Clinical Predictors of Mortality from Asbestosis in the North American Insulator Cohort, 1981 to 1991

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Recorded mortality from asbestosis has increased markedly in the United States in recent decades, from 0.49 to 3.06 per million persons between 1970 and 1990. Although asbestosis is generally considered to be a slowly progressive disorder, little is known about how clinical and exposure parameters among individuals with asbestosis quantitatively predict subsequent risk of death from asbestosis. We followed 2,609 insulators from the North American insulator cohort 10 yr to determine cause of death and to relate clinical findings to risk of death. This group had undergone clinical and radiologic examination between 1981 and 1983 in 19 cities in the United States. Seventy-four (11.0%) of 674 deaths during the subsequent 10 yr were due to asbestosis, according to the best clinical and radiologic evidence available at the time of death. The 10 yr risk of death (expressed as a percentage) due to asbestosis rose sharply with increasing interstitial fibrosis as identified on the baseline chest X-ray, from 0.9% to 2.4%, 10.8%, and 35.4% for International Labor Office (ILO) profusion categories 0, 1, 2, and 3, respectively. Dyspnea, a low FVC, and/or physical examination findings typical of interstitial fibrosis (rales, clubbing, or cyanosis) raised the risk of subsequent death from asbestosis by 2- to 6-fold. The effect of cigarette smoking on risk of death from asbestosis was small and disappeared after adjustment for ILO profusion score. Markowitz SB, Morabia A, Lilis R, Miller A, Nicholson WJ, Levin S. Clinical predictors of mortality from asbestosis in the North American Insulator Cohort, 1981 to 1991.

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Recorded mortality from asbestosis has increased markedly in the United States during the past two decades. The age-adjusted mortality rate from asbestosis, when cited as one of multiple causes of death on the death certificate, rose 6-fold between 1970 and 1990, from 0.49 to 3.06 per million members of the United States population (1). Asbestosis was cited as a direct or as a contributing cause on 948 death certificates in the United States in 1990, as compared with only 87 deaths from asbestosis in 1970. The degree to which this trend reflects improved recognition of the disease, as opposed to an increased incidence of asbestosis, is not known.

Cross-sectional studies done in the past 15 yr show that asbestosis has a high prevalence in some sectors of the general population. Prevalence rates of radiographic interstitial opacities characteristic of asbestosis are as high as 20% to 50% among long-term workers in common occupations such as sheet-metal work, plumbing, pipefitting, insulation, and railroad and utility work, and among school custodians (2–7). That asbestosis now occurs predominantly in these trades reflects the shift in inadequately controlled workplace exposure to asbestos from the shipyard, mining, and manufacturing industries in the 1940s and 1950s to the construction and other building-related industries in the 1950s and 1960s (8, 9).

How morbidity and mortality from asbestosis interrelate, however, is still unclear. Asbestosis is generally considered to be a progressive disorder (10, 11), but little is known about how clinical and exposure parameters among individuals with asbestosis quantitatively predict subsequent risk of death from this disease. In 1980, Liddell and McDonald reported on the relative risks (RRs) of death from pneumoconiosis and other diseases in relation to chest X-ray findings in Quebec miners and millers (12). They did not report on absolute risk of death from asbestosis. More recently, Hughes and Weill evaluated the prognostic value of chest radiographs in the prediction of lung cancer among asbestos cement workers, but the cohort was small, precluding analysis of pneumoconiosis deaths (13). Numerous studies published in the 1990s have reported on longitudinal changes in pulmonary function, respiratory symptoms, and other clinical parameters among asbestos-exposed workers, but fail to relate these changes to risk of death (14–16).

The rising mortality from asbestosis, and the high prevalence of asbestosis in selected occupations, suggest that information on the risk of death from pneumoconiosis, especially in relation to routinely collected data, is timely and important.

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We report here on mortality in the 10-yr follow-up of the North American insulator cohort study (17).

METHODS

Study Population and Clinical Examination

The study population was a subset of the ongoing mortality follow-up of 17,800 asbestos insulation workers (members of the International Association of Heat and Frost Insulators and Asbestos Workers) that has been conducted since January 1, 1967. The mortality experience of the entire group over the two decades from 1967 through 1986 has been recently described (17).

In July 1981, all surviving insulators from the original cohort who had begun work as insulators 30 or more years previously were invited to participate in a clinical examination. This group included 5,355 active and retired insulation workers. Between November 1981 and November 1983, investigators from Mount Sinai School of Medicine examined 2,907 North American insulators in 19 cities in the United States. The examined population consisted of 2,077 (39%) of the 5,355 invited insulators; 436 additional insulators who had reached the 30-yr tenure criterion during the 1981-to-1983 study interval; and 394 insulators who had less than 30 yr since beginning work in the trade, but who presented themselves at the study sites.

Of the 5,355 insulators targeted for examination, 3,278 did not participate in the study (nonresponders). In a sample of 42% (1,393) of nonresponders contacted to ascertain the reasons for nonparticipation, only 17% cited illness as their chief cause for nonparticipation (18). In addition, as part of the ongoing mortality follow-up of the original cohort of 17,800 insulators, Selikoff and Seidman examined the mortality experience between July 1981 and December 1987, comparing the responding insulators (2,077) with the nonresponders (3,278) (18). Relative risks of overall mortality, lung cancer, and mesothelioma were somewhat higher in the examined group than among the nonresponders. However, the rate of death due to asbestosis, the subject of the current study, was approximately 20% higher in the nonresponders than in the examined group (18).

The final group used in the current study included 2,609 (90%) of the 2,907 insulators who were examined between 1981 and 1983. Incomplete clinical, radiographic, or pulmonary-function data precluded inclusion of 298 (10%) study participants in the current analysis.

The clinical examination that was conducted between 1981 and 1983 included occupational and medical histories, physical examinations, chest radiographs, spirometry, and selected blood tests. The study methods used have been previously described (19–22) and will be briefly summarized. Posteroanterior and lateral chest radiographs were interpreted by a single expert (NIOSH B) reader (Ruth Lilis) according to the (ILO) International Classification of Radiographs of the Pneumoconioses 1980 (23), without knowledge of the patients medical, occupational, or cigarette-smoking history. Respiratory symptoms were elicited and graded with a standard questionnaire and the criteria established by the Medical Research Council (MRC) (24–25).

Pulmonary function was assessed by spirometric testing adhering to current guidelines (26). At least three acceptable efforts were obtained for each subject. Predicted values developed and published by the Pulmonary Function Laboratory at the Mount Sinai School of Medicine were utilized (27). These predicted values closely resemble other, more widely used values (28, 29). Frequencies of abnormal values were determined for FVC by using the lower 95% confidence interval (CI) of predicted values, and for FEV_1/FVC, by using the lower limits of 0.70 for ages $\leq$ 59 yr and 0.65 for ages 60 $\geq$ yr.

Mutually exclusive spirometric categories of normal; restrictive; obstructive; combined, predominantly restrictive; and combined, predominantly obstructive, were used, according to the following definitions (22):

Normal spirometry: normal FVC, FEV_1, (FEV_1)/FVC, and forced expiratory time from 25 to 75% ($FET_{25-75\%}$) (< 0.78 s).

Restrictive: FEV $<$ 95% of lower CI, FEV_1/FVC normal.

Obstructive: FVC normal, $FEV_1/FVC < 0.70$ for ages $\leq$ 59 yr and < 0.65 for ages $\geq$ 60 yr.

Small airways dysfunction: FVC normal, FEV_1/FVC normal, $FET_{25-75\%}$ increased.

Combined, primarily restrictive: both FVC and FEV_1/FVC decreased; decrease in FVC exceeds decrease in FEV_1/FVC by two or more categories when FVC and FEV_1/FVC are quantitated as previously published.

Combined, primarily obstructive: decrease in FEV_1/FVC exceeds decrease in FVC.

Never-smokers were defined as insulators who smoked less than one cigarette per day, had smoked $\leq$ 10 cigarettes per day for $<$ 6 mo, or smoked only cigars and pipes, without inhaling. Current smokers exceeded these limits. Ex-smokers also exceeded these limits, and had discontinued smoking $\geq$ 2 yr previously.

The results of chest radiographs and pulmonary function testing of the insulators examined between 1981 and 1983 have been extensively described in previous publications (19–22).

Mortality Follow-up

Mortality in the overall cohort of 17,800 insulation workers since January 1, 1967, has been characterized (17, 30). Deaths of long-term insulators are identified by their union, the International Association of Heat and Frost Insulators and Asbestos Workers, which pays death benefits to survivors. The union notifies the study investigators at Mount Sinai of the name and address of the deceased member, and the date and location of death, and provides a death certificate, if available. If not available from the union, the death certificate is obtained from the relevant state health department. The cause of death as listed on the death certificate is categorized by an experienced nosologist. All available medical records, chest radiographs, and histology slides pertaining to the circumstances of death of the individual are obtained if they exist. These materials are reviewed at Mount Sinai and are considered the "best evidence" available for determining the cause of death. Results of the distribution of causes of death according to the death certificate versus best evidence have been reported by Selikoff and colleagues (17, 30). Selikoff published observations about the comparison of the two methods of attributing cause of death in 1992 (31). Unless otherwise specified, the cause of death reported here was determined by use of the best-evidence method. An asbestosis death in this study refers to death from parenchymal asbestosis.

Statistical Analysis

The independent variables measured at the baseline examination from 1981 to 1983 were treated categorically. Dyspnea was graded according to the MRC scale as none, minimal, moderate, or severe. Physical examination findings that were considered to be evidence of interstitial fibrosis, including the presence of rales, clubbing, and cyanosis, were analyzed dichotomously (absent versus present). As noted previously, the chest radiographs were read according to the ILO scale and were analyzed either by major category (0, 1, 2, or 3) or according to the full 11-point ILO scale (0/0, 0/1, 1/0, 1/1, 1/2, 2/1, 2/2, 2/3, 3/2, 3/3, and 3/4). A score of 0/$-$ was considered the same as 0/0. Radiographs interpreted as 0/0 and 0/1 were considered normal.

Mortality follow-up was conducted between the date of examination for each insulator and December 31, 1991. The number of person-years contributed by each insulator was calculated as the time interval between the date of the initial examination and the date of death or, for surviving study participants, December 31, 1991. Death rates were calculated as incidence densities (i.e., number of deaths divided by person-years). To convert incidence densities to cumulative incidences we used the following formula to compute the 10-yr risk of death from asbestosis: cumulative incidence $= 1 - e^{-(\text{incidence density} \times 10\ \text{yr})}$ (32). The overall number of deaths (n = 74) precluded estimation of the different risks by year of follow up. Thus, the 10-yr risk of death from asbestosis is the average incidence density multiplied by 10 yr. RRs were determined as the ratio of death rates by using normal as the reference category. The method of Breslow and Day (33) was used to calculate 95% CIs for the unadjusted relative risks.

Age and multivariate-adjusted relative risks, and their 95% CIs, were obtained using the Cox proportional hazard analysis (proc PHREG). SAS/PC for Windows (SAS Institute, Cary, NC) was used to perform all statistical procedures (34).

RESULTS

Table 1 summarizes the clinical and exposure status of the study group at examination from 1981 to 1983. The group mean age was 57.5 yr (± 8.1 yr SD). As determined according to the study criteria, most (72%) of the study participants had worked with asbestos for at least 30 yr prior to examination. Eighty percent had a history of cigarette smoking. The prevalence of asbestosis in this group of insulators was high. Sixty percent (1,557) had radiographic opacities characteristic of asbestosis, although only 13% (347) of the overall group had radiographic opacities that were rated as profusion categories 2 or 3 on the ILO scale. Other clinical and physiologic parameters of asbestosis were only slightly less common. Forty-four percent (1,142) of the study group had a low FVC; 47% (1,234) reported dyspnea; and 58% (1,522) had rales, clubbing, or cyanosis, findings that are associated with interstitial fibrosis. Most (82%) had a normal FEV_1/FVC. Additional details on the radiographic and physiologic findings in the study group had been previously published (19–22).

From 1981 to 1991, a total of 674 insulators died, including 74 (11%) whose cause of death was asbestosis. The mean age of death among insulators dying from asbestosis was 65.9 yr (SD = 8.6 yr), and the median was 67 yr, respectively. Approximately one-third of asbestosis deaths occurred in each of the following decades of age: 50 to 59 yr (23 deaths or 31%), 60 to 69 yr (22 deaths, or 30%), and 70 to 79 yr (23 deaths or 31%). Increasing age was significantly related to risk of death from asbestosis.

Among the 74 asbestosis deaths, the death certificate cited asbestosis as the cause of death in 37 (50%). For the remaining 37 insulators, the death certificates specified the following causes of death: cardiovascular and cerebrovascular diseases (17 deaths, or 23%), chronic obstructive lung disease (10 deaths, or 13.5%), influenza or pneumonia (five deaths, or 6.8%), and other lung diseases (five deaths, or 6.8%).

Table 2 provides the 10-yr risks and relative risks of death from asbestosis according to the findings on the chest X-rays at baseline examination. Insulators without radiographic evidence of asbestosis (ILO Category 0) had approximately a 1% risk of death from asbestosis during the subsequent 10-yr of follow-up. As expected, 10-yr risk of death increased with higher ILO profusion categories from 2.4% for Category 1, to 10.8% for Category 2, and to 35.4% for insulators with ILO Category 3 profusion. The relative risks of death from asbestosis for each major ILO category further reflect these increases. Note that the change in RRs between adjacent ILO categories (i.e., between 0 and 1, 1 and 2, and 2 and 3) is of similar magnitude on a multiplicative scale.

Table 2 also shows asbestosis death risks and relative risks according to the full 11-point ILO profusion scale applied to the chest X-rays of insulators at baseline examination. There is a clear upward trend in 10-yr mortality risks and accompanying RRs, using 0/0 as the reference category (chi-square for trend = 111.3, $p < 0.0001$). Figure 1 illustrates this trend as well. Indeed, with the sole exception of category 3/2, each ILO subcategory within each ILO major category (i.e., 1, 2, and 3) differs in the expected manner from the adjacent subcategory.

TABLE 1

BASELINE CHARACTERISTICS OF 2,609 NORTH AMERICAN INSULATORS EXAMINED IN 1981 TO 1983

Variable			
Age, mean (interquartile range), yr		57.5	(53–62)
Duration of exposure to asbestos			
Mean (interquartile range), yr		31.6	(29–36)
< 30 yr	n (%)	735	(28.2%)
30–39 yr	n (%)	1,533	(58.8%)
≥ 40 yr	n (%)	341	(13.1%)
Duration from onset of exposure to asbestos			
Mean (interquartile range), yr		35.1	(31–40)
< 30 yr	n (%)	341	(13.1%)
30–39 yr	n (%)	1,613	(61.8%)
≥ 40 yr	n (%)	655	(25.1%)
Cigarette-smoking history			
Never	n (%)	515	(19.7%)
Past	n (%)	1,220	(46.8%)
Current	n (%)	874	(33.5%)
Radiographic abnormalities			
Parenchymal opacities (ILO profusion categories)			
Category 0	n (%)	1,052	(40.3%)
Category 1	n (%)	1,210	(46.4%)
Category 2	n (%)	269	(10.3%)
Category 3	n (%)	78	(3.0%)
Pleural abnormalities			
Absent	n (%)	721	(27.6%)
Present	n (%)	1,888	(72.4%)
Pulmonary function abnormalities			
FVC, % pred			
Normal	n (%)	1,467	(56.2%)
Low	n (%)	1,142	(43.8%)
FEV_1/FVC, % pred			
Normal	n (%)	2,143	(82.1%)
Low	n (%)	466	(17.9%)
Dyspnea, MRC grade			
None	n (%)	1,375	(27.3%)
Minimal	n (%)	711	(27.3%)
Moderate	n (%)	259	(9.9%)
Marked	n (%)	264	(10.1%)
Physical examination findings			
Rales	n (%)	1,195	(45.8%)
Clubbing	n (%)	709	(27.2%)
Cyanosis	n (%)	120	(4.6%)
Any of the above	n (%)	1,522	(58.3%)
None of the above	n (%)	1,087	(41.7%)

TABLE 2

TEN YEAR RISKS AND RELATIVE RISKS OF ASBESTOSIS DEATH ACCORDING TO BASELINE RADIOGRAPHIC FINDINGS OF 2,609 NORTH AMERICAN INSULATORS

Radiographic Abnormalities	Asbestosis Deaths	Person-years	Ten-year Risk of Death (× *100*)*	Crude Relative Risk	Age-adjusted Relative Risk	95% CI
Parenchymal opacities, ILO profusion categories						
Category 0	8	9,162	0.87	1†	1†	—
Category 1	25	10,019	2.4	2.8	2.0	0.9–4.4
Category 2	22	1,916	10.8	12.5	8.1	3.6–18.2
Category 3	19	435	35.4	40.7	31.2	12.9–75.3
Parenchymal opacities, full ILO classification						
0/0	3	3,680	0.81	1†	1†	—
0/1	5	5,482	0.91	1.1	0.9	0.2–3.9
1/0	5	3,882	1.3	1.6	1.1	0.3–4.6
1/1	14	5,118	2.7	3.3	2.1	0.6–7.3
1/2	6	1,019	5.7	7.0	3.4	0.9–13.6
2/1	4	641	6.0	7.4	4.1	0.9–18.3
2/2	12	1,048	10.8	13.3	7.6	2.1–26.9
2/3	6	227	23.2	28.6	20.1	5.0–80.4
3/2	4	204	17.8	21.9	14.1	3.2–63.0
3/3	11	201	42.1	51.9	39.4	11.0–141
3/4	4	30	73.6	90.7	60.7	13.6–271
Pleural abnormalities						
Absent	8	6,183	1.3	1†	1†	—
Present	66	15,348	4.2	3.3	2.1	1.0–4.4

* Ten-year risk of death = $1 - e^{-(\text{incidence density} \times 10)}$ (expressed as a percentage), where incidence density = asbestosis deaths/person-years.

† Reference category.

This occurs despite the small numbers of deaths in each ILO subcategory.

When considered as a dichotomous variable, pleural abnormalities associated with asbestos exposure confer a limited increase in risk of death from asbestosis, with a relative risk of 2.1 (Table 2). However, after inclusion in a multivariate model with age and parenchymal opacities, the RR reduces to 1.5 and is no longer significant ($p = 0.55$).

Parameters of asbestosis other than radiographic abnormalities also predict subsequent death from asbestosis although not as strongly as profusion of opacities visible on chest X-ray (Table 3). A low FVC, but not a low FEV_1/FVC, increases the risk of death from asbestosis by 6-fold. Any report of dyspnea as measured by the MRC scale is also associated with a significant increase in risk of mortality from asbestosis though most sharply for insulators reporting marked shortness of breath (Table 3). In addition, any finding of rales, clubbing, or cyanosis on physical examination increases the risk of death from asbestosis, with an age-adjusted RR = 4.0 ($p = 0.0001$). The magnitude of increase in the age adjusted RR of asbestosis mortality for all clinical parameters other than chest X-ray (i.e., abnormal vital capacity, symptoms, and signs) was similar, ranging from 2 to 6 RR.

After adjustment for age, insulators who were still smoking at the time of examination from 1981 to 1983 had an increased risk of death from asbestosis (RR = 2.2, 95% CI = 1.1, 4.3). A smaller increase was also seen among ex-smokers, although this increase did not achieve statistical significance (RR = 1.3; 95% CI = 0.7, 2.4) (Table 3).

Chest X-ray findings of irregular interstitial opacities at the lung bases are more specific for the diagnosis of asbestosis than are a low FVC, dyspnea, or rales, cyanosis, and clubbing, and show higher RRs of subsequent death from asbestosis than do the latter parameters. It is therefore of interest to evaluate whether clinical data for pulmonary function, symptom review, and physical examination contribute additional information about risk of death from asbestosis once the X-ray findings are known. Table 4 shows selected results of stratification by all four parameters of asbestosis: chest X-ray profusion, FVC, dyspnea, and physical findings. Insulators who had a normal chest X-ray at baseline (ILO Category 0) but who had a low FVC, reported dyspnea, and had physical-examination findings associated with interstitial fibrosis experienced a subsequent 10-yr cumulative risk of asbestosis death of 6.1%. This rate was 21 times higher than all other insulators whose chest X-rays were free of parenchymal opacities at baseline and who had any other combination of findings on pulmonary function testing, symptom review, and physical examination. Indeed, six of the eight insulators whose baseline chest X-rays were of ILO profusion Category 0 and who subsequently died from asbestosis during the 10-yr follow-up period had a low FVC, were dyspneic, and had rales, clubbing, or cyanosis (Table 4). Conversely, of the 459 insulators (contributing 4,121 person-years) with Category 0 or 1 profusion on chest X-ray but whose FVC and physical examination were normal and who were not dyspneic, none died from asbestosis during the subsequent 10-yr (not shown in Table 4).

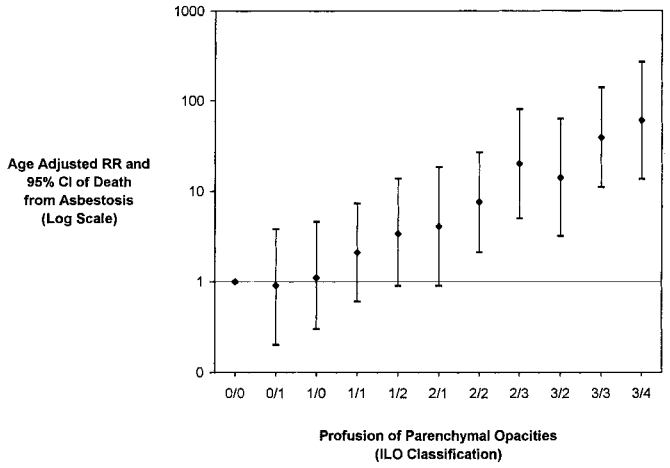

Figure 1. Age-adjusted relative risks and 95% confidence intervals for death from asbestosis in 10-yr follow-up according to profusion of parenchymal opacities at baseline examination.

Of interest are the clinical, pulmonary function, and radiologic details in the 1981 to 1983 baseline examination of the eight insulators whose chest radiographs were read as ILO Category 0 at baseline examination and who subsequently died from asbestosis. All but one had moderate to marked dyspnea at baseline examination. Four of these insulators never smoked cigarettes, and an additional two had quit smoking 20 or more years prior to examination. Seven of the eight insulators had FVC values $< 60\%$ predicted (range: 37% to 58% predicted), and six of the eight insulators had FEV_1/FVC values above 75%. Although free of parenchymal opacities on chest X-ray, four of the eight insulators had advanced pleural scarring bilaterally, and all but one had at least some pleural thickening on chest X-ray.

A more detailed categorical analysis of the relationship between pulmonary-function abnormality and mortality from asbestosis is provided in Table 5. As expected, the presence of a restrictive impairment increases the subsequent cumulative risk of death from asbestosis to 5.9% during the 10-yr period. Obstructive impairment only slightly increases the RR of asbestosis death (RR = 1.7), and this increase is not statistically significant. Interestingly, the RR associated with asbestosis among insulators who had combined restrictive and obstructive lung disease from 1981 to 1983 (RR = 10.1) was a multiplicative product of the risks for each of the groups with restrictive (RR = 6.1) or obstructive impairment (RR = 1.7) alone. On a multiplicative scale, there was no evidence of synergism between these two types of profiles of lung impairment, though the small numbers of asbestosis deaths among insulators with obstructive impairment alone confers substantial imprecision. When combined disease is predominantly of one type or the other, the associated subsequent 10-yr risk of death and RRs are the expected direction and magnitude, given the previously described findings (Table 5).

Table 6 provides the results of the proportional hazards analysis for all relevant clinical, exposure, and radiographic variables. Although the magnitude of the RRs associated with these variables differs from the results of the univariate analysis, the direction and relative importance of the risks remain similar. RRs of death from asbestosis associated with radiographic opacities, a low FVC physical examination findings consistent with interstitial fibrosis, and dyspnea remain excessive, whereas no excess risks are seen with pleural fibrosis, a history of cigarette smoking, or duration from onset of exposure to asbestos in the multivariate model. After radiographic opacities, a low FVC demonstrated the strongest RR of death from asbestos during the subsequent 10-yr (RR = 3.7)

DISCUSSION

Asbestosis continued to be a significant cause of death among North American insulators in the 1980s and early 1990s. In-

TABLE 3

TEN YEAR RISKS AND RELATIVE RISKS OF ASBESTOSIS DEATH ACCORDING TO CLINICAL, PHYSIOLOGIC, AND EXPOSURE CHARACTERISTICS OF 2,609 NORTH AMERICAN INSULATORS

Clinical or Exposure Variable	Asbestosis Death	Person-years	Ten-year Risk of Death (× *100*)*	Crude Relative Risk	Age-adjusted Relative Risk	95% CI
Pulmonary function abnormalities						
FVC, % pred						
Normal	13	12,653	1.0	1†	1†	—
Low	61	8,878	6.6	6.5	5.6	3.1–10.2
FEV_1/FVC						
Normal	57	17,938	3.1	1†	1†	—
Low	17	3,953	4.2	1.3	1.3	0.8–2.2
Dyspnea, MRC grade						
None	18	11,821	1.5	1†	1†	—
Minimal	20	5,805	3.4	2.2	2.0	1.1–3.8
Moderate	9	2,088	4.2	2.8	2.7	1.2–6.0
Marked	27	1,817	13.8	9.1	6.9	3.8–12.5
Physical examination findings‡						
Normal	9	9,483	0.94	1†	1†	—
Abnormal	65	12,049	5.3	5.6	4.0	2.0–8.0
Cigarette smoking						
Never	13	4,466	2.9	1†	1†	—
Past	38	10,080	3.7	1.3	1.3	0.7–2.4
Current	23	6,986	3.2	1.1	2.2	1.1–4.3
Duration from onset of exposure to asbestos						
< 30 yr	2	3,067	0.6	1†	1†	—
30 to 39 yr	28	13,515	2.0	3.1	1.3	0.3–5.5
≥ 40 yr	44	4,950	8.5	13.1	1.8	0.4–7.4

* Ten year risk of death = $1 - e^{-(\text{incidence density} \times 10)}$ (expressed as percentage), where incidence density = asbestosis deaths/person-years.
† Reference category.
‡ Abnormal physical examination is defined as the presence of rales, clubbing, or cyanosis.

deed, the percentage of the deaths due to asbestosis in this subset of the larger cohort of 17,800 insulators, 11%, was somewhat higher than the 9.4% of deaths due to asbestosis during the first decade of study of the full cohort of 17,800 insulators, from l967 to 1976. Since most of the insulators examined from 1981 to 1983 had previously worked as insulators for ⩾ 30 yr (i.e., mostly in the 1950s and 1960s), the continued deaths from asbestosis reflect the failure to control ambient levels of asbestos in the workplace until the 1970s.

Insulators die from asbestosis at a relatively young age. Only one-half reach the traditional retirement age of 65 yr, and a third of asbestosis deaths among insulators occur while they are still in their 50s.

Not surprisingly, the demonstration of irregular interstitial opacities on chest radiography is not only the most specific sign of asbestosis, it is also the best predictor of subsequent death from asbestosis. The 10-yr risk of asbestosis death for insulators with ILO Category 2 or 3 profusion is high. The cu-

TABLE 4

RISK OF DEATH FROM ASBESTOSIS BY INTERACTION OF CLINICAL AND PHYSIOLOGIC PARAMETERS

CXR Profusion	Clinical Presentation			No. Deaths/ No. Person-years	Ten-year Risk of Death (× *100*)*	Age-adjusted Relative Risk	95% CI
0	Low FVC	+ Dyspnea	Abnormal physical examination†	6/961	6.05	21.0	4.2–104.0
		All others		2/8,200	0.24	Reference	
1	Low FVC	+ Dyspnea	Abnormal physical examination†	13/1,472	8.45	5.4	2.5–11.8
		All others		12/8,546	1.39	Reference	
2	Low FVC	+ Dyspnea	Abnormal physical examination†	12/752	14.75	2.0	0.86–4.6
		All others		10/1,164	8.23	Reference	
3	Low FVC	+ Dyspnea	Abnormal physical examination†	12/207	43.99	1.7	0.67–4.3
		All others		7/229	26.34	Reference	

* Ten-year risk of death = $1 - e^{-(\text{incidence density} \times 10)}$ (expressed as a percentage), where incidence density = asbestosis deaths/person-years.
† Abnormal physical examination is defined as the presence of rales, clubbing, or cyanosis.

TABLE 5

TEN YEAR RISKS AND RELATIVE RISKS OF ASBESTOSIS DEATH ACCORDING TO CATEGORY OF IMPAIRMENT OF PULMONARY FUNCTION

Category of Impairment*	Asbestosis Deaths	Person-years	Ten-year Risk of Death ($\times$ 100)†	Age Adjusted Relative Risk	95% CI
None	5	6,556	0.8	—	—
Small airways only	5	3,965	1.3	1.3	0.4–4.5
Restrictive	41	6,733	5.9	6.1	2.4–15.4
Obstructive	3	2,131	1.4	1.7	0.4–7.1
Combined: total	20	2,145	8.9	10.1	3.8–26.9
Combined: predominantly restrictive	17	1,571	10.3	12.8	4.7–34.7
Combined: predominantly obstructive	3	574	5.1	4.6	1.1–19.2

* Numeric definitions of categories are provided in the method section.

† Ten-year risk of death $= 1 - e^{-(\text{incidence density} \times 10)}$ (expressed as a percentage), density = asbestosis deaths/person-years.

‡ Reference category.

mulative risk of death from asbestosis for insulators with Category 3 disease is 35%. However, since only 347, or 13%, of insulators had advanced asbestosis, the overall number of asbestosis deaths among insulators during the subsequent 10-yr was limited.

The 10-yr cumulative risk of death from asbestosis among insulators whose chest films showed no or only slight asbestosis was lower than that for insulators with more advanced disease, but was still appreciable, at 1% for insulators with ILO Category 0 and 2.4% for insulators with ILO Category 1 asbestosis. Both levels of risk rose markedly if the insulator had other evidence of interstitial fibrosis (dyspnea, low 30 FVC, and rales, clubbing, or cyanosis), to 6.1% for insulators with ILO Category 0 and 8.5% for insulators with ILO Category 1 asbestosis. This consistency of prognostic findings among the four clinical parameters of asbestosis contributes to the plausibility of the study results.

Liddell and McDonald similarly found that a number of Quebec miners and millers who had chest X-rays free of visible small opacities subsequently died from asbestosis (12). Of 31 pneumoconiosis deaths in their cohort, one-half (l6) had a profusion of small opacities less extensive than that of major ILO Category 2 or 3 on the chest X-ray taken when they were still alive. Specifically eight workers had no evidence of small opacities on their last previous radiograph, two workers had 0/1 profusion, and six workers had 1/1 or 1/2 profusion of small opacities on the chest radiograph. Liddell and McDonald did not specify the time interval between chest X-ray and subsequent death in their study (12). Other limitations of their study included the use of death certificates, the use of the chest radiograph as the sole predictive clinical tool, and failure to report absolute risks of death from asbestosis.

It is well known that the chest radiograph may underestimate the degree of interstitial fibrosis determined to be present pathologically (35). Indeed, the chest X-ray can be normal even in the face of severe interstitial fibrosis. Kipen and colleagues reported on the concordance of asbestosis measured radiographically and pathologically in long-term insulators who had died of lung cancer (36). They found that 23 of 25 insulators who had chest X-rays without definite evidence of parenchymal opacities (ILO Categories 0/0 or 0/1) had moderate to severe interstitial fibrosis on histologic examination of nonmalignant lung tissue. Such findings lend credibility to our finding that a significant number of the insulators in our study who died from asbestosis had a chest X-ray that was scored as a ILO Category 0 or 1 within 10-yr before their deaths.

Although the nonradiographic parameters of asbestosis (pulmonary function, respiratory symptoms, and findings on physical examination) were less useful than the chest X-ray in predicting subsequent death from asbestosis, the excess risks associated with these factors remained after adjustment for radiographic findings. Considered as a group, low FVC, dyspnea, and the presence of rales, clubbing, or cyanosis were most informative about subsequent risk of death from asbestosis when the chest X-ray showed no or a slight degree of small opacities. The overall number of 74 deaths from asbestosis, although large for a single asbestos-exposed cohort, was too limited to provide useful results when all four parameters were each stratified by even a small number of ILO categories (i.e., 2 to 4).

The strikingly consistent trend of increasing risk of death with increasing profusion of small irregular opacities as scored on the 11-point ILO scale (Table 2 and Figure 1) serves as a measure of validity in multiple ways. It validates the ILO classification system, since the study results show that the distinctions in degree of profusion accurately segregate risk of the most important outcome of asbestosis: death. Second, the expert reader who interpreted the films in our study appears to have applied the ILO classification system in a meaningful way, since her readings, even within major categories, accurately predict risk of death from asbestosis. The careful distinctions made by the occupational-medicine clinicians and

TABLE 6

COX PROPORTIONAL HAZARDS ANALYSIS OF EXPOSURE, RADIOGRAPHIC, AND CLINICAL VARIABLES IN RELATION TO SUBSEQUENT RISK OF DEATH FROM ASBESTOSIS

Variable	Estimate of β	Standard Error of β	Risk Ratio	95% CI
Age, yr	0.112	0.018	1.1	1.08–1.16
ILO Category 1	0.529	0.413	1.7	0.75–3.81
ILO Category 2	1.520	0.430	4.6	1.97–10.62
ILO Category 3	2.736	0.451	15.4	6.37–37.34
Pleural fibrosis	0.225	0.380	1.3	0.59–2.64
Dyspnea	0.641	0.279	1.9	1.10–3.28
Rales, clubbing, or cyanosis	0.660	0.376	1.9	0.93–4.04
Low FVC	1.315	0.312	3.7	2.02–6.87
Smoking, current and past	−0.191	0.241	0.8	0.52–1.32
Duration from onset of asbestos exposure, 30 to 39 yr	−0.219	0.743	0.8	0.19–3.45
Duration from onset of asbestos exposure, ≥ 40yr	0.017	0.766	1.0	0.27–4.56

radiologists, who are trained and proficient in reading chest X-rays according to the ILO classification system, yield vital information about the prognosis for the patient with asbestosis or at risk for asbestosis.

Additionally, the clear-cut relationship between ILO score and risk of death implies that the best-evidence method of identifying asbestosis deaths, used by Selikoff and colleagues for many years (17, 30), truly identifies such deaths. If deaths from other causes, especially chronic obstructive lung disease, had been misclassified as asbestosis deaths, then one would hardly have expected to see the very consistent stepwise trend of increasing deaths from asbestosis with increasing profusion of irregular opacities evident in Table 2. Clearly, comorbidity with cardiovascular disease and other pulmonary diseases plays a role in causing death in many cases of asbestosis. However, the validity of labeling such deaths as asbestosis in the present study is borne out of the results shown in Table 2.

The validity of the assignment of asbestosis as the cause of death on the basis of the best available evidence is further supported by the clinical and physiologic profiles of the eight insulators whose chest X-rays did not show asbestosis at baseline but who nonetheless died from asbestosis within the next 10-yr. Despite the chest X-ray results, nearly all of these eight insulators had moderate to marked dyspnea, and most showed a restrictive or predominantly restrictive impairment of pulmonary function. Six of the eight never smoked or had ceased smoking 20 or more years previously. As a group, the eight workers neither demonstrated a high risk for chronic obstructive lung disease nor showed much evidence of it at baseline examination. To the contrary, except for the X-ray results, their clinical and physiologic profile was quite characteristic of significant asbestosis. Hence, it seems unlikely that they died from chronic obstructive lung disease that was misclassified as asbestosis.

That only 50% of deaths from asbestosis identified through the use of the best available evidence were also identified on death certificates implies that routinely collected mortality data understate the true number of deaths from asbestosis. If there were any single occupational group for whom there should have existed a high index of suspicion of asbestosis in the 1980s, it would have been insulators. The recognition of asbestosis as a cause of illness and of death is probably even less for other asbestos-exposed workers. Despite the recent rise in recorded asbestosis mortality (1), which suggests improved recognition, underdiagosis of asbestosis as a cause of death remains a serious problem.

Asbestos-exposed workers who smoke cigarettes tend to have higher scores for profusion of irregular opacities on their chest X-rays (6, 22). In the current study, the impact of cigarette consumption on mortality from asbestosis was very limited in the univariate analysis and disappeared in the multivariate analysis. Its relation to asbestosis mortality is captured by the relationship between the appearance of interstitial fibrosis on the chest X-ray and subsequent asbestosis mortality. Cigarette smoking has no independent impact on risk of death from asbestosis. In their study of Quebec miners and millers, Liddell and McDonald also found no excess risk of death from pneumoconiosis associated with cigarette smoking (12).

The present study had a number of limitations. The possibility of selection bias is raised by the relatively low participation rate of insulators (40%) who were invited to the 1981 to 1983 survey. Nonparticipants were subsequently followed by Selikoff and Seidman (18), and were found to have a 20% higher rate of death from asbestosis than the group included in the current study. Hence, the overall risk of death from asbestosis among insulators is underestimated in the present study. Indeed, if insulators with more advanced asbestosis tended to stay home during the study because of illness, the risks of death from asbestosis among insulators with ILO Category 2 or 3 profusion on chest X-ray, dyspnea, a low FVC, and/or abnormal physical examination would have been higher than found in the current analysis.

In conclusion, we quantified the risk of death from asbestosis in a group of workers heavily exposed to asbestos, and related this risk to easily obtained clinical parameters. To our knowledge, this is the first study to have done so. The risk of mortality from all asbestos-related diseases, including cancer, for this heavily exposed cohort is considerably higher than the risk of death from asbestosis alone. In combination with knowledge about asbestos-related cancer risk, the current analysis should lead to improved counseling of patients with asbestosis about their prognosis and the need for preventive pulmonary care, including prompt treatment of respiratory infections, vaccination against pneumonia and influenza, and smoking cessation.

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