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MINERAL FIBRE CONTENT OF LUNG IN MESOTHELIAL TUMOURS IN NORTH AMERICA

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Abstract—In a survey through pathologists of all fatal malignant mesothelial tumours in North America in 1972, 274 cases were ascertained and case–control studies were carried out. Specimens of lung tissue were obtained for 99 (76 male and 23 female) of the 172 autopsied case–control pairs and were analysed for asbestos fibres by electron microscopy and X-ray energy-dispersive analysis. Equal quantities of chrysotile fibres were found in cases and controls. An amosite fibre content of more than 1×10^6 per g dried lung was found in 26 male cases and 8 controls and of crocidolite in 15 cases and 5 controls. The two men who had ever worked in an asbestos factory, 6 of the 8 who had worked as insulators and 9 of the 14 who had worked in a shipyard had more than 1×10^6 fibres of one or both of these amphiboles. In the 23 female pairs studied, there was a small excess of amphiboles (3 cases and 1 control) and of chrysotile (23 cases and 17 controls) in cases compared with controls.

INTRODUCTION

AN ASSOCIATION between malignant mesothelial tumours and exposure to asbestos was first recognized in about 1960. With the aim of studying the incidence of these tumours in Canada and their association with occupational exposure to asbestos and other possible agents, we began in 1966 to ascertain and register all cases in Canada. We communicated with all pathologists who were members of the main Canadian pathological societies asking for information about all cases diagnosed since 1959. By further letters and telephone calls we obtained a reply from every pathologist. This procedure was repeated in 1970, and in 1973, using the same methods, we surveyed the entire U.S.A. and Canada; this involved communicating with over 7000 pathologists. We carried out case–control studies of the cases registered by methods which have been described (McDONALD *et al.*, 1970) and with results recently summarized (McDONALD and McDONALD, 1980). In brief, for each case a control was selected with pulmonary metastases from a primary tumour other than lung cancer and matched for sex and age. Relatives and friends of the deceased patients were interviewed by field investigators who were ignorant of whether they were cases or controls. They completed a standard questionnaire which included a full occupational history. This was coded 'blind' by clerks, using a classification described elsewhere (McDONALD, 1979).

In all, 274 mesothelial tumours were ascertained in North America in 1972, 102 diagnosed at biopsy and 172 at autopsy. These 172 autopsied mesothelial tumours (129 in males and 43 in females) and their matched controls are the subjects of this study.

METHODS

Specimens of lung were sought from pathologists for all 172 cases and their matched controls. Pieces of lung tissue (in paraffin or formalin) were obtained for 99 case–control pairs (76 male and 23 female). For the remaining 73 pairs, no lung tissue was available for the case or the control or both. However, the cases studied resembled the whole series in terms of asbestos-related occupations except for relatively fewer asbestos factory workers because of a lack of material from New Jersey. Before analysis, cases and controls were assembled in random order in one series and renumbered; the analyses were thus carried out 'blind'. They were analysed in five batches, constituted in the order in which specimens were received, the two members of a case–control pair being included in the same batch. The lung tissue specimens were prepared and examined by the methods described by POOLEY and CLARK (1979, 1980) using an electron microscope and X-ray energy-dispersive analyser. For each specimen, an estimate was made of the numbers of different types of mineral fibres per g dried lung. Fibres were defined as having a length/breadth ratio of 3 or more. A preliminary report on the asbestos content of the first 37 case-control pairs that were analysed has been published (McDONALD, 1980a). We now report the analyses of all 99 case–control pairs.

FINDINGS

Five mineral types of asbestos were found in the lung specimens. The distributions of the counts are shown in Table 1. In the 76 pairs of males, 86% of both cases and controls had more than 1×10^6 fibres per g dried lung and there was no difference in chrysotile fibre content between cases and controls. For amosite, 26 cases had more than 1×10^6 fibres compared with 8 controls, and for crocidolite, 15 cases and 5 controls. Six cases and 3 controls had more than 1×10^6 fibres of anthophyllite and there was also a small excess of cases with more than 10×10^6 fibres of tremolite. In the males 21 (35%) of the 60 lung specimens from pleural mesothelial tumours contained more 1×10^6 fibres of amosite or crocidolite and 8 (50%) of the 16 peritoneal tumours.

TABLE 1. NUMBER ($\times 10^6$) OF ASBESTOS FIBRES PER g DRIED LUNG TISSUE IN 76 MALE AND 23 FEMALE CASES OF MESOTHELIOMA IN NORTH AMERICA AND MATCHED CONTROLS

No. of fibres	Chrysotile Cases	Chrysotile Controls	Amosite Cases	Amosite Controls	Crocidolite Cases	Crocidolite Controls	Anthophyllite Cases	Anthophyllite Controls	Tremolite Cases	Tremolite Controls
Males										
None	3	1	37	47	47	60	58	61	29	31
<1	8	11	13	21	14	11	11	12	33	28
1<10	38	38	14	7	6	5	4	3	10	16
10<100	25	22	8	1	8	—	2	—	3	1
100<1000	2	2	3	—	1	—	—	—	—	—
1000 and over	—	2	1	—	—	—	—	—	1	—
Females										
None	—	—	17	15	15	16	18	17	[illegible]	9
<1	—	5	4	7	6	6	2	5	[illegible]	8
1<10	12	11	2	1	2	1	3	1	7	6
10<100	10	7	—	—	—	—	—	—	—	—
100 and over	1	—	—	—	—	—	—	—	—	—

Occupational histories were known in 70 (92%) of the 76 male cases studied. Table 2 shows the numbers of men with mesothelial tumours who were ever employed in certain occupations for which an association with mesothelioma has been reported. These groups are not mutually exclusive. More than 1×10^6 fibres of either amosite or crocidolite or both were found in the two employees of factories which had manufactured or used asbestos, 6 of the 8 insulators, 9 of the 14 men who had worked in construction and 6 of the 21 who had worked in heating trades. In many instances both amphiboles were present; when only one mineral type was found, it was generally amosite and in only 1 case (an electrician who had worked in the naval shipyard at Charleston, SC) was it crocidolite.

Table 3 shows the chrysotile content of the lung specimens according to whether more than 1×10^6 fibres of amphibole were present in the cases. The 29 mesothelial tumours with an amphibole content of 1×10^6 fibres or more had a similar quantity of chrysotile to their matched controls. The chrysotile content of cases with less than 1×10^6 fibres of amphibole was a little lower, but again the cases closely resembled the matched controls.

All 23 female cases had more than 1×10^6 chrysotile fibres per g lung compared with 18 controls; 3 cases and 1 control had this quantity of amosite or crocidolite. There was also a small excess of anthophyllite (3 cases to 1 control) but 2 of these cases also contained amosite or crocidolite.

TABLE 2. AMPHIBOLE FIBRES IN LUNG TISSUE OF MEN WITH MESOTHELIOMA EVER EMPLOYED IN CERTAIN OCCUPATIONS

	Ever employed	More than 1×10^6 fibres per g of dried lung: Either amosite or crocidolite	Amosite only	Crocidolite only
Heating trades	21	6	4	1
Shipyards	14	9	3	1
Construction	15	6	3	—
Insulation	8	6	1	—
Factory (asbestos)	2	2	2	—

TABLE 3. CHRYSOTILE FIBRE CONTENT OF LUNG IN CASES AND MATCHED CONTROLS ACCORDING TO THE AMPHIBOLE (AMOSITE OR CROCIDOLITE) CONTENT OF THE CASES

Chrysotile fibres 1×10^6 per g lung	Amphibole $\geq 1 \times 10^6$ fibres per g lung		Amphibole $< 1 \times 10^6$ fibres per g lung	
	Cases	Controls	Cases	Controls
Nil	1	—	2	1
<1	3	4	5	7
$1<10$	12	14	26	24
$10<100$	11	10	14	12
100 and over	2	1	—	3
	29	29	47	47

DISCUSSION

An association between malignant mesothelial tumours and exposure to crocidolite is well documented for both mining and milling (WAGNER *et al.*, 1960; TALENT *et al.*, 1980; HOBBS *et al.*, 1980) and manufacture (JONES *et al.*, 1980b; McDONALD, 1978a). In this series there was evidence that amosite was associated with mesothelial tumours, but not evidence that crocidolite was independently associated with them. A large excess of mesotheliomas has been reported in amosite factory workers (SEIDMAN *et al.*, 1979), but only a few cases have been observed in amosite miners and millers (WEBSTER, 1973), although no cohort study has yet been undertaken. Amosite has been extensively used for insulation in the United States (SELIKOFF *et al.*, 1970; COOPER and BALZER, 1968). It has been suggested from the epidemiological evidence that the high incidence of mesothelial tumours in North American insulators might be due to their exposure to amosite (McDONALD, 1978b); the present findings are consistent with this explanation.

The equal quantities of chrysotile fibres found in lung tissue from cases and controls fail to support any association between this mineral type of asbestos and mesothelial tumours. However, the lung chrysotile fibre content at death must be interpreted cautiously, as these fibres probably disappear in the course of time (ROWLANDS *et al.*, 1982). In a British study JONES *et al.* (1980a) also found that lung tissue from cases of mesothelioma contained no more chrysotile than controls. If chrysotile were responsible for a proportion of the mesothelial tumours in the present study, higher counts of chrysotile fibres might be expected among cases without an excess of amphibole fibres, but this was not found. The failure to find an association with chrysotile in the present study is consistent with the very low incidence of mesothelioma reported in a large cohort study of workers exposed only to chrysotile in mining and milling (McDONALD *et al.*, 1980) and its virtual absence in factories (ELWOOD and COCHRANE, 1964; WEISS, 1977; DEMENT *et al.*, 1982; NEWHOUSE *et al.*, 1982).

The epidemiological findings for cases in 1972 showed a 36% excess of occupations entailing exposure to asbestos in cases compared with controls. The 26% excess found in the present study of mesothelial tumours with more than 1×10^6 fibres of amosite or crocidolite is of the same order.

In females the possible small association between amphibole content and mesothelial tumours is consistent with the epidemiological finding that only about 2% of these tumours in females were attributable to an occupational exposure to asbestos. On the other hand, female cases were rather more frequently employed in industry (although not working with asbestos) than controls, which could account for the slightly higher chrysotile content of their lungs.

Differences of opinion occur among pathologists over the diagnosis of mesothelial tumours. A pathological review of these 99 cases will shortly be completed by the UICC mesothelioma panel in the U.S.A. The series will then be re-analysed in the light of their findings.

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DISCUSSION

G. Berry: In your concluding remarks, you quoted a paper presented at the IARC Symposium on Biological Effects of Mineral Fibres, Lyon, 1979, by Jones *et al.*, as saying that dust studies in the U.K. had demonstrated an association between mesothelioma and crocidolite rather than amosite. As one of the authors of that paper I would like to correct your quotation; what was actually said was: 'This study provides no evidence on the relative hazards of amosite and crocidolite in producing mesotheliomas'.

Professor A. D. McDonald: I stand corrected. What I should have said was that in Britain crocidolite and amosite appeared to be equally present in the lungs of cases of mesothelioma, but in North America amosite was far commoner than crocidolite and where only one of these amphibole types was present, it was amosite.

H. Weill: While your conclusions are, in general, suitably cautious, you may be over cautious on the disappearance of chrysotile from tissue. Your data show that chrysotile fibres are present in the tissue; it does not disappear completely. If there has been some loss of chrysotile, there seems no reason to believe that this would be different between cases and controls, your conclusions concerning the pathogenicity of amphibole should not therefore be affected.

Professor A. D. McDonald: There is substantial evidence that chrysotile fibres disappear from lung tissue in the course of time. Exposure at different intervals before death could have resulted in equal quantities of crysotile in the lungs of cases and controls. It seems unlikely, as you point out, that differential removal of chrysotile occurred in cases compared with controls.

M. Lippmann: I would like clarification on how you selected your controls; did they have known exposures to asbestos?

Professor A. D. McDonald: The controls were cases of metastatic carcinoma of the lung arising from primary tumours other than those of lung or pleura; they were matched for hospital and for age and sex. They were also selected so that their mode of death might not have been very different from that of the mesothelioma cases. The interviewers were given cases and controls 'blind', so that they interviewed without knowing whether they were interviewing relatives of cases or controls. Prior to the interview they knew nothing about the occupational histories. The occupations recorded were then coded by clerks who did not know which were cases and which controls.

F. H. Y. Green: What was the rationale for choosing cases with metastatic carcinoma of the lung as your control group? How did you ensure that the control tissues were free of tumour?

Professor A. D. McDonald: These were specimens that had been taken at autopsy; pathologists generally keep one or more pieces of lung tissue. Before incineration for fibre analysis, sections were cut from the blocks and any tumour present was removed from the blocks.

G. Major: More detailed classification of occupations than demonstrated in Table 2 is desirable. As a practising occupational hygienist, I know that insulators are employed in shipyards and that the broad term 'construction' is too wide to be helpful.

Professor A. D. McDonald: The method of classification and coding of occupations was described in a paper 2 yr ago at the American Academy of Science. I agree that this is a great problem and, to make it as objective as possible, we asked Prof. Selikoff for a classification which he had used in a study of autopsies in New York. We took his series of questions regarding different occupations and got the clerk to apply them to cases and controls in a blind fashion so that each successive question was answered. We have previously examined shipyard and construction workers without insulation and heating trades and found that there was still an association with mesothelioma. In Table 2 the shipyard and construction workers included insulation and heating trades (as stated in the text).

W. H. Walton: Almost half the male and nearly all the female cases had no amphibole in their lungs and yet all had chrysotile. How can you deduce from that, that the cause is the amphibole and not the chrysotile?

Professor A. D. McDonald: Mestheliomas have been reported well before the industrial exploitation of asbestos and they are by no means all caused by asbestos. Most cases did have chrysotile fibres in their lung tissue, but so did most controls, and in similar quantities. Taken at face value this finding suggests that there is no association between chrysotile and mesothelioma. The substantially larger number of cases than controls with more than 1×10^6 fibres of amosite and crocidolite indicate an association between these mineral types of asbestos and mesothelioma.