Clinical Investigations

Respiration

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DOI: 10.1159/000163443

Received: December 31, 2007
Accepted after revision: July 11, 2008
Published online: October 9, 2008

Mortality from Occupational Exposure to Relatively Pure Chrysotile: A 39-Year Study

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Key Words
Asbestos · Epidemiology · Lung cancer · Mesothelioma · Chrysotile

Abstract
Background: Asbestos exposure is related to serious adverse health effects. However, there is disagreement about the relationship between chrysotile exposure and mesothelioma or lung cancer. ***Objectives:*** Our aim was to investigate the mortality rate among workers exposed to relatively pure chrysotile in an asbestos cement factory. ***Patients and Methods:*** In an asbestos cement plant opened in 1968, we prospectively studied all 317 workers. A quantity of 2,000 tons of chrysotile, with minimal amphibole contamination, was used annually until 1 January 2005. Asbestos fiber concentration was measured regularly. Date and cause of death were recorded among active and retired workers. ***Results:*** Asbestos fiber concentration was always below permissible levels. Fifty-two workers died during the study. The cause was cancer in 28 subjects; lung cancer was diagnosed in 16 of them. No case of mesothelioma was reported. Death was attributed to cardiovascular diseases in 23 subjects and to liver cirrhosis in 1. Overall mortality rate was significantly lower than that of the Greek general population, standardized mortality ratio (SMR) was 0.71 (95% CI 0.53–0.93). Mortality due to cancer was increased (SMR 1.15, 95% CI 0.77–1.67), mainly due to lung cancer mortality (SMR 1.71, 95% CI 0.98–2.78), but not significantly. ***Conclusions:*** Occupational exposure to relatively pure chrysotile within permissible levels was not associated with a significant increase in lung cancer or with mesothelioma. Decreased overall mortality of workers indicates a healthy worker effect, which – together with the relatively small cohort size – could have prevented small risks to be detected.

Introduction

The term asbestos is used to describe a group of natural mineral fibers, which present extensively in the earth's crust and have silica as their main component [1]. Based on their physical properties, asbestos fibers are divided into 2 main types: (1) serpentines (flexible curly fibers; chrysotile is the main representative) and (2) amphibole forms (straight, needle-like fibers; crocidolite, amosite, anthophyllite, tremolite and actinolite are included in this group). Asbestos fibers inhalation, even in small quantities, is considered dangerous. The Commission of the European Communities recently adopted a directive (2003/18/EC) that obliges member states to prohibit the marketing and use of chrysotile asbestos [2]. The prohibition became effective on 1 January 2005.

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This directive was received in the light of recent studies, which concluded that chrysotile, even though less toxic than amphiboles, could induce mesotheliomas and lung cancer [3–6]. On the other hand, studies on asbestos cement workers have shown that mesothelioma is associated with the use of amphibole asbestos [7] and that exposure to moderate chrysotile concentrations does not increase the risk of lung cancer [8, 9]. It was argued that the frequent contamination of chrysotile deposits by amphibole fibers might contribute to the carcinogenic effects of occupational exposure [10, 11]. A recent review article concluded that available data could not prove a causative relationship between exposure to pure chrysotile and mesothelioma [12].

The reasons for these conflicting conclusions may be a number of confounding factors such as chrysotile purity, job type, exposure duration and intensity, smoking history as well as epidemiologic methodology [13].

To study mortality among workers in an asbestos cement plant, where chrysotile with minimal amphibole contamination was used, we undertook a long-standing, prospective cohort study. Specifically, we investigated workers' mortality under low concentrations of relatively pure chrysotile fibers, a subject that has not been studied extensively.

We believe that the present study contributes to a more rational policy regarding asbestos usage and surveillance.

Subjects and Methods

Occupational Environment

In an asbestos cement products plant that has operated since 1968, asbestos was used until 1 January 2005, when the European Union banned chrysotile asbestos usage; 317 subjects worked there. This plant is located near Thessaloniki, Greece, and its surface area is approximately 244,000 m^2. Two thousand tons of raw asbestos were used annually. Only chrysotile asbestos that was imported from Canada (Johns Manville Corporation, Lake Asbestos Mine) and Russia (Ural Asbestos Mining and Ore Dressing Company, Orenburgasbest) up to 1983 and then obtained from a mine in Zidani, Greece, was used in the plant. The average chrysotile contamination with amphiboles was 0.5% while, in rare cases, the maximum concentration approached 3%. Asbestos cement products contained chrysotile in a percentage of about 8–12%, whereas 25,000–30,000 tons of asbestos cement was produced annually.

Measurement of Airborne Fiber Concentration

Airborne asbestos fiber concentration in the workplace was measured regularly by the Environmental Control Laboratory of the factory. Measurements took place in 32 different points 4 times annually, and the mean measurement period was 8 h every time. A specific air pump (Casella ARC 124; Casella CEL, Bedford, UK) was used for air suction, while air supply was fixed at 1 liter/min. Millipore type AA filters with 0.8-μm pore diameter were used (Millipore Corporation, Bedford, Mass., USA). Then the filters were checked with contrast phase microscope (×450). Asbestos fibers were counted in 100 different optical fields of filter surface. Only the fibers with length >5 μm, diameter <3 μm and ratio length/diameter ≥3/1 were counted [14]. Airborne fiber concentration was expressed as fibers/cm^3. Fiber concentration was reduced from 6.49 to 1.7 fibers/cm^3 during the time period 1968–1983. From 1984, concentration was always below 1 fiber/cm^3 (mean values reduced from 0.8 to 0.07) according to directive 83/477/EU [14].

Concentration of asbestos fibers in the plant ranged from 6.49 to 3.51 fibers/cm^3 before 1980, while after that year stricter safety measures were undertaken causing a reduction in fiber concentration to 1.70–1.13 fibers/cm^3 during the period 1981–1983. After 1983, concentration was constantly below 1 fiber/cm^3 as the European Union directive imposed.

Subjects

We followed 317 workers from 1968, when the factory started its operation, until 31 December 2006. Occupation for at least 5 years was an inclusion criterion for the study. On 31 December 2006, there were still 41 workers in the plant, which now bases its production on nonasbestos materials. Of the remaining 276 subjects, 224 had retired and were still alive, while 52 workers had died.

There was a permanent occupational medical doctor who followed workers annually (clinical examination, spirometry, radiographs). Smoking history was recorded at the beginning of employment and then annually. All retired persons were followed on a regular basis. Date and cause of death were recorded, among active workers as well as retired subjects, based on death certificates, occupational medical records and personal communication between occupational doctor and general practitioner. The Medical Ethics Committee of the G. Papanicolaou Hospital in Thessaloniki approved the study protocol.

The mean age at hire was 31.9 ± 9.1 years for the 265 subjects who were still alive at the end of the study and 39.7 ± 7.9 years for the workers who had died. Total follow-up time was 9,537 person years. Taking into account only the person years observed after age 40, the most risky period for developing lung cancer, we calculated that 72.5% (6,918 person years) of our follow-up time referred to a critical period for these subjects to develop cancer.

The mean age and years of occupation ± standard deviation for the 265 subjects who were still alive at the end of the study was 63.1 ± 12.1 and 19.3 ± 7.6 years, respectively. Workers who had died had a mean age of 63 ± 9.5 years, while they had worked in the plant for 16.7 ± 5.6 years.

Among the workers who were still alive at the end of the study, 123 were current smokers and 65 were ex-smokers with a mean exposure of 24.5 ± 24.6 pack years. Among subjects who died, 33 were active smokers and 10 ex-smokers with a smoking history of 38.4 ± 30.3 pack years. Quantitative exposure to asbestos was 42.9 ± 27.8 fibers/cm^3 × years of exposure for those who were still alive and 52.4 ± 23.7 for workers who had died. Detailed descriptive statistics for workers are shown in table 1.

Table 1. Descriptive statistics of age distribution, smoking history and chrysotile exposure of workers

	Alive				Deceased			
	mean ± SD	median	range	interquartile range	mean ± SD	median	range	interquartile range
Age at hire, years	31.9 ± 9.1	31	15–56	25–38	39.7 ± 7.9	41	23–55	36–45
Age at the end of the study, years	63.1 ± 12.1	63	14–93	55–72	63.0 ± 9.5	63.5	42–79	56–70
Smoking, pack years[1]	34.7 ± 22.4	44.5	0.6–85.2	15.3–71.1	47.6 ± 26.4	41.5	2–115	31.5–60
Occupation, years	19.3 ± 7.6	20	5–33	14–25	16.7 ± 5.6	16.5	5–30	12–19.8
Fibers/cm^3 × years	42.9 ± 27.8	44.5	0.6–85.2	15.6–66.6	52.4 ± 23.7	54.7	1.4–84.1	37.4–71.9

[1] Only smokers and ex-smokers were considered.

Table 2. Observed and expected number of deaths and SMR adjusted for age and sex among workers during the follow-up period 1968–2006

Cause of death	Observed	Expected	SMR	95% CI
All causes	52	73.19	0.71	0.53–0.93
Malignant neoplasms	28	24.24	1.15	0.77–1.67
Lung neoplasms	16	9.35	1.71	0.98–2.78
Diseases of circulatory system	23	29.82	0.77	0.49–1.16
Other causes of death[1]	1	19.12	0.05	0.01–0.29

[1] Cirrhosis.

Statistical Analysis

Standardized mortality ratios (SMR) were calculated as ratios between observed and expected numbers of deaths, adjusting for age and sex, according to life tables for the Greek male population of 2003 (General Secretariat of National Statistical Service of Greece: www.statistics.gr). Confidence intervals (CI) were calculated using exact methods [15]. Follow-up for each individual started at 1968 or at the date of engagement if they started work after 1968. The follow-up was up to 31 December 2006 or the death date if that occurred before that date.

Exposure time, pack years smoked and asbestos fiber concentration were considered as candidate predictors for death since first exposure to chrysotile. Predictive analyses used Cox models, after ascertaining that proportionality of hazards was not violated [16]. Unadjusted and adjusted hazard ratios for smoking and age are presented. The adjustment for smoking was undertaken by adding the pack years smoked as a covariate in the model. Multivariate models were built using backward elimination of variables according to likelihood ratio criteria, starting with all variables with $p < 0.1$ in univariate models. Also, the forward selection of variables according to likelihood ratio criteria was applied to see if the final model differed. Three outcomes were considered: all-cause deaths, malignant neoplasm deaths and lung cancer deaths. All tests of statistical significance were two-sided and performed using Stata Statistical Software (version 8.0; Stata Corporation, College Station, Tex., USA) and SPSS (version 14.0; SPSS Inc., Chicago, Ill., USA).

Results

Fifty-two deaths were recorded during the study. Twenty-three of them were attributed to cardiovascular diseases, 28 to malignant neoplasms and 1 to liver cirrhosis. Of 28 cancer deaths, 16 were due to lung cancer (12 squamous cell, 2 adenocarcimonas and 2 small cell lung cancer), while the origin of the remaining were as follows: 4 stomach, 2 pancreas, 2 nervous system, 2 hematologic system, 1 colon and 1 skin.

The overall mortality among male workers was significantly decreased (SMR 0.71, 95% CI 0.53–0.93; table 2). However, death from malignant neoplasms was increased in males but not significantly different compared to the Greek male population (SMR 1.15, 95% CI 0.77–1.67) mainly due to lung cancer mortality (SMR 1.71, 95% CI 0.98–2.78). Relative risk for lung cancer was estimated to be 6.61 (3.30–11.84) for smokers compared to nonsmokers and 4.55 (1.24–11.67) for ex-smokers compared to nonsmokers. Conversely, mortality rate due to circulatory diseases or to other causes was decreased (SMR 0.77 and 0.05, respectively).

Table 3. Predictors of death since first chrysotile exposure; unadjusted and adjusted analysis for age and smoking

	Mean[a]	Hazard ratio[b]	p value	Hazard ratio[b]	p value
Years of chrysotile exposure					
All-cause deaths	16.71 (5.57)	0.92 (0.89–0.96)	<0.001	0.92 (0.89–0.96)	<0.001
Malignant neoplasm deaths	16.57 (5.63)	0.92 (0.88–0.97)	0.003	0.91 (0.87–0.96)	0.001
Lung cancer deaths	15.38 (5.99)	0.90 (0.84–0.97)	0.005	0.89 (0.83–0.96)	0.002
Alive	19.26 (7.62)				
Pack years of smoking					
All-cause deaths	38.44 (30.30)	1.15 (1.05–1.26)[c]	0.002	1.15 (1.05–1.26)[c]	0.003
Malignant neoplasm deaths	48.54 (28.09)	1.27 (1.14–1.42)[c]	<0.001	1.26 (1.13–1.41)[c]	<0.001
Lung cancer deaths	50.13 (26.46)	1.28 (1.12–1.48)[c]	0.001	1.28 (1.12–1.48)[c]	0.001
Alive	24.47 (24.59)				
Fibers/cm^3 × years					
All-cause deaths	52.36 (23.72)	0.99 (0.88–1.12)[c]	0.887	1.02 (0.90–1.16)[c]	0.789
Malignant neoplasm deaths	56.76 (21.75)	1.07 (0.91–1.27)[c]	0.374	1.06 (0.89–1.28)[c]	0.495
Lung cancer deaths	57.89 (21.89)	1.10 (0.99–1.37)[c]	0.362	1.08 (0.85–1.38)[c]	0.495
Alive	42.91 (27.82)				

[a] Figures in parentheses are standard deviations.
[b] Adjusting for age and smoking; figures in parentheses are 95% CI.
[c] For every 10-unit increase; figures in parentheses are 95% CI.

Workers with greater chrysotile exposure had better survival (table 3). Specifically, the risk of death from all causes and from malignant neoplasms was 8% lower for every year of chrysotile exposure ($p = 0.001$ and 0.003, respectively), while the risk of death from lung cancer was 10% lower for every year of chrysotile exposure ($p = 0.005$). These associations remained after adjusting for age and smoking ($p < 0.001$, 0.001 and 0.002, respectively). Notably, the deceased workers had a heavier history of asbestos exposure than the living workers (tables 1 and 3).

Sichletidis et al. [17] studied 21,854 subjects of the general population in northern Greece and found high prevalence of smoking (47.8% for males) among them. Specifically the subgroup of age 61–80 years, which was comparable with our population at the end of the study, showed 27.2% smokers, 32.9% ex-smokers and 39.9% nonsmokers. The corresponding percentages for our study group were 48.6% (n = 154), 23.7% (n = 75) and 27.8% (n = 88), respectively. We should notice that consumption of cigarettes (pack years) of the living workers was less than that of the general population, while those who died had similar pack years as the general population.

As anticipated, smoking contributed significantly to all-cause mortality, all cancer mortality and specifically lung cancer mortality ($p \leq 0.002$ for all 3 comparisons; table 3). For every 10 pack years of smoking, the risk of death from all causes increased 1.15 times and the risk of death from all cancers increased 1.27 times, while the risk of death from lung cancer increased 1.28 times. These associations remained after adjusting for age ($p = 0.003$, 0.001 and 0.001, respectively). Asbestos fiber concentration was not significantly associated with time to death since first exposure in any of the 3 outcomes ($p = 0.887$, 0.374 and 0.362, respectively).

In multivariate modeling, only smoking ($p < 0.001$) was a significant independent predictor for all 3 mortality outcomes. Additionally, the hazard ratio for lung cancer was 16.36 (95% CI 8.64–30.96, $p < 0.001$) after adjustment for age and smoking.

Discussion

The present long-standing, prospective study showed that subjects exposed to relatively pure chrysotile asbestos, with airborne fiber concentrations much lower than the permissible upper limits, had no increased risk for mesothelioma and lung cancer. SMR for lung cancer was calculated to be 1.71 and attributed almost exclusively to cigarette smoking. No case of mesothelioma was reported.

The major advantages of the study are that, for the period 1968–2006, we followed a specific population under low level of relatively pure chrysotile exposure, while smoking history was recorded in a quantitative manner.

According to older studies, chrysotile asbestos was considered responsible for mesothelioma and lung cancer. Studies among workers in the textile industry (3,211 in the UK [4] and 1,247 in the USA [18]) and asbestos cement production (7,996 in Denmark [19] and 2,565 in the USA [20]), where chrysotile asbestos had variable contamination with amphiboles, showed that SMR ranged between 1.17 and 2.25 for lung cancer. Moreover, proportional mortality rate (per 1,000) for mesothelioma ranged between 2.5 and 20.7. Chrysotile contamination to a variable degree was a constant characteristic of all studies that showed increased risk for lung cancer or mesothelioma [21].

In a recent study concerning 515 workers in China who had been exposed to pure chrysotile and followed for 25 years, the relative risk for lung cancer was calculated to be 6.6 compared to control workers, while only 2 cases of mesothelioma were diagnosed [6]. We should point out that exposure was heavy with airborne fiber concentration ranging from 4.5 to 7.6 fibers/cm^3.

On the contrary, Newhouse and Sullivan [22] did not find increased risk for lung cancer (SMR 1.03) among 9,104 workers in the UK who had been exposed to chrysotile containing low concentration of amphiboles. A meta-analysis of 71 asbestos cohorts exposed to free asbestos fibers does not support the hypothesis that pure chrysotile causes mesothelioma [7]. In a clinicopathological study in the USA concerning 1,445 cases of malignant mesothelioma with known exposure to asbestos, 268 had fiber burden analysis of lung tissue and chrysotile fibers were detectable in 36. In only 2 of these, chrysotile was the exclusive detectable asbestos type [11].

Hodgson and Darnton [23] tried to calculate the quantitative risk of mesothelioma and lung cancer in relation to asbestos exposure. They identified all cohort mortality studies for which quantified data on exposure were available and concluded that the specific risk of mesothelioma was in the ratio 1:100:500 for chrysotile, amosite and crocidolite, respectively. For lung cancer, the conclusions were less clear-cut, suggesting a relative risk between chrysotile and the 2 kinds of amphibole fibers between 1:10 and 1:50.

It is suggested that the frequent contamination of chrysotile by amphibole fibers to variable degrees [10] as well as the intensity of exposure to chrysotile when used uncontaminated [6] are the most critical factors that provoke malignant diseases of the chest. The same position was supported by Bernstein and Hoskins [24] in a recent review on the topic. They concluded that heavy and prolonged exposure to chrysotile could produce lung cancer, while low exposures to pure chrysotile do not present a detectable risk to health.

This remark is supported by in vitro studies which showed that chrysotile clearance from the lungs is rapid, with clearance half times ranging between 0.3 and 11.4 days for fibers >20 μm in length. On the other hand, inhalation clearance half time was 536 days for crocidolite and even longer for tremolite [25].

In the present study, we did not record any case of mesothelioma and the mortality rate of the workers due to lung cancer did not differ from the general population. Based on the study of Hughes et al. [26], which dealt with asbestos cement workers with similar exposure level to chrysotile (40 fibers/cm^3 × years), we estimated that the expected number of mesotheliomas would have been less than 1.

We corrected lung cancer mortality using duration of exposure, intensity of exposure (fibers/cm^3 × years) and smoking history. Uni- and multivariate models were used and concluded that only smoking history was an independent factor contributing to lung cancer mortality risk. The healthy worker effect could explain the lower overall mortality among the workers group compared with the control population. It is possible that individualized factors related to asbestos resistance might conceal the negative relationship between chrysotile exposure and relative risk for malignancies.

The decrease in risk with years of chrysotile exposure is a phenomenon that is difficult to explain. Diachronic reduction of fiber concentration in the factory has already been described in detail. The number of ex-smokers grew in a parallel way. These 2 facts might be the main reasons for the observed decrease in risk with years of chrysotile exposure. On the other hand, it is true that deceased workers had a heavier history of asbestos exposure than living workers.

Our results are in accordance with current studies about the health effects of chrysotile [12, 21]. Unfortunately, usage of chrysotile is declining steadily in developed countries. Epidemiologic and toxicological data about organic and synthetic fibers, which may substitute chrysotile, showed that these fibers had physical and biological properties resembling amphiboles [27, 28].

We conclude that occupational exposure to relatively pure chrysotile under strict permissible levels does not increase the relative risk for mesothelioma and lung cancer. Decreased overall mortality of workers indicates a healthy worker effect, which – together with the relatively small cohort size – could have prevented small risks to be detected.

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