



Cancer Mortality among Workers Exposed to Amphibole-free Chrysotile Asbestos

PLAINTIFF'S EXHIBIT

SA-501

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The issue of whether exposure to chrysotile asbestos alone, without contamination from amphibole asbestos, causes lung cancer and mesothelioma was investigated in a 25-year longitudinal study (1972–1996) in Chongqin, China. The study cohort comprised 515 male asbestos plant workers exposed to chrysotile only; the control cohort included 650 non-dust-exposed workers. The results of analysis in which the proportional hazards model was used indicated that mortality due to all causes, all cancers, and lung cancer was related to asbestos exposure; the relative risks, adjusted for age and smoking, were 2.9, 4.3, and 6.6, respectively. Fiber concentrations in the raw material section and the textile section of the plant were 7.6 and 4.5 fibers/ml, respectively. Because of differences between the study and control plants, the authors also compared various sections of the asbestos plant that had different levels of dust exposure. The adjusted relative risk of lung cancer was 8.1 for workers exposed to high versus low levels of asbestos. Two cases of malignant mesothelioma, one pleural and the other peritoneal, were found in the asbestos cohort. These results suggest that heavy exposure to pure chrysotile asbestos alone, with negligible amphibole contamination, can cause lung cancer and malignant mesothelioma in exposed workers. *Am J Epidemiol* 2001;154:538–43.

asbestos; longitudinal studies; lung neoplasms; mesothelioma; occupational exposure; smoking

Asbestos is a commercial group of natural mineral fibers that mainly comprises chrysotile and the amphibole subgroup of asbestos. The Commission of the European Communities recently adopted a directive that obliges member states to prohibit the marketing and use of chrysotile asbestos, a directive similar to that previously applied to amphibole blue asbestos crocidolite (1). Initial reports of the risk of lung cancer (2) and mesothelioma (3) among asbestos workers have been confirmed in subsequent occupational studies (4, 5). In some studies, however, workers exposed to only chrysotile asbestos have shown no increased risk of lung cancer (6–8). As a consequence, researchers have implicated not chrysotile per se but a contaminant amphibole fiber as the specific cause of lung cancer (9) and malignant mesothelioma (10, 11). Another extensive study of a textile plant in which only chrysotile is used found a clearly increased incidence of lung cancer (12). The reasons for the apparent discordance in the results might be

due to a number of confounding factors, for example asbestos fiber type, job type, exposure duration, smoking effect, and epidemiologic methodology (13, 14). To study mortality due to lung cancer and mesothelioma in workers exposed to chrysotile alone, we undertook a prospective cohort study in an asbestos plant in Chongqin, China, controlling for several important confounding factors. Previous dust analysis had shown that a virtually pure form of chrysotile asbestos was used exclusively throughout the plant.

MATERIALS AND METHODS

A prospective, fixed cohort was established in the asbestos plant. The plant opened in 1939 and, since 1958, has greatly expanded both in size and variety of products; 6,000 tons of raw asbestos were used in 1996. In the 1970s, the products were classified into textiles, asbestos-cement products, friction materials, rubber products, and heat-resistant materials. Only chrysotile asbestos obtained from two mines in Sichuan, China, has been used in the plant.

The amphibole contamination in commercial chrysotile has been assessed by N. Kohyama (National Institute for Industrial Health, Kawasaki, Japan, personal communication, 2000). He used the x-ray diffraction analysis and analytical transmission electron microscopy method, which can detect amphibole contamination of 0.001 percent or more. Four commercial samples, derived from the two mines in Sichuan and used exclusively in the Chongqin chrysotile asbestos plant, were shown to contain less than 0.001 percent of tremolite fiber.

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Abbreviations: CI, confidence interval; RIR, relative risk.

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In spite of several attempts to improve the workplace environment in the Chongqin plant, poor ventilation and improper personnel protection were still evident, and workplace smoking was not prohibited. No regular measurement of airborne fiber concentration had been instituted, but respirable dust concentration was measured every 4 years. Records showed that the general dust concentration far exceeded the Chinese national standard of 2 mg/m^3 . To determine the fiber exposure of workers, airborne dust and fiber concentrations were measured from personal samplers that workers wore for 3 days in June 1999. For each worker, triplicate measurements were performed, and as many as five workers in each asbestos plant section were monitored.

In January 1972, 754 workers were actively working in the asbestos plant; none had any signs of serious disease. Of this group, all 130 females and 109 males who by that time had worked there for less than 1 year were excluded. Finally, 515 men were selected for the study cohort and were followed up for 25 years (from January 1, 1972, to December 31, 1996). None of the workers employed after January 1, 1972, was included in the cohort (15). In the plant, workers were grouped into seven major job categories: office, asbestos cement, textile, maintenance, raw material, rear service, and rubber (friction) plate.

An electronics manufacturing plant located in the suburbs of Chongqin, comparable—except for asbestos exposure—in terms of socioeconomic, geographic, and working conditions, was selected as a control. The original control population contained 1,239 workers, none of whom had any signs of malignant tumors. After we excluded 535 females, 28 workers who had worked there less than 1 year by January 1, 1972, and 26 workers who had been exposed to workplace dust, 650 male workers were finally selected for the control cohort. They were followed concomitantly with the asbestos study cohort for 25 years.

The vital status of every cohort member was determined annually by using the personnel records maintained at the plant. Information was recorded on death, leave, retirement, and development of a malignant tumor. Mortality records were kept in the personnel section of the plant, and causes of death were also checked in the plant and in municipal hospitals.

The jobs of most of the workers in each plant were relatively stable during the entire follow-up period. No major job changes occurred, but 20 asbestos workers and 33 control group workers left the plants before retirement. The vital status of these workers was followed up by interviewing their close friends or relatives. A majority of the cohort members retired during the follow-up period, but they continued to live in company housing and come to the plant every month to receive their pension. Consequently, information on the vital status of the workers who had retired was also readily obtained. Five control workers could not be followed up. Those lost-to-follow-up workers were eliminated from the analysis (16).

When the two cohorts were compared, the relative risks of death from all causes, all cancers, and lung cancer were calculated by using the Cox proportional hazards model (17); the starting time for each worker was set as the time of

initial employment. Since there were significant differences in the age distribution and smoking habits between the two cohorts, multivariate analyses were used to calculate the adjusted relative risks. The three dependent variables of death from all causes, all cancers, and lung cancer were coded dichotomously and were analyzed separately in the calculations. Among the three independent variables asbestos exposure and smoking were coded dichotomously considering that the number of workers who had quit smoking during the observation period was small (three in the asbestos cohort and five in the control cohort). Age at the starting time of observation (January 1, 1972) was used directly in the calculations. For the cases of lung cancer those confirmed by pathologic examination were analyzed separately. To examine the different risks for the seven worker job categories, the relative risk of lung cancer for each category was calculated by using dummy variables. In addition, we compared the various sections of the asbestos plant for three groups of workers exposed to high, intermediate, and low levels of asbestos fibers. All calculations were performed by using PC-SAS, version 6.12 software (SAS Institute, Inc., Cary, North Carolina), and the statistical significance level was set at $p < 0.05$, unless otherwise noted.

RESULTS

Table 1 shows the geometric mean fiber and dust concentrations in the major sections of the asbestos plant. In selecting particular workers to wear the personal sampler for dust and fibers, we tried to choose those who had the higher exposure level in each section of the plant. However, the results varied widely depending on the individual work and the type of operation performed. The highest fiber concentration was found in the raw material section, especially in the bagging operation. The second-highest fiber concentration was found in the textile section, where carding, spinning, and weaving were performed. There was an apparent discordance between the concentrations of airborne dust and fibers.

TABLE 1. Concentrations of fiber and dust for workers in major sections of the Chongqin, China, asbestos plant, by job category, 1999*

Job category	Fiber (fibers/ml (range))	Dust ($\mu\text{g}/\text{m}^3$ (range))
Raw material (opening)	8.5 (5.8–7.5)	8.8 (8.1–12.3)
Raw material (bagging)	12.6 (5.2–58.4)	18.2 (14.5–22.4)
Rubber plate†	2.8 (2.6–3.1)	237.5 (178.0–320.5)
Textile	4.5 (0.7–17.0)	22.4 (15.8–35.5)
Asbestos cement‡	0.1	22.3

* Geometric mean (range) for three to five workers exposed in each asbestos plant section.

† In the rubber plate section, workers were engaged mainly in dumping mica and various raw materials into a pit in a small room without ventilation.

‡ In the asbestos cement section, the number of workers in the dust environment was small, and only one worker who was engaged in dumping raw materials into the pit was monitored.

The basic characteristics and the proportions of death from major causes for the two cohorts are shown in table 2. Cancer was the leading cause of death in both cohorts. Fifty workers in the asbestos group developed malignant tumors, and lung cancer was the most common, followed by liver cancer (11 cases). Eleven control workers developed cancer (during the follow-up period), but the proportion of lung cancer was the same as that of liver cancer. Other types of cancers found in the asbestos plant were four gastrointesti-

nal, three esophageal, two laryngeal, and one each for cancer of the brain, kidney, bile duct, penis, thymus, and adrenals. The two cases of mesothelioma, one pleural and the other peritoneal, constituted 1.5 percent of total mortality in the asbestos cohort from 11,525 person-years of observation. The second most frequent causes of death were respiratory diseases in the asbestos cohort but cardiovascular diseases in the control cohort.

According to the analysis in which the Cox proportional hazards model was used, after adjustment for age at study entry and for smoking habits, the relative risk for the association between asbestos exposure and lung cancer was 6.6. Asbestos exposure also was a risk factor for all causes of death and all cancer deaths (table 3). When only the cases of cancer confirmed pathologically were analyzed separately the adjusted relative risk for the relation between asbestos exposure and all cancer deaths was still significant, and the relative risk for the association with lung cancer was 1.9.

When the risk of lung cancer and other causes of death for each plant section was compared with that for the control plant, the highest adjusted relative risk for lung cancer was associated with the raw material section (relative risk (RR) = 17.6, 95 percent confidence interval (CI): 4.5, 69.3) followed by the textile section (RR = 9.8, 95 percent CI 2.1, 44.4). The relative risk for the maintenance section was also elevated significantly (RR = 7.3, 95 percent CI: 1.6, 33.5). Despite the fact that the asbestos cement section and the rubber plate section had high concentrations of dust, the relative risks for lung cancer were not significant (RR = 2.5, 95 percent CI: 0.4, 15.5 and RR = 5.3, 95 percent CI 0.5, 51.2, respectively). There were no lung cancer cases among the office workers.

TABLE 2. Basic characteristics and mortality of workers in the asbestos and control cohorts in Chongqin, China, followed up between January 1972 and December 1996

	Asbestos workers	Control workers
No. of workers	515	645
Average year of birth	1930	1937
Average age at employment (years)	29.4	23.8
Average no. of years of employment	24.6	26.8
Average no. of years of observation	33.8	34.3
Total person-years of observation	11,525	15,671
Percentage of smokers	77.1	50.4
No. of total deaths (% of total workers)	132 (25.6)	42 (6.5)
Mortality rate (per 1,000 person-years)	11.4	2.8
All cancers (% of total deaths)	50 (37.9)	11 (26.1)
Lung cancer (% of all cancers)	22 (44)	3 (27)
Nonmalignant respiratory diseases	38	9
No. of cases of mesothelioma	2	0

TABLE 3. Adjusted relative risk and 95% confidence interval* of death from all causes, all cancers, and lung cancer in relation to age at study entry (1972), smoking, and employment in the Chongqin, China, asbestos plant

Cause of death and factor	All cases		Pathologically confirmed cases†	
	Adjusted RR‡§	95% CI‡	Adjusted RRs	95% CI
All causes				
Age	1.06	1.04, 1.08		
Smoking	0.97	0.70, 1.34		
Asbestos plant employment	2.87	2.00, 4.12		
All cancers				
Age	1.05	1.02, 1.08	0.94	0.91, 0.98
Smoking	1.89	0.88, 3.67	1.95	0.80, 4.77
Asbestos plant employment	4.29	2.17, 8.46	3.33	1.39, 7.98
Lung cancer				
Age	1.07	1.02, 1.12	0.92	0.86, 0.99
Smoking	3.03	0.90, 10.2	4.85	0.62, 38.2
Asbestos plant employment	6.64	1.92, 23.0	1.94	0.48, 7.79

* Analyzed by using the Cox proportional hazards model.

† For the all cancers and lung cancer cases, those whose disease was confirmed pathologically were analyzed separately.

‡ RR, relative risk; CI, confidence interval.

§ Adjusted RR obtained from multivariate analysis by using the Cox proportional hazards model.

|| Age at the time of entry into the cohort (1972) was used as a continuous variable in the calculation; smoking and asbestos exposure were dichotomous variables.

The pleural mesothelioma case worked in the raw material section and the peritoneal mesothelioma case in the textile section; both cases of disease were confirmed by pathologic examination. For the pleural case, the duration between first exposure and death was 13.8 years, while it was 21.8 years for the peritoneal case.

Because of the possibility of uncontrolled differences between the two cohorts, a comparison was made within the asbestos cohort of groups for three levels of asbestos exposure. Workers in the raw material and textile sections were always exposed to high levels of asbestos in poorly ventilated rooms. In contrast, the asbestos cement section was well ventilated. Office workers in the administration section were also included in the less-exposed group. Workers in the other sections with widely varying levels of asbestos were included in the intermediately exposed group. As the results indicate, although age and smoking prevalence were similar among the three groups, the incidence of lung cancer was much higher in the group exposed to high levels of asbestos (RR = 8.1) followed by the group exposed to intermediate levels (RR = 3.6) (table 4). When we restricted the analysis to lung cancer confirmed pathologically, the age- and smoking-adjusted relative risk comparing the groups exposed to high versus low levels of asbestos was 1.1 (95 percent CI: 0.9, 1.4); however, only a small number of cases had been confirmed pathologically (five in the high exposed group vs. one in the low exposed group).

Using the Cox model, we evaluated the interaction of smoking and of asbestos exposure with the occurrence of lung cancer. The results indicated that the relative risks of lung cancer by smoking, asbestos exposure, and both asbestos and smoking exposure, after adjustment for age, were 1.5,

3.4, and 12.6, respectively. Only the last one was significant ($p = 0.014$), suggesting the existence of an interaction between asbestos exposure and smoking, as has been noted previously (18).

DISCUSSION

For nearly a decade, the so-called amphibole hypothesis has generated an often-heated debate among scientists researching the hazards of asbestos (19, 20). The hypothesis postulates that chrysotile is far less carcinogenic than the amphiboles and that cases of mesothelioma observed among workers exposed to chrysotile can be explained by confounding exposure to contaminating amphibole asbestos. Fiber-type analysis of the lung tissue of mesothelioma cases initiated the hypothesis justifying the use of chrysotile but not amphiboles for industrial purposes (11, 21), and this view was further supported by epidemiologic studies of the mortality of chrysotile miners in Quebec, Canada (22, 23). In these studies, contaminated tremolite in chrysotile ore was suspected as the primary pathogenic agent. However, a comparison with evidence obtained from a textile plant in Charleston, South Carolina, and from Quebec miners and millers failed to support the predicted higher incidence of lung cancer, caused by tremolite contamination, in the miners and millers (24). Likewise, the findings of the preceding studies on chrysotile-related lung cancer showed wide variability, with an associated risk negative to nearly equal that for amphibole asbestos. However, such discordance is to be expected in the absence of uniform and consistent protocols of epidemiologic study and because of the varying composition of different fiber types. Therefore, a study of workers

TABLE 4. Relative risk of lung cancer, all cancers, and other causes of death among groups of workers exposed to low, intermediate, and high levels of asbestos in the Chongqin, China, asbestos plant between 1972 and 1996*

	Level of exposure: asbestos plant section		
	Low: office, asbestos cement	Intermediate: maintenance, rear service, rubber plate	High: raw materials, textile
No. of workers	162	203	150
Age at employment (years) (mean (SD)†)	30.1 (7.8)	28.4 (8.4)	30.1 (8.7)
No. of years of employment (mean (SD))	24.4 (6.8)	25.5 (8.1)	23.5 (6.6)
No. of years of observation (mean (SD))	34.7 (7.2)	33.8 (7.7)	33.2 (7.7)
No. of smokers (%)	133 (82.1)	149 (73.4)	115 (76.7)
Total deaths (no. (%))	39 (24.1)	41 (20.2)	52 (34.7)
RR‡ (95% CI)	1.0	1.0 (0.7, 1.6)	1.5 (1.0, 2.3)
All cancers (no. (%))	13 (8.0)	15 (7.4)	22 (14.7)
RR‡ (95% CI)	1.0	1.2 (0.6, 2.5)	2.1 (1.1, 4.1)
Lung cancer (no. (%))	2 (1.2)	7 (3.4)	13 (8.7)
RR‡ (95% CI)	1.0	3.6 (0.7, 17.5)	8.1 (1.8, 36.1)

* Data analyzed by using the Cox proportional hazards model.

† SD, standard deviation.

‡ Relative risk (RR) and 95% confidence interval (CI): age- and smoking-adjusted relative risk of workers exposed to high levels in the raw material and textile sections compared with workers exposed to low levels in the office and asbestos cement sections.

exposed specifically to an extremely pure form of chrysotile might be expected to provide stronger evidence for the carcinogenic potency of chrysotile asbestos *per se*. In our study, subjects were exposed to only amphibole-free chrysotile, and amphibole asbestos has never been used in the Chongqin plant.

A well-recognized characteristic of asbestos-related lung cancer is its synergism with smoking (25). In our study cohorts, we confirmed the interaction of smoking and asbestos exposure with occurrence of lung cancer. We also found that the relative risk of lung cancer for smokers without exposure to asbestos did not increase significantly. It has been recognized that, for smokers in China, the relative risk of developing lung cancer is lower than that reported in western countries. In a review of several cohort studies of male workers in China, the relative risk of lung cancer was found to vary between 2 and 4 (26–28).

As the results indicate, we found no evidence in support of the amphibole contaminant hypothesis. To the contrary, a strong potential for chrysotile asbestos alone to cause lung cancer and mesothelioma was suggested.

In our study, several potential sources of bias could have led to an overestimation of the effect of chrysotile exposure on lung cancer. Fiber concentrations were measured for the first time by following an internationally approved procedure (NIOSH procedure 7400; National Institute for Occupational Safety and Health, Cincinnati, Ohio). Nonetheless, fiber concentrations were probably much higher in the past because of poor industrial hygiene, thus introducing the possibility of overestimation of the effect. In the past, workers also took asbestos home, extending their exposure. The diagnostic and record-keeping procedures in the study and control plants were similar. However, only a small proportion of malignant tumors were confirmed pathologically, which could have caused misclassification. Nevertheless, separate pathology-based analyses essentially confirmed our major findings, although the risk estimates were reduced. Selection bias might have been introduced by excluding the five workers lost to follow-up. If all of these workers developed lung cancer after they left the control plant, lung cancer mortality in the control cohort would be markedly underestimated, which would also lead to an overestimation of the effect of asbestos exposure. The likelihood that all five workers had lung cancer is small, because their actual reasons for leaving the plant were not related to any health problems.

As for confounding bias, the average age and the prevalence of smoking were higher in the asbestos cohort, which required statistical adjustment. Since there may have been unrecognized differences between the workers in the asbestos plant and those in the control plant, a comparison within the asbestos-exposed cohort was made. The relative risk of lung cancer we obtained from this comparison was even larger than the one from the original comparison. This finding suggests that the association between asbestos and lung cancer was not due to confounding by differences between the two cohorts. On the other hand, our measure of smoking was dichotomous, and, given the strong link between smoking and lung cancer, it is possible that smok-

ing differences were not well controlled in either of the two cohorts or within cohort comparisons.

With regard to mesothelioma, Stayner et al. (29) reviewed cohort studies of workers exposed to predominantly chrysotile asbestos and demonstrated that the overall proportional mortality of mesothelioma was 0.3 percent; in the present study, mesothelioma accounted for 1.5 percent of the total deaths. Camus et al. detected no measurable excess risk of lung cancer among women exposed to chrysotile asbestos (30) but, in the same study, found an excess risk of mesothelioma, with a proportional mortality of 0.3 percent (7 of 2,242 deaths). Their estimate of average cumulative lifetime exposure to asbestos was 25 fiber-years/ml, far below the level determined in our study. It is generally recognized that the incidence of mesothelioma increases exponentially with follow-up time. Because the average observation time was only 33.8 years, and nearly three quarters of the asbestos workers remained alive, the proportion of mesothelioma may yet increase further. In fact, in addition to the two cases we found, an asbestos worker's son developed mesothelioma only 8 years after he was employed by the asbestos plant. During his childhood, this boy helped his family for several years by weaving asbestos by hand after school. However, because he was employed after the cohort started, this worker was not included in our study.

A total of 139 workers with asbestosis were found in the asbestos cohort during the entire follow-up period. However, because 1/0 in the ILO classification (31) is not diagnosed as pneumoconiosis according to the Chinese standard, the total may be an underestimate. The proportional mortality of nonmalignant respiratory diseases, which include asbestosis, was also increased, but not significantly so, in the asbestos workers (29 vs. 21 percent).

In conclusion, the present study demonstrates that exposure to uncontaminated chrysotile asbestos only may be related to an increased risk of lung cancer to an extent comparable to that caused by mixed-type asbestos. In addition, it suggests that exposure to pure chrysotile can also cause mesothelioma.

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