A Case Control Study of Lung Cancer and Exposure to Chrysotile and Amphibole at a Slovenian Asbestos-Cement Plant

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A lung cancer case-control study was conducted in a Slovenian asbestos-cement factory for which unusually good records of asbestos exposures were available. The cohort consisted of all 6714 workers employed at the Salonit Anhovo factory after 31 December 1946 who worked there for at least one day between 1964 and 1994. Fifty-eight histologically confirmed cases of primary lung cancer and 290 controls were selected from the cohort. Working life exposure histories to amphibole and chrysotile forms of asbestos were estimated separately. Airborne asbestos concentrations were low. For example, the arithmetic mean exposure to all forms of asbestos in the highest exposure period (1947–1971) was 1.2 f/cm³. Chrysotile asbestos made up about 90% of this exposure (mean 1.1 f/cm³), whereas amphibole accounted for 10% (0.1 f/cm³). Comparing those above and below the 90 percentile of cumulative exposure, the odds ratios for all asbestos, chrysotile and amphibole were 1.5, 1.6 and 2.0, respectively, but confidence intervals were wide. There are only a few asbestos-lung cancer studies with high-quality exposure data and exposures in this low range. Though imprecise, the findings are important to the ongoing debate about asbestos risks.

Keywords: amphiboles; amphibole theory; asbestos; chrysotile; lung cancer

INTRODUCTION

A lung cancer case-control study was conducted in a Slovenian asbestos-cement factory. Unusually good records of the ambient airborne concentrations of asbestos in the factory in the past as well as detailed work histories presented an opportunity to study quantitative exposure-response relationships. Further, asbestos-cement products were made from both chrysotile and amphibole forms of asbestos, but these were processed in different parts of the plant. Detailed records permitted the estimation of separate individual exposure histories for these two forms of asbestos. There has been considerable controversy in recent years concerning the relative toxicity of chrysotile versus amphibole asbestos, and so a study in the Slovenian plant seemed particularly opportune. The Slovenian National Cancer Register, one of the oldest in Europe, was used to identify cases.

METHODS

The factory and asbestos raw materials

The Salonit Anhovo factory is located on the right bank of the River Soča in western Slovenia, close to the Italian border. There were three major production areas in the plant: (1) cement production (cement and clinker were produced in two facilities); (2) production of asbestos-cement pipes and corrugated sheets and (3) production of polyethylene and man-made mineral fiber pipes which began in 1990. All the production buildings were built close together.
Production began in 1921 and a year later the first asbestos was used. From the beginning to 1947 the factory was owned by Italians. From 1947 onwards the owner was the Slovenian republic. At the end of 1996, asbestos was banned by law in Slovenia.

The plant kept record of the quantity of asbestos (separately for chrysotile and amphibole) used in the production process. Chrysotile, received mainly from Canada, Rhodesia, Italy, Russia and then the Yugoslavia, was mixed with amphiboles in small but known quantities. In pipe production, the use of amphiboles slowly increased to a peak at the beginning of the 1980s, and then rapidly decreased. The factory used amphibole asbestos for the last time in 1990. The quantities of amphiboles in pipes did not follow a particular recipe, but varied over time. In cement asbestos sheet production, amphiboles were first used in 1974. The quantities of amphiboles added to this second product depended on the market price and did not show any particular trend, but were a small fraction of total asbestos consumption (0.009–2.1%).

The first available employment data date back to 1939, when 731 workers were employed in the factory. At the end of World War II, the number of workers fell to 520, but this number grew rapidly in the post-war period. By 1953, the number exceeded 1000 workers, and in 1981 reached a peak of 2651. About 30% were women. The number of workers directly exposed to asbestos varied from year to year and was between 300 and 800.

Several features of the factory are relevant to this study: (1) the factory building where cement asbestos products were produced was structured in two physically separate production areas or units, each dedicated to the production of a single product—asbestos sheet in one, and asbestos pipe in the other; (2) there were detailed asbestos consumption records available for each production unit; (3) each production unit was organized as a separate factory with different management and employment systems. Workers were hired in one unit and transfers to the other unit were quite rare (the management began to transfer workers from one unit to the other in 1990); (4) once hired, workers tended to remain in the job for which they were hired; (5) detailed time management records were available for most jobs in each production area and (6) complete work history records were available for all workers in the study population.

**Exposure assessment methodology**

A detailed presentation of the asbestos exposure data and the methods used to reconstruct exposure are provided elsewhere (Dodic-Fikfak, 1998, 2003). The monitoring of airborne fiber concentrations in the facility (mostly for compliance) began in 1961 and continued to 1996. The exposure circumstances of the workers did not change substantially until 1986 when workers first began to use respirators (although they did not use them regularly) and an effective ventilation system was installed. Airborne fiber concentrations could be estimated with a fairly high degree of confidence and it was possible to separately estimate workers’ exposures to amphibole and chrysotile forms of asbestos.

A total of 1030 air measurements from the asbestos factory were available for the period from 1961 to 1995, using several different monitoring methods and including a set of 78 paired measurements where both the gravimetric and membrane filter methods were used side by side. All air sampling measurements were taken at fixed locations, collected close to a worker’s breathing zone. Conversion factors were developed from the side by side samples to combine the data gathered by the different exposure assessment methods. A non-parametric classification and regression tree (CART) method was used to calculate conversion factors for different combinations of fiber type, product and production method, while maximizing precision and minimizing bias (Dodic-Fikfak, 1998). Based on the air measurements, conversion factors and production records, the concentrations of total asbestos, chrysotile and amphiboles were estimated for each production job in each year of the study.

When air measurements were not available for a particular year or group of years, the exposures were estimated using the previous or next values or using an average of both depending on the production process changes occurring in that year (Dodic-Fikfak, 1998).

For a few jobs, there were no applicable air sample measurements. The factory officials assumed that those jobs were not exposed, or the workers in those jobs had no fixed work locations and no single monitoring station could be applied to their exposure. Such jobs included maintenance workers, drivers, laboratory workers and construction workers. For these positions, individual exposure matrices were developed by a consultation group. The members of the consultation group were not subjects selected for the study, but they worked with the individual whose exposure was being assessed and were familiar with the subjects’ jobs. The group consisted of the factory safety engineer and at least three workers who had worked directly with the subject whose exposure was being estimated. Also included were production engineers with direct knowledge of the machinery in use in the time and work locations of the subject.

The group had two tasks: first to locate the work locations and time spent in each location using historical maps of the facility. Second, they were asked to choose a production task, which they believed, had a similar level of asbestos exposure for each work/task location of the subject. Using these two estimates...
and the exposure intensities for the comparable measured jobs, exposure intensities by year by subject were calculated for total asbestos, amphibole and chrysotile.

Work histories for all production workers were obtained from company personnel files and these were combined with the exposure data by job and year to yield individual annual exposure histories. In the event that a worker had two jobs in one year, a weighted average of both jobs was calculated for that year. Annual exposures to amphibole and chrysotile were then summed over time to yield individual cumulative exposures. Total asbestos cumulative exposure was simply the sum of the amphibole and chrysotile exposures. Cumulative exposure was calculated separately in four time windows (0–15 years, 16–25, 26–35 and >35 years) prior to the risk date (date of diagnosis of case or for controls, the date of diagnosis of their matched case). Because the exposures were lower than expected, it was later decided to use only two windows in the analysis: ≤15 and >15 years prior to risk date. To exclude the influence of the amphiboles, which were not used in the factory before 1951, the entire cohort was also divided into two time windows in a separate analysis: ≤35 and >35 years.

In addition to asbestos and asbestos-cement dust, some workers in Salonit Anhovo were exposed to silica dust (free SiO2) or to cement dust (containing Cr6+), both lung carcinogens (IARC, 1997; U.S. Department of Labor, 2006). Airborne concentration data were not available for either silica or chromium, but it was possible to assign presence/absence of each contaminant in each year in each job. Using these data, the duration of silica and chromium exposures were obtained and investigated in lung cancer risk models.

Epidemiologic methods

All 6714 workers employed at the Salonit Anhovo factory who were hired after 31 December 1946, and who worked there at least one day between 1964 and 1994 were identified. To construct the cohort, we used wage lists and a computerized list of workers maintained by the company. The decision to begin the follow up in 1964 was based on the fact that the national cancer registration data from 1964 onwards are available in a computerized form.

The identification of all incident lung cancer cases in the cohort was accomplished by linking the cohort list with the Slovenian cancer register. The Slovenian national cancer register was established in 1957 and includes all cancer cases diagnosed in Slovenia after that date. All lung cancer cases were histologically confirmed.

The controls were selected from the total cohort using date of birth, gender and year of hire (pre-1959 or post-1959) as matching factors. Year of hire was matched on to insure the comparability of the exposure data quality, which was believed to be poorer from 1947 to 1958 compared to later. For each case, five controls closest to the case in date of birth were selected. Each control had to be alive at the date of the case’s diagnosis. The dates of death of controls were checked in the national mortality register at the Public Health Institute of Slovenia as well as the Institute of Slovenia for Statistics (Population Register). These two institutes produce the official national mortality data.

A smoking questionnaire was developed. The questions were taken from the standard American Thoracic Society smoking history questionnaire (Ferris, 1978). All cases but one were dead at the time of the study. The smoking questionnaire was sent to the closest next-of-kin for cases and dead controls. If the control was alive, the questionnaire was sent to him or her. Addresses and information on the closest next-of-kin were obtained from the factory employment service. An interviewer visited all interviewees who did not answer the mailed questionnaire. The interviewer was blind to case-control status and diagnosis. In cases for whom no relatives were found, the case’s or control’s personal doctor was asked for information about the patient’s smoking habits. Smoking data were obtained for all subjects but one. Duration of smoking and the number of pack-years of smoking were calculated for each subject.

The statistical methods followed the usual pattern of univariate descriptive procedures, then simple bivariate categorical analyses, followed by multivariate model construction. A comparison of analyses matched on pre/post 1959 hire with unmatched analyses revealed no evidence that this matching introduced any confounding into unmatched analyses, and so this match was not maintained in the results presented here.

Models of exposure and risk adjusted for confounding were constructed using conditional or unconditional multivariate logistic regression. When unconditional models were constructed, the matching variables were included as covariates. For each cumulative exposure variable and duration of exposure to asbestos, amphibole and chrysotile in each window (0–15, 16–25, 26–35 and >35 years prior to diagnosis), odds ratios (OR) and 95% confidence intervals (95% CI) were calculated: first crudely, and then separately for smokers and non-smokers. Because exposures were lower than expected during the design of the study, it was decided to combine several exposure time windows that had been chosen a priori (i.e. 16–25 and 26–35 windows were merged in one 16–35 window). Finally two windows were used: the first one 15 years prior to diagnosis, and the second one more than 15 years before (<15 and >15 years). Exposure variables were first treated as categorical exposed yes/no, and with one cut-point at the median. Later, when we learned that exposures...
were generally low, we also created a dichotomous variable for exposure above/below the 90 percentile. Logistic regression models were constructed for each of these dichotomous exposure definitions for cumulative exposure in the time windows adjusted for smoking and introducing interactions between smoking (yes/no) and the dichotomous cumulative exposure definition for each window. Next, either cumulative exposure or the natural logarithm of cumulative exposure was included as a continuous variable in the time windows. The logarithmic transformation was used to investigate the possibility that the strongly skewed cumulative exposure data resulted in a few very high-exposure subjects reducing the fit of the model.

Duration of exposure to SiO₂ and Cr₆⁺ were included in the logistic regression model with 15 year latency and with and without simultaneous fitting of smoking and asbestos variables.

RESULTS

There were 67 cases of lung cancer in the total cohort; of these 58 were hired after 1947, and were thus included in these analyses (Table 1). There were 335 controls (5 controls/case) selected.

Eighty-one percent of cases and 87% of controls were ever exposed to asbestos. Eighty-eight percent of cases and only 64% of controls were ever smokers. The mean age at diagnosis for cases was 60.1 years. There were 67 cases of lung cancer in the total cohort and 58 cases were included in these analyses (Table 1). There were 335 controls (5 controls/case) selected.

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There were several experiments with ventilation systems at that time, but almost all were quite inefficient. Despite this, there was an overall decrease in the mean exposures to both types of asbestos (although the medians actually increased slightly). The mean intensity for chrysotile was 2.26 f/cm³, and for amphibole it was 0.32 f/cm³. In 1986, the installation of a ventilation system was completed, and the exposures decreased substantially—chrysotile exposures averaged 0.66 f/cm³, and amphibole exposures 0.01 f/cm³.

The first window (0–15 years) was not expected to be associated with risk because of the well-established latency period for asbestos and lung cancer. Other dichotomous cutoffs were examined, including 10 and 20 years prior to diagnosis, and the results were essentially unchanged. The mean cumulative exposures to asbestos and to the two fiber types for cases and controls are summarized in time windows prior to risk date in Table 3.

The arithmetic mean cumulative exposures to asbestos (both fiber types) in the 15 years prior to the risk date was considerably greater for cases than for controls, although the medians were not. For earlier exposures, both cases and controls cumulated less exposure than in later periods, and the cases had less consistently a higher mean cumulative exposure than the controls. An essentially similar pattern was seen as well when the 90th percentile of cumulative exposure was compared between the cases and the controls. Cumulative exposures were very low especially for amphibole exposure. For example, the upper 25% of cases and controls had cumulative exposure to amphibole of only 0.1 f/cm²-years or more.

Table 1. Characteristics of cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 58*)</th>
<th>Controls (n = 290)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean S.D.**</td>
<td>Mean S.D.</td>
</tr>
<tr>
<td>Year of birth</td>
<td>1927 10.0</td>
<td>1927 10.0</td>
</tr>
<tr>
<td>Year began work</td>
<td>1962 7.3</td>
<td>1962 7.6</td>
</tr>
<tr>
<td>Year stopped work</td>
<td>1977 8.4</td>
<td>1980 9.0</td>
</tr>
<tr>
<td>Age started work</td>
<td>35 10.6</td>
<td>35.8 10.8</td>
</tr>
<tr>
<td>Age stopped work</td>
<td>50.0 10.8</td>
<td>53.0 8.9</td>
</tr>
<tr>
<td>Employment duration (year)</td>
<td>15.3 10.5</td>
<td>17.5 10.7</td>
</tr>
<tr>
<td>n %</td>
<td>n %</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4 6.9</td>
<td>20 6.9</td>
</tr>
<tr>
<td>Dead at time of study</td>
<td>57 98.3</td>
<td>118 40.7</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>51 88</td>
<td>186 64</td>
</tr>
<tr>
<td>Ever exposed to asbestos</td>
<td>47 81</td>
<td>252 87</td>
</tr>
</tbody>
</table>

*Number of subjects.  **Standard deviation.
Among the 57 cases with smoking data, only 6 (11%) workers did not smoke, while among controls, the percentage of non-smokers was higher (36%). On average, cases smoked 33.4 years, significantly more than controls (20.3 years, $P < 0.05$). The difference in pack-years of smoking was also very different ($P < 0.001$) between cases (34.7 years) and controls (24.6 years).

The crude unconditional odds ratio (OR) for smoking (ever versus never) and lung cancer was 3.8 (95% CI $= 1.8–9.1$). Using a conditional logistic regression, the OR for lung cancer was similar: 3.9 (95% CI $= 1.6–9.3$) for ever smokers compared to never smokers. The risk of lung cancer when pack-years were included as a continuous variable was estimated to be $1.02/pack-year$ (95% CI $= 1.01–1.03$).

Conditional logistic regression models were used to evaluate exposure-risk associations, conditional on the matching factors. Associations between lung cancer and exposure were close to null for asbestos as well as for the two fiber types when exposure was defined as ever versus never in each of the time windows (Table 4). All further results shown here are restricted to the period of more than 15 years prior to the risk date.

Raising the cut-point from ever versus never to above/below the median cumulative exposure, the odds ratios were slightly elevated, although the confidence intervals were still wide (Table 4). When the cut-point was set at the 90 percentile of cumulative exposure, the ORs for the cumulative exposure to total asbestos, chrysotile or amphibole increased to $1.5, 1.6$ and $2.0$, respectively (Table 4). Similar results were obtained when cumulative exposure to asbestos or either fiber type was modeled as a continuous variable, either on the native or logarithmic scales (data not shown).

To investigate the possibility of confounding or effect modification by smoking, separate models were estimated including smoking (defined as ever versus never smoked, and cumulative exposure at three cut-points (ever/never exposed, cut-point median and cut-point 90% exposure), and an interaction between them. ORs of the interaction between smoking and cumulative exposure were quite high, suggesting a different risk for smokers and non-smokers. However, these results were quite unstable, due to the small number of cases involved. There were only six non-smoking cases, and none with cumulative exposure above the 90 percentile. As a result, models for asbestos-associated lung cancer risk among non-smokers were very unstable. Smokers above the 90 percentile of either chrysotile (OR $= 1.8$, 95% CI $= 0.7–4.7$) or amphibole (OR $= 2.2$, 95% CI $= 0.9–5.5$) in the period more than 15 years before the case diagnosis had approximately twice the risk of those with lower exposures, albeit with wide-confidence intervals.

Prior to 1951, no amphiboles were used in the factory. We therefore divided the entire cohort into those who were exposed and those who were not exposed in the period of more than 35 years before the risk date because this window preceded 1951 for all cases. There were 8 cases and 34 controls who were exposed for 35 years or more before the risk date. The odds ratio for any exposure in this window was OR $= 2.2$, 95% CI $= 0.4–11.9$.

The 90 percentile cut-point for amphibole exposure more than 15 years before the risk date was $\sim 1.0$ f/cm$^3$-year, while for chrysotile it was much higher (Table 3). In order to compare the risks of the two fiber types, we estimated both risks using the same $1.0$ f/cm$^3$-year cut-point. The odds ratios comparing those above to those below this level were $2.0$ (95% CI $= 0.9–4.7$) for amphibole and $1.6$ (95% CI $= 0.6–1.8$) for chrysotile (Table 4).

We found no evidence that duration of exposure to either cement or silica dust was associated with lung cancer risk. A 15 year latency period was assumed and the >15 years window was the observation limit for the effect of exposure.

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<table>
<thead>
<tr>
<th>Time period</th>
<th>Asbestos (f/cm$^3$)</th>
<th>Chrysotile (f/cm$^3$)</th>
<th>Amphibole (f/cm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>1947–1971</td>
<td>3.33</td>
<td>0.33</td>
<td>0.01–300.27</td>
</tr>
<tr>
<td>1972–1985</td>
<td>2.44</td>
<td>0.5</td>
<td>0.00–99.24</td>
</tr>
<tr>
<td>1986–1994</td>
<td>0.67</td>
<td>0.15</td>
<td>0.00–22.14</td>
</tr>
</tbody>
</table>
period. Exposure and smoking were defined as dichotomous—yes/no variables. In the >15 years exposure window, only non-smokers exposed to cement had an elevated risk of lung cancer (OR = 2.2; CI = 0.1–44.9). However, the CI was very wide and included 1.0. Models were constructed to investigate the possibility that the cement or silica dust might have confounded or modified the asbestos-lung risk. No such evidence was observed, nor that either exposure confounded the associations with asbestos exposure (data not shown).

DISCUSSION

This study was conducted in an asbestos-cement plant that was unusual in several respects. First, a relatively large number of exposure measurements (more than 1000) were available covering a good portion of the plant’s history. Also available were detailed time-motion studies of each production job. The combination of these two types of data enabled a detailed exposure reconstruction for chrysotile and amphibole forms of asbestos (Dodic-Fikfak, 1998). Complete follow up as well as reliable cancer incidence and smoking data are additional strengths of this study. The smoking data for cases were gathered from next-of-kin while the data for living controls was obtained by postal questionnaire; next-of-kin were only relied upon to provide smoking information for controls who were deceased. This asymmetry might have introduced some recall bias, although we doubt that this bias could have had an important effect on the asbestos—lung cancer association because the magnitude of the smoking effect was consistent with other studies.

One reason for low dust concentrations was probably that a significant amount of the processing (prior to the mid-1960s) was performed with wet asbestos, which is a fairly effective dust control measure. Given that mean exposure intensities were generally below 1.0 f/cm³, it is perhaps not surprising that the study found only suggestive evidence of associations between lung cancer and asbestos.

We hypothesized this study would allow us to separately estimate risks from exposure to chrysotile and amphiboles. The main limitation interfering with this aim was low statistical power-confidence intervals.
for the separate fiber type estimates were wide. This comparison may also have been biased by cross contamination between the separate parts of the factory although the low statistical power is most likely the more important limitation. The literature reports a range of different findings from studies of asbestos-cement plants (no estimated risk separately by fiber type). Studies in North America (Hendersen and Enterline, 1979; Weill et al., 1979; Finkelstein, 1983; Finkelstein, 1984; Hughes et al., 1987) tended to find increased lung cancer risk and higher exposures than we observed. However, several European studies have found exposures closer to those in the Slovenian plant, and low to non-detectable lung cancer risks (Ohlson and Hogstedt, 1985; Gardner et al., 1986; Albin et al., 1990). A Norwegian study (Ulvestad et al., 2002) did find an elevated lung cancer risk, but only a few exposure measurements were available. A meta-analysis by Lash et al. (1997) permits a comparison of exposure levels and lung cancer risks among studies of asbestos-cement factories (Figure 2). The European studies reported median cumulative exposures in the range from 10 to 40 f/cm²-years. No asbestos-related excess mortality was observed in two (Ohlson and Hogstedt, 1985; Gardner et al., 1986), while a small excess was observed in the third (Albin et al., 1990). When the median and 90 percentile of cumulative exposure and their associated odds ratios from the present study are plotted alongside exposure-response relationships from the other studies, it is seen that the low risk estimates obtained from the low cumulative exposures we observed are consistent with the results of previous studies. Figure 2 shows the results for studies reporting cumulative exposures <100 f/cm²-years; a few studies with higher exposures found an increased lung cancer risk (Hendersen and Enterline, 1979; Finkelstein, 1983, 1984).

In the present dataset, the mean year of diagnosis was 1986, so that the time window more than 15 years earlier ended in 1971. The peak years of production were coincidentally between these dates (Figure 1). This explains why higher exposures were accumulated in the 0–15 years window than in the earlier period.

This study is significant for several reasons. First, the quality of the historical data was such that we have confidence in the cumulative exposure assignments. When combined with complete tumor ascertainment, this study has documented the lung cancer experience of an asbestos-cement factory with low-exposure levels. The resulting risk estimates were close to the null; and it would take a very extensive study to produce ‘statistically significant’ odds ratios in the observed range—less than 2.0. Nevertheless, it is useful to note the upper bounds of the 95% confidence intervals for these low risk estimates (Table 4). For example, the OR of 1.1 comparing those above and below the median cumulative chrysotile exposure had upper bounds of only 2.1, which means that much higher risks are inconsistent with these data.

This study is also significant because the Salonit Anhovo factory has demonstrated that it was possible to control asbestos dust, primarily by using wet methods, and limit exposures to concentrations well-below those observed in other asbestos factories.

Fig. 2. Comparison of risks among asbestos-cement plant studies. Based on meta-analysis of Lash et al. (1997). Vertical bars indicate 95% confidence intervals. Current study results indicated by arrows at median and 90 percentile of cumulative exposure for the cohort.
of the post-World War II era (Dodic-Fikfak, 2003). These exposure controls would not be adequate by today’s standards, but it is important to recognize that not all asbestos factories were heavily contaminated. Finally, this study has observed a somewhat higher lung cancer risk of amphibole than chrysotile forms of asbestos, albeit with limited precision as discussed above (Dodic-Fikfak, 2003). This difference in risk by fiber type is consistent with previous studies (Weill et al., 1979; McDonald et al., 1980, 1982, 1984, 1993; Liddell et al., 1997; McDonald and McDonald, 1997; Hodgson and Darnton, 2000; McDonald et al., 2004).

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