk is directly related to the exposure to asbestos or to the lung fibrosis.

This issue is considered in a prospective mortality study which includes information on four possible determinants of lung cancer risk—namely, age, cigarette smoking, exposure to asbestos, and radiographic evidence of asbestosis. As in any study of asbestos workers, mesothelioma risk is assessed.

We are unaware, however, of a hypothesis that lung fibrosis may be causally related to the development of mesothelioma, and such a potential relation is not the focus of this study.

Population and methods

The study population consisted of all workers in two New Orleans asbestos cement manufacturing plants in 1969. Over a period of about one year, an interview and pulmonary function tests were administered and chest x ray films taken. Lung function and x ray film results in relation to exposure to asbestos have been reported previously.⁸

Information concerning the types of asbestos used in these plants and air sampling data have been described elsewhere⁹; job histories in conjunction with hygiene data were used to estimate cumulative exposures for individual subjects.

Chest x ray films were obtained for 908 workers, of which 68 were excluded from analyses: 32 retirees (a possible survivor population) and 36 women, leaving a total cohort of 840 men (roughly 88% of the 1969 employees).

Chest x ray films were classified independently in 1970-1 by three experienced readers (Benjamin Felson, John C Gilson, and Morton M Ziskind) using the International Labour Office (ILO) U/C international classification of radiographs of the pneumoconioses (1971), and without knowledge of the person's history of exposure. Of the 840 x ray films, one was judged, by the criteria of two or more readers, to be unreadable; the person was excluded from all results. By median reading for quality, of the remaining 839, eight (1%) were category 3 (poor); 638 (76%) were category 1 (optimal).

Follow up (through 1983) was performed as part of a mortality study of all persons ever employed in these plants; these results have been reported previously.⁸ For the 839 who are the subject of this report, 838 were successfully traced; of these, 154 had died. Death certificates, obtained for 153, were coded using the 8th revision of the International Classification of Diseases (the two workers either not traced or without a death certificate were aged 32 and 35 in 1969, respectively, so are unlikely to have died of lung cancer).

In the standardised mortality ratio (SMR)

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221

analyses, cause specific mortality was compared with that expected based on Louisiana rates. In these analyses, only mortality experience at least six months after the chest x ray film and 20 years from hire was considered, thus allowing sufficient latency time for any exposure induced cancers. During 1970-9, age adjusted death rates for lung cancer for the two parishes (counties) in which the plants were located were 25% and 12% higher than the overall State rate for white and non-white men respectively. The calculated SMRs are therefore likely to be somewhat inflated due to use of Louisiana rates, but parish rates were judged too unstable for use.

In comparing two SMRs, the likelihood ratio test based on the Poisson distribution was used.¹⁰

To quantitatively assess the role of smoking and other factors on the risk of lung cancer, survival analyses, based on the Cox proportional hazards model, was performed (using BMDP procedure 2L). The same workers as in the SMR analyses were included (those at least 20 years after hire during follow up), and the study period was the same (each worker entering analysis at six months after radiography or 20 years after hire, whichever was later, and follow up ending at death or at the end of 1983).

Results

The age and smoking distributions of workers in the two plants were similar in 1969. Overall, the mean age was 45.1 (range 21-68), with a mean duration of employment of 17.1 years. For cigarette smoking, 25% were ex-smokers and 52% current smokers, a prevalence similar to the 55% reported for male United States blue collar workers aged 20-64 in 1970.¹¹

Using the median reading, each film was classified into one of several mutually exclusive, ordered x ray categories; presence of large opacities (four films); small opacities without large opacities (79 films); pleural changes only (71); and no abnormalities (595). (In keeping with the 1971 classification, in which films were judged separately for irregular and rounded small opacities, films with small opacities were first classified on the basis of irregular or only rounded opacities, but subsequent mortality analyses found no relation between mortality and type of small opacity; type was therefore ignored.) As only four workers had large opacities, they were excluded from all further analyses (all died during the follow up period; the causes of death were ischaemic heart disease, asbestosis, lung cancer, and lung fibrosis).

Agreement of the x ray film readers was good: for profusion of small opacities by the three readers respectively, 94%, 94%, and 88% of the readings were within one subcategory of the median. Of the 79 films classified $\geq 1/0$ by median reading, the three readers classified 82%, 86%, and 90% of these films as $\geq 1/0$.

Table 1 Prevalence of small opacities (median reading) by cumulative asbestos exposure category

Cumulative exposure :mppcf-y,*	Years employed (mean (SD))	No in group†	Small opacities (ILO class)	
			% $\geq 1/0$	% $\geq 0/1$
<25	4.4 (3.1)	228	1.3	4.0
25-99	19.5 (5.2)	240	7.5	14.0
100-149	22.6 (3.4)	185	12.4	14.2
≥ 150	24.3 (4.3)	182	19.2	18.4
Total	17.1 (9.0)	835	9.5	11.9

*Millions of particles per cubic foot of air $\times$ years.

†Four with large opacities excluded.

Table 2 Observed (O) and expected (E) deaths 20 or more years from hire during June 1970-December 1983 (n = 646, 4897 person-years)

Cause (ICD 8th rev)	O:E	SMR (100 $\times$ O/E)
All causes	134/163.5	82.0
All malignancies (140-209):	52.39/0	133.5*
Respiratory (162-3)	26/15.4	169.0**
Mesothelioma	8	—
Larynx (161)	0/0.6	0
Buccal/pharynx (140-9)	0/1.5	0
Digestive (150-9)	6/9.2	65.0
Bladder, kidney (188-9)	2/1.4	143.2
Lymphatic (200-9)	1/2.5	39.6
Miscellaneous†	7/4.3†	164.0
Residual	2/4.1	48.8
Cardiovascular (390-448)	44/81.1	54.3
Non-malignant respiratory diseases (470-4, 480-6, 490-3)	1/5.7	17.5
Pneumoconiosis (515)	6	—
External causes (800-998)	7/12.5	55.9
Residual	24/25.2	95.2

* **Significantly elevated, Poisson one tailed test; $p = 0.02$

$p < 0.01$ (**).

†See text for definition.

‡Seven cases observed includes two liver cancers; if primary the code would be 155 bringing the observed digestive cancers closer to expected.

Primarily to assess the validation of the x ray readings, factors related to presence of small opacities were investigated. By multiple logistic regression, the presence of small opacities profusion $\geq 1/0$ was found to be significantly related to age, cigarette smoking (either pack-years or ever smoking), cumulative asbestos exposure, and plant, with a higher prevalence in plant 2 (all p values < 0.001 after accounting for the other factors). By smoking group 10.2% of current and ex-smokers (66 of 645), and 6.5% (13 of 190) of never smokers had small opacities $\geq 1/0$. By plant the percentages were 5.4% and 11.9%. Table 1 shows the prevalences of small opacities by cumulative asbestos category.

With the exception of plant, the same variables (age, smoking, and cumulative asbestos exposure) were significantly related to presence of opacities $0/1$

($p < 0.01$ for each variable after accounting for the others).

MORTALITY

Of the 154 deaths occurring during follow up, 29 were from lung cancer (all cigarette smokers), six from asbestosis, and eight from mesothelioma.

Of the total 839 x ray film participants in 1969, 646 were hired in 1963 or earlier, thus achieving at least 20 years of follow up by the end of 1983. These workers were, on average, 48.9 years old in 1969 and had been employed for 21.3 years.

Twenty or more years after hire, the SMR for all causes combined was not raised (table 2). Mortality due to cancer, however, was significantly raised (52 observed deaths *v* 39.0 expected; $p = 0.02$), as was respiratory cancer (26 *v* 15.4; $p < 0.01$). The category of miscellaneous cancers, which included secondary respiratory or digestive cancers, and cancers with no specification of site, was also raised (7 *v* 4.3), though not significantly ($p = 0.14$). Of the seven cases in this category, two were liver cancer, with no designation as to whether this was primary or secondary; if primary, they would have accounted for some of the existing deficit of digestive cancers (6 *v* 9.2).

All of the excess cancer, including respiratory cancer, occurred in the second plant, that with the

higher prevalence of small opacities. This difference in risk is consistent with that reported previously⁹ for the larger cohort of all workers ever employed in these plants (and followed up through 1981). Mortality in relation to x ray film category was, however, reasonably consistent for the two plants and potential plant factors were taken into account in all analyses. Therefore, all further results are reported for the two plants combined.

In the larger cohort, risk for cancer was found to be related to cumulative asbestos exposure.⁹ In the subset which is the subject of this report, lung cancer risk was not significantly associated with duration of employment or cumulative exposure. This may be due to a restricted range for these variables—for example, in 1969, 72% had worked in the plant for 18 to 25 years.

MORTALITY IN RELATION TO X RAY CATEGORY

Table 3 gives a description of workers with at least 20 years of follow up, classified by x ray film category. Those without abnormalities on x ray film have been divided into two groups by the median duration of employment.

Those without abnormalities but employed at least 21.5 years are reasonably comparable with those with small opacities, although there are differences as would be expected from the previously stated deter-

Table 3 Description of workers* with follow up ≥ 20 years by category of x ray film abnormality in 1969 (median reading)

	No abnormalities			Small opacities (ILO class)	
	Employed ≤ 21.5 y	Employed > 21.5 y	Pleural only	0/1	$\geq 1/0$
No	209	211	62	83	77
Age (y)	45.0 (8.4)	50.5 (6.7)	48.9 (6.5)	51.1 (7.4)	52.7 (6.4)
% Ever smokers	77	73	69	84	83
Years employed	16.6 (5.1)	24.3 (3.6)	21.6 (4.0)	23.1 (5.4)	23.4 (4.4)
Exposure concentration (mppcf)	4.7 (2.8)	6.2 (3.4)	5.2 (2.5)	6.7 (5.8)	7.5 (5.2)
Cumulative exposure (mppcf-y)	83 (60)	151 (88)	114 (54)	162 (162)	177 (126)
Years of follow up	31.1 (5.0)	37.7 (4.9)	35.0 (4.6)	36.0 (5.8)	35.5 (5.6)

*Means (SD) unless otherwise noted.

Table 4 Mortality from selected causes ≥ 20 years after hire; by category of x ray film abnormality in 1969

	No abnormalities			Small opacities (ILO class)	
	Employed ≤ 21.5 y O/E (SMR)	Employed > 21.5 y O/E (SMR)	Pleural only (n = 62) O/E (SMR)	0/1 (n = 83) O/E (SMR)	$\geq 1/0$ (n = 77) O/E (SMR)
All causes	26/39.9 (65.2)	35/61.0 (57.4)	12/15.9 (75.3)	27/23.7 (113.8)	30/22.3 (134.8)
All cancers	10/9.3 (107.7)	12/14.7 (81.8)	5/3.8 (129.9)	12/5.7 (211.1)	12/5.3 (225.6)**
Respiratory cancer	4/3.7 (109.3)	6/5.8 (103.0)	2/1.5 (133.0)	4/2.3 (177.5)	9/2.1 (432.5)**†
Mesothelioma‡	2	3	1	2	0

* **Significantly raised, Poisson distribution; $p < 0.02$ (*); $p < 0.01$ (**).

†Significantly different from corresponding risk in those without abnormalities; employed ≥ 21.5 years; likelihood ratio test.

‡Another mesothelioma death occurred after the end of follow up.

Table 5 Lung cancer deaths ≥ 20 years after hire: workers without chest x ray film abnormalities in 1969, by cumulative exposure quintiles

Cumulative exposure (mppcf-y)	No	Years worked (mean (SD))	O/E	SMR (100 $\times$ O/E)
<51	83	13.5 (6.4)	2/1.1	189.0
≥ 51 <86	86	20.5 (4.3)	1/1.9	53.7
≥ 86 <122	84	21.2 (3.7)	1/2.2	46.1
≥ 122 <170	83	22.6 (3.2)	2/2.2	90.2
≥ 170	84	24.3 (4.5)	4/2.2	183.5
Total	420	20.5 (5.8)	10/9.5	105.5

minants of small opacities. One difference is in prevalence of cigarette smoking (73% v. 83%).

Among workers with no x ray film abnormalities in 1969, the lung cancer risk was not raised (five mesotheliomas, however, were found). For the long term workers in this group, there were six lung cancers compared with 5.8 expected (table 4). By contrast, among those with small opacities, profusion $\geq 1/0$, there were around seven excess malignancies, all of them due to lung cancer; the lung cancer risk was significantly raised (9 v. 2.1; $p < 0.001$) and significantly different from the risk in long term workers without abnormalities ($p < 0.01$, likelihood ratio test).

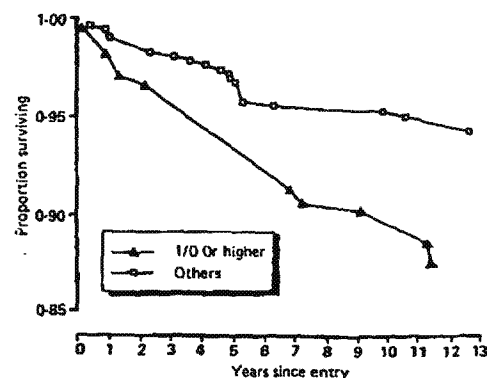
A small excess of lung cancer was found among those with small opacities 0/1 (4 v. 2.3) (as well as two mesotheliomas), but this was not a significant increase, nor was it significantly different from that of workers without abnormalities.

LUNG CANCER AMONG WORKERS WITH NEGATIVE FILMS
When lung cancer risk among the 420 workers without abnormalities was examined by quintile of cumulative exposure to asbestos, no consistent trend was seen, with the highest SMRs occurring among those in the lowest and highest quintiles (table 5). The 83 workers in the lowest category had worked in the plants for a median of 12.9 years, so the somewhat raised risk for this group is likely to be a chance occurrence, rather than the occasionally observed phenomenon of increased risk among short term workers.

SURVIVAL ANALYSIS

Survival analysis was used to determine how much of the substantial difference in risk for lung cancer between workers with small opacities ($\geq 1/0$) and those without such abnormalities on x ray film can be explained by the differences in age, smoking, and exposure. In this analysis, those with small opacities $\geq 1/0$ were compared with all others combined.

When all 642 workers were included in the analysis, the most statistically significant factors for death due to lung cancer were pack-years of smoking and age ($p < 0.01$ for each, after accounting for the other). After accounting for pack-years, age, and exposure to asbestos (both cumulative and average



Adjusted lung cancer survival curves for workers with small opacities (profusion $\geq 1/0$) and all others combined, for current and ex-smokers only.

concentration, although neither was statistically significant), x ray category was significant (one tailed $p = 0.04$). If only ever smokers are included, similar results are obtained ($p = 0.03$ for x ray category). Among ever smokers, the adjusted relative risk for lung cancer for those with small opacities $\geq 1/0$, compared with the other groups combined, was 2.88 (whereas the ratio of the SMRs for the $\geq 1/0$ workers and for all others combined was 3.6).

To illustrate these results, the adjusted survival curves for ever smokers are shown in the figure; these show the probability of not dying of lung cancer by time since entering follow up for workers with and without small opacities $\geq 1/0$, adjusted for age at pack-years of smoking.

Discussion

In this study, asbestos workers without x ray film evidence of lung fibrosis did not experience a raised lung cancer risk whereas in workers with small opacities $\geq 1/0$ it was substantially increased even though their exposures to asbestos were similar to the long term workers without opacities. These findings are consistent with lung fibrosis (asbestosis) having been a necessary precursor for asbestos induced lung cancer in this population. Workers entered and terminated follow up, on average, at 22 and 35 years after hire, respectively; 21% entered follow up more than 25 years after hire. The follow up interval therefore included the period after the start of exposure when much of the excess risk of lung cancer is likely to occur.

In any study assessing the role of asbestosis in the development of lung cancer, the exposure estimates are essential in determining if the presence of asbestosis is simply a surrogate for level of exposure. The validity of the exposure estimates in this study is supported by the fact that these estimates have previously been used to establish the dose relations between exposure and chest x ray film abnormalities,

pulmonary function reduction, and risk of lung cancer.¹⁰ Also, there is no reason to believe that they should systematically underestimate the exposures of those with positive x ray films, or overestimate the exposures of those with negative films.

The findings of our study are consistent with other epidemiological and pathological data for man on the effects of exposure to asbestos. There was evidence a decade ago that an exposure dose which resulted in excess risk of lung cancer would also produce asbestosis,¹² although this finding is also consistent with asbestosis and lung cancer being independent dose related diseases. A pathological study of lung cancer in insulators found that 82% had radiographic evidence of asbestosis, and 100% had histological evidence of fibrosis,¹³ whereas a study of London factory workers found 90% of cases to have histological evidence.¹⁴

Recently, a necropsy series of amphibole asbestos miners found that two thirds of the cases of lung cancer also had histological evidence of asbestosis, that lung cancer proportional mortality was raised only in those with asbestosis, and the severity of asbestosis was a significant factor after accounting for age, smoking, and duration of exposure.^{15,16}

On the other hand, in a study of Quebec miners and millers,¹⁷ the authors concluded that most, but not necessarily all, cases of asbestos attributable lung cancer would show opacities before death. Fibrosis could have become detectable, however, in some of the cases during the sometimes prolonged interval between x ray film and death (> 20 years for 17% of cases).

By contrast with virtually all other known human carcinogens, asbestos has been defined as non-genotoxic,¹⁸ suggesting the need for a mediating influence to explain the observed lung cancer risk.

Other forms of lung fibrosis, whether idiopathic or associated with collagen vascular disorders¹⁹ have also been associated with an increased risk of lung cancer. Silicotic subjects have been shown to experience raised risk of lung cancer, even though investigations of silica exposed workers have failed to convincingly show an overall lung cancer risk.²⁰

The current study is the latest in an emerging body of evidence supporting the view that asbestos is a lung carcinogen because of its ability to cause lung fibrosis. Nevertheless, further results in support of these findings are necessary before a firm conclusion concerning such a mechanism can be reached.

Such a mechanism for asbestos induced lung cancer would have important practical implications. Because detectable asbestosis is not likely to result from current occupational and general environmental asbestos exposures, the prevention of the effect of exposure on lung fibrosis is likely also to prevent the excess risk of lung cancer. Conversely, when asbestosis is detected in an exposed population, excess

lung cancers can be expected. Finally, these data may provide further evidence to support the common practice of attributing lung cancer to exposure to asbestos only if asbestosis is also present; otherwise, these tumours are, in most cases, due to cigarette smoking.

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