Conference Paper

THE AMPHIBOLE HYPOTHESIS - A NESTED CASE-CONTROL STUDY OF LUNG CANCER AND EXPOSURE TO CHRYSOTILE AND AMPHIBOLES*

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This paper describes a case control study investigating separately the lung cancer risk of exposure to chrysotile and to amphiboles. Logistic regression models were used to estimate separate exposure-response curves for the two fibre types, controlling for smoking. In the period longer than 15 years before lung cancer diagnosis, smokers above the 90th percentile of cumulative exposure to either chrysotile (OR=1.8, 95 % CI=0.6-5.2) or amphibole (OR=2.3, 95 % CI=0.9-6.2) had a somewhat higher risk than those with lower exposure. The author found suggestive evidence of an association between chrysotile and lung cancer, and especially between amphiboles and lung cancer. In this study, cumulative exposures to amphiboles were on average 40 times lower than cumulative exposures to chrysotile, and the author assumes that the amphibole effect would be much higher if the amphibole level of cumulative exposure were the same as that of chrysotile.

KEY WORDS: *asbestos, cumulative exposure, odds ratio, smoking*

The carcinogenic potential of chrysotile asbestos has become a controversial issue in recent years. Some researchers suggest that chrysotile has little potential for producing mesothelioma (1-8) while others claim the opposite (9-11).

Some authors suggest that chrysotile produces a risk of lung cancer similar to other asbestos fibre types (9, 10, 12-17, 19-24). In 1990, *Mossman and co-workers* (25) published an article in *Science* in which they proposed that chrysotile asbestos fibres posed little carcinogenic risk, especially in comparison to amphiboles. In a large cohort mortality study of Quebec chrysotile miners and millers, *McDonald and co-workers* (6) concluded that the observed excess cancer mortality and asbestosis mortality were probably related to contaminant tremolite. Some authors claim that it is not known whether the lungs of workers exposed to chrysotile-finished products contain sufficient levels of the contaminant tremolite to cause disease (26, 27). *Nicholson and Landrigan* (28**)** have argued that these conclusions are erroneous. Most case control studies that evaluated the potential relationship between the mesothelioma risk and lung concentrations of the different fibre types of asbestos demonstrated a clear relationship with amphibole lung burdens, but failed to find a relationship with lung chrysotile concentrations (2, 29-32). *Nicholson and Landrigan* (28) stated that the ratio of mesothelioma to excess lung cancer is the same for exposures to 97 % chrysotile, 100 % amosite, and mixtures of chrysotile, amosite, and crocidolite. Retrospective cohort mortality studies of workers who were predominantly exposed to chrysotile (9, 10, 12, 14-17, 19-23) provide strong evidence that exposure to chrysotile asbestos is associated with an excess risk of lung cancer, and this risk is similar to that in studies of cohorts with amphibole or mixed exposure (10, 18, 24, 33-35). In an analysis of the cohort of 11,000

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Quebec chrysotile workers *J. C. McDonald and A. D. McDonald* (36) found that the risk of lung cancer and mesothelioma was elevated substantially for workers exposed to high concentrations of tremolite (central mines), but there was little or no evidence of increased risk in workers exposed to lower concentrations of tremolite (peripheral mines) (7). *Liddell and co-workers* (8) followed the same cohort of Quebec chrysotile miners and millers: SMRs for all causes and lung cancer showed no elevation for workers exposed <1000 fibres/mL-years. Exposure to asbestos of at least 300 mppcf-years showed stronger associations with the disease; smokers consuming 20+ cigarettes a day had an SMR for lung cancer of 4.6. *Hughes and Weill* (37, 38) found a four-fold increase in lung cancer among asbestos-cement workers. This risk was limited to those who had radiological evidence of asbestosis at the start of the mortality follow-up.

Stayner and co-workers (10) examined the credibility and policy implications of the "amphibole hypothesis". They concluded that the mechanistic and lung burden studies did not provide convincing evidence for the amphibole hypothesis. Their conclusion was corroborated by a review by *Cullen* (39). *Smith and Wright* also concluded that the "examination of all pertinent studies makes it clear that chrysotile asbestos is similar in potency to amphibole asbestos" (11).

The amphibole theory is supported by the knowledge of chrysotile and amphibole behaviour in the lungs. Chrysotile disintegrates into constituent fibrils quickly. This may facilitate dissolution and disintegration. This is not the case with amphiboles, which are more durable and remain in the lung years after exposure. Chrysotile, despite its quick disintegration, remains in the lungs much longer. A multistage cancer process would require that fibres persist in the lung cells through many cell divisions. It is not yet certain, however, if the same fibre must be present in the target cells for each of the multiple stages. In occupational exposure, lung cells are usually continuously exposed to fibres and fibres are continuously present in the cells during their division even if no single fibre persists beyond one mitotic cycle (40).

Currently, there are no studies in which dose-response relationships have been estimated separately for cancer risk and exposure to different fibre types in the same exposed population.

The main objective of this study was to estimate quantitative dose-response relationships separately for amphibole and chrysotile asbestos exposure and the risk of lung cancer. This objective was achieved through a thorough quantitative exposure reconstruction using extensive available historical data and a lung cancer case control study estimating separate quantitative relationships between lung cancer risk and exposure to chrysotile and amphiboles.

SUBJECTS AND METHODS

Subjects

The case control study was nested in a cohort of 6714 workers at Salonit Anhovo, Slovenia, who worked at least one day between 1964 and 1994.

The investigated post-1947 cohort comprised 58 lung cancer cases and 290 controls. Eighty-one percent of cases and 87 % of controls were exposed to asbestos. Eighty-eight percent of cases and 64 % of controls were smokers.

At hire, the mean age for workers included in the cohort was 33.6 years, whereas the mean age at diagnosis was 60.6 year. The mean latency period, or the time since the first exposure, was 27 years.

Methods

All incident lung cancer cases in the cohort were identified by linking the cohort list with the list of lung cancer cases from the Slovenian cancer registry.

Controls were selected from the total cohort using date of birth and gender as matching factors. After the completion of the exposure reconstruction process, it was decided that the exposure estimates for 1959 could reasonably be assumed to be representative of the period back to 1947, since no technological changes occurred in that period. As a result, the analyses of the post-1947 cohort is mostly unmatched.

Each lung cancer case was matched as closely as possible by five controls according to the date of birth. Each control had to be alive at the date of the case's diagnosis. The dates of deaths of controls were checked in the national mortality registry at the Public Health Institute and the Statistics Institute of Slovenia.

Work histories were checked for all cases and controls. The factory identification number, the title of the job, department, date of hire, and the date of termination were noted for each job that each worker held throughout her or his work history. Job codes from the 1980 job-list were used to replace job titles in the workers' histories. Their names were also replaced

by identity codes. Work histories were completed for all subjects.

A smoking questionnaire was developed. The questions were taken from the standard American Thoracic Society smoking history questionnaire (41). All cases but one were dead at the time of the study. The smoking questionnaire was sent to the closest kin for cases and dead controls. If the control was alive, the questionnaire was sent to him or her (42-52).

An interviewer visited all interviewees who did not answer the questionnaire. In cases where no relatives were found, the case's or control's personal doctor was asked for information about patient's smoking habits. Smoking data were obtained on all subjects, but one.

Exposure Assessment Methodology

The monitoring of airborne fibre concentrations in the facility (mostly for compliance) began in 1961 and continued until 1997. The conditions of exposure did not change substantially until 1985 when the workers began using respirators, although they did not use them regularly. The extensive use of dry operations started in 1964 when the first autoclaves were introduced into production. After 1968, almost all operations were dry.

All air sampling measurements were taken as fixed location samples collected close to the workers' breathing zone.

Table 1 *Monitoring methods used in different time periods*

Period	Method	Unit of measurement
1961-1972	Konimeter	particles/cm^3
1974-1975	Membrane filter	fibers/cm^3
1975-1985	Gravimetric method	milligrams/m^3
1985 - present	Membrane filter	fibers/cm^3

Three methods (konimeter, gravimetric and membrane filter method) producing data in different units were used to measure airborne asbestos concentrations in the past (Table 1). The need to express exposure in only one unit of measurement appeared when it became desirable to evaluate the association between cumulative exposure for a particular worker or for a group of workers with the risk of a disease. Various researchers and agencies recommended different conversion factors (34, 35, 53-63). In 1985, 1986, 1987 and 1989, industrial hygienists collected side-by-side air samples using gravimetric and membrane filter methods. This produced a total of 78 paired measurements, 60 measurement pairs in the pipe and 18 measurement pairs in the sheet manufacture department. Because of the limited number of data points, we used a nonparametric method to calculate conversion factors from mg/m^3 to fibres/cm^3 (f/cm^3). Based on the department, amount of asbestos used, process type, and the product, five different conversion factors to convert measurements from mg/m^3 to f/cm^3 were obtained (64). Their values ranged from 0.3 to 4.7.

No side-by-side samples measuring f/cm^3 and p/cm^3 were available from the period when the konimeter was used. In 1974/75, 16 measurements were made using the membrane filter method yielding results in f/cm^3. The last measurements (N=31) expressed in p/cm^3 are available from 1969. These 16 and 31 measurements were used as paired data, and five different conversion factors from p/cm^3 to f/cm^3 were obtained for the two departments using the same nonparametric method as for conversions from mg/m^3 to f/cm^3 (64). The values of conversion factors ranged from 0.0002 to 0.003.

For each worker, job duration in days was calculated for each year and multiplied by the intensity of exposure to asbestos (chrysotile, amphibole) for that particular job, and then divided by 365.25.

Because air measurements for a particular task were made approximately every three years, there were gaps in available air sampling measurements. Exposure to airborne asbestos for these gaps was estimated in two ways: a) using available air measurement values from the previous or subsequent period or b) using the average for these periods and information about production process changes in each department.

The information on the duration of the job, the tasks performed, the percentage of time for each task, the percentage of amphibole and chrysotile used by each department each year, the production processes, product type, appropriate conversion factors and units of measurement (p/cm^3, mg/m^3 or f/cm^3) were fed to a Microsoft Access® database software to calculate the exposure intensity by job by year and by fibre (64). Annual cumulative asbestos exposure was summed up separately for each of the time windows (0-15 years, 16-25 years, 26-35 years and 35+ years before the date of lung cancer diagnosis or selection of corresponding control).

Statistical methods

Statistical methods followed the usual pattern of univariate descriptive procedures, simple bivariate

categorical analyses, followed by a multivariate model construction.

Descriptive statistics were used to look for errors in data not identified by data checking, and to determine the ranges of available data. Correlation coefficients were calculated between different exposure variables. Calculations included *t*-tests for differences of means of exposure variables between cases and controls and crude odds ratios (OR) using two by two tables for all exposure and smoking variables and all windows. Models of exposure and risk adjusted for confounding were constructed using Stata software conditional logistic regression models. Analyses were done using a multivariate logistic regression to preserve the matching according to age and birth date. Variables (cumulative exposure to asbestos, chrysotile, and amphibole) were first treated as categorical variables: exposed yes/no, and with one cut-point (chosen alternatively as the median and the 90th percentile of cumulative exposure). Simple conditional logistic models were constructed for each of these dichotomous exposure definitions for the three cumulative exposure variables adjusted for smoking and introducing interactions between smoking (yes/no) and the dichotomous cumulative exposure definition for each window.

RESULTS

The OR for lung cancer was 3.2 (CI=1.5-7.0) for those who had ever smoked compared to those who had never smoked.

The average exposures (Table 2) and cumulative exposure to total asbestos was smaller than expected, with the greatest cumulative exposure in the 0-15 year window. This period was the assumed latency period, and was not included in the basic analysis. The initial analyses with dichotomous exposure variables focused on the 16+ window, that is, on all exposures which occurred more than 15 years before case diagnosis (Table 3).

Odds ratios for "ever exposed" versus "never exposed" to total asbestos, chrysotile or amphibole were close to 1.0 in the 16+ window. All confidence intervals (CI) were <1.0. When cumulative exposure was stratified by smoking, the ORs among smokers became a little greater than 1.0, but the CI range still included values <1.0.

When the cut-point was set at high cumulative exposure (the 90th percentile of cumulative exposure), the smokers had slightly higher ORs for cumulative exposure to either total asbestos, chrysotile or amphibole (Table 3), but all CI ranges still included values <1.0. Because only six cases were non-smokers, the calculated risk for non-smokers was almost 0.

DISCUSSION

This study focused on the difference in the incidence of lung cancer between those asbestos-cement workers in the Salonit Anhovo factory who were exposed mostly to chrysotile and those who were exposed mostly to amphiboles. Despite a longstanding controversy over different carcinogenic potentials of chrysotile and amphibole asbestos, currently there are no epidemiologic studies which estimate dose-response relationships separately for exposure to

Table 2 *Geometric Mean (GM) Asbestos Exposure by Operation in Three Periods: 1947-1971, 1972-1985, and 1986-1994 in f/ cm^3*

Operations	Total asbestos (GM) 1947-1971 f/cm^3	Total asbestos (GM) 1972-1985 f/cm^3	Total asbestos (GM) 1986-1994 f/cm^3
Pipe			
Dry Preparation (asbestos)	7.75	4.74	0.35
Wet Production (asbestos cement)	0.30	0.19	0.12
Dry Production (asbestos cement)	0.31	1.14	0.30
Dry Finishing (asbestos cement)	0.42	1.21	0.30
Sheet			
Dry Preparation (asbestos)	2.90	2.38	0.60
Wet Production (asbestos cement)	0.10	0.19	0.15
Dry Production (asbestos cement)	0.10	0.40	0.15
Dry Finishing (asbestos cement)	0.44	0.48	0.16

Table 3 *Cumulative exposure to asbestos above the 90th percentile and lung cancer risk in post-1947 cohort, 16+ year window*

Subjects	Cases/ controls	Total asbestos OR	95 % CI	Chrysotile OR	95 % CI	Amphibole CI	95 % CI
All	58/290	1.5	0.6-3.9	1.6	0.6-4.1	2.0	0.9-4.7
Smokers	52/185	1.6	0.6-4.6	1.8	0.6-5.2	2.3	0.9-6.2
Non-smokers	6/105	almost 0		almost 0		almost 0	

chrysotile and to amphiboles. Having the information about the annual consumption of different types of asbestos, accurate workers' histories, quantitative exposure measurements, information about smoking for all workers, and centralised reporting of all incident cancers for more than 35 years, we believe that our research could contribute to the debate about the amphibole theory.

The quantities of amphiboles used at Salonit Anhovo over the years were much higher than those cited by *McDonald* (2). The peak consumption totalled 2987 tons in sheet and pipe manufacturing departments together. As the amphiboles were used from 1951 to 1990, and exposure levels were larger than trace, we expected to find a greater risk of lung cancer among those workers who were exposed to higher amphibole concentrations than in those who were exposed mostly to chrysotile with amphiboles only in traces.

A crude comparison of our results shows that average exposure levels to chrysotile or asbestos fibres are much lower than in some studies (1, 4), but similar to those reported in cement asbestos factories in Sweden and the UK (65-67). No studies were found with which it would be possible to compare the average amphibole concentrations in factories where both fibre types were used.

The effect of smoking was as expected; workers from the cohort who had ever smoked ran three times higher risk of getting lung cancer than non-smokers. The synergistic effect of smoking and asbestos may have contributed to these increased cancer risks, but, as the earlier studies suggest, the asbestos exposure was still too low to expect an increase.

In the conditional logistic regression models, the analysis included a dichotomous categorical cumulative exposure definition for the 16+ year window separately for smokers and non-smokers. When the 90th percentile was included as the cut-point of cumulative exposure, the results showed significant differences in the risks. The risk for workers above the 90th percentile of cumulative exposure to chrysotile (11.60 f/cm^3-years) and total asbestos (11.98 f/cm^3-years), smokers and non-smokers alike, was 50 % higher than for those below the 90th percentile of cumulative exposure. The risk for workers above the 90th percentile of cumulative exposure to amphiboles (0.54 f/cm^3-years) was twice as high as for those below the 90th percentile of cumulative exposure. The confidence interval for cumulative exposure to amphiboles was close to 1.0.

Although associations in this study are generally weak, evidence suggests an association between chrysotile and lung cancer, and especially between amphiboles and lung cancer. When exposures in the period longer than 15 years after the case's diagnosis were studied, smokers above the 90th percentile of either chrysotile (OR=1.8, 95 % CI=0.6-5.2) or amphibole (OR=2.3, 95 % CI=0.9-6.2) had a higher risk than those with lower exposure. It is worth stressing that cumulative exposures to amphiboles were on average 40 times lower than cumulative exposures to chrysotile, and we assume that the amphibole effect would be much higher if the level of cumulative exposure to amphiboles were the same as that of chrysotile.

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Sažetak

AMFIBOLSKA HIPOTEZA – ISTRAŽIVANJE ODNOSA IZMEĐU KOHORTE PAROVA OBOLJELIH OD KARCINOMA PLUĆA/KONTROLE I IZLOŽENOSTI KRIZOTILU I AMFIBOLIMA

U ovome epidemiološkom istraživanju kohorte parova slučaj/kontrola (engl. *nested case-control cohort study*) ispitan je komparativni rizik od pojave karcinoma pluća u kohorti od 6714 muškaraca izloženih mineralnim vlaknima krizotila i amfibola u tvornici Salonit, Anhovo, Slovenija u razdoblju od 1964. do 1994. godine. Na poduzorku od 52 pušača s karcinomom pluća i 185 po dobi i spolu odgovarajućih kontrola u razdoblju duljem od 15 godina prije utvrđivanja dijagnoze, logistička je regresija pokazala da su radnici s više od 90-te percentile kumulativne izloženosti krizotilu (stupanj rizika, tzv. odds ratio, OR=1,8; interval pouzdanosti, 95 % CI=0,6-5,2) ili amfibolu (OR=2,3; 95 % CI=0,9-6,2) imali povećani rizik od pojave karcinoma pluća naspram kumulativno manje izloženih osoba. Kako je u ovom poduzorku kumulativna izloženost amfibolu bila u prosjeku 40 puta niža od izloženosti krizotilu, u radu se pretpostavlja da bi uz jednaku kumulativnu izloženost učinak amfibola bio znatno jači.

KLJUČNE RIJEČI: *azbest, kumulativna izloženost, odds ratio, pušenje*

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