Malignant Mesothelioma in North America

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Ascertainment, through 7,400 pathologists, of all fatal malignant mesothelial tumors in Canada (1960–75) and the U. S. A. (1972) gave a total of 668 cases (272 in 1972). In Canada, the annual number of male cases rose from about 17 in 1966 to 25 in 1972 but the number of female cases remained fairly steady at a much lower level. The annual incidence in North America in 1972 was estimated at 2.8 per million males and 0.7 per million females aged 15 years and over. Occupational histories were obtained "blind" for 480 of the 557 cases through 1972, and their matched controls; relative risks were as follows: insulation work, 46.0, asbestos production and manufacture, 6.1, heating trades (other than insulation) 4.4. For nearly half the male cases and for about 5% of female cases, the tumor could be attributed to occupational exposure to asbestos, of which a fifth were in shipyards. No indication was found of other possible causes (including man-made mineral fibers, tobacco smoking, or residence near zeolite deposits). Four subjects were men who had been employed in Quebec chrysotile mines and 3 were children of employees, but no other subject had lived in the mining area. The findings remain consistent with a much greater mesothelioma-producing potential for crocidolite and amosite than for chrysotile; however, further studies of factory workers exposed to chrysotile only are needed to confirm this. Mineral fiber analysis of lung tissue from patients and controls is in progress.

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AT INTERVALS SINCE 1970, we have reported continuing studies of malignant mesothelial tumors throughout Canada and more recently in the United States.[12–14,17] Complete ascertainment of all fatal cases known to pathologists has been attempted, followed by detailed case-control enquiries. The need to monitor this disease and available methods of case finding have also been recently reviewed.[11] The purpose of this report is to bring together the information derived from these surveys, published and unpublished, and to consider the epidemiologic interpretation, with particular regard for the carcinogenicity of the various mineral types of asbestos fiber and the roles of other possible etiologic factors.

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Materials and Methods

At the end of 1967, we wrote to all members of the main pathologic societies in Canada enquiring about all fatal cases of primary malignant mesothelial tumors diagnosed by means of autopsy or biopsy examination since 1959. These enquiries were continued until a reply was received from every pathologist. The procedure was repeated at two to three year intervals and by this means, all known cases were ascertained to the end of 1975. In 1973, letters were written to all 6,977 pathologists listed by the United States Armed Forces Institute of Pathology, enquiring about any fatal case in 1972.[17] Responses were obtained from all but 394 pathologists, 311 of whom had worked at a hospital from which a reply had been received, so we believe coverage in the U. S. A. was also close to complete. In each case, a physician on our staff visited the hospital, reviewed the records with the pathologist and selected, as a control, a case matched for sex, age and year of death in which pulmonary metastases were present from a nonpulmonary malignant tumor. Relatives were then visited, usually by a public health nurse who, without knowledge of the identity of cases and controls, completed a detailed four-page standard questionnaire covering full occupational and residential history and smoking habits. For each occupation reported, the respondents were systematically questioned about exposure to dust from

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cement, wood, fiberglass, asbestos, rubber, copper, or nickel. Respondents were also asked whether any member of the household had brought home dusty clothing, and if so, the nature of the work. In Canada, 312 cases were registered during the period from 1960 through 1972, and questionnaires completed for 95%, including 281 case-control pairs. In the U. S. A., 245 cases were registered for 1972 and questionnaires completed for 91%, including 209 case-control pairs.

A list of occupations associated with asbestos exposure was supplied by Professor I. J. Selikoff. This had been used in New York and in the Netherlands[25] and included a series of jobs with which our clerk coded the occupations, blind as to the identity of subjects and controls. The jobs listed were separately assessed at four centers experienced in asbestos research (Table 2, footnote*) as to the probability that they entailed exposure to asbestos. There was good agreement over the "definite" and "unlikely" categories but some difference in separating 'probable' from 'possible' (Table 2).

Occupations were classified under seven main headings (A–G), five in which an association with mesothelioma has been recognised (A, insulation; B, asbestos production and manufacture; C, heating trades; D, shipyards; E, construction), a sixth group, F, of other listed jobs thought to entail asbestos exposure, and a seventh group, G, of unlisted jobs. Place of residence was classified as urban or rural and examined to see whether it was within 20 miles of an asbestos mine and, in the U. S. A., of a known zeolite deposit. The latter was added because of the recent report of a very high incidence of malignant mesothelioma in certain villages in Turkey with a natural occurence of zeolites.[1]

The cases in which a biopsy or autopsy specimen could be obtained are being reviewed by the Canadian and American mesothelioma panels of pathologists* and specimens of lung tissue from case-control pairs are being examined by Dr. F. D. Pooley for mineral fibers by means of electron microscopy and x-ray energy-dispersive analysis. The results of this work will be reported later.

Results

Sex and Age and Tumor Site

Of 557 cases reported to the end of 1972, 395 (71%) were male and 162 (29%) were female. In males, 307 (78%) were pleural (including three pericardial tumors) and 88 (22%) were peritoneal including 14 also affecting the pleura). In females, 99 (61%) were pleural (including six pericardial tumors) and 63 (39%) were peritoneal (including seven also affecting the pleura). At the time of death 11% of male subjects were under 45 years of age; 50% were 45–64 years old; and 39%, 65 years or older. Only one subject, a male, was under 15 years of age.

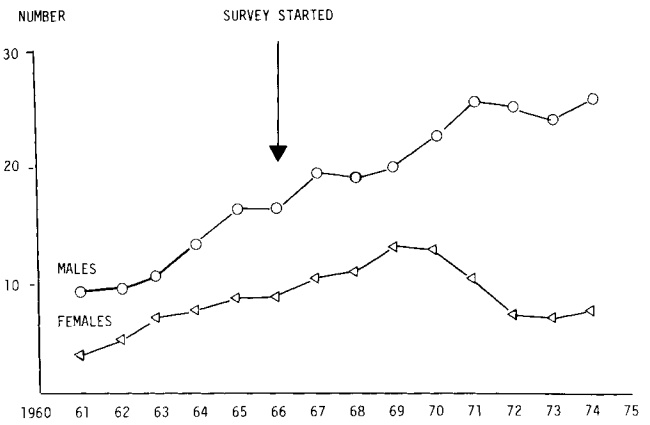

FIG. 1. Annual number and sex of fatal cases of malignant mesothelioma reported by pathologists in Canada, 1960–75 (three-year moving averages).

Incidence

As malignant mesothelioma is usually fatal within 18 months of first symptoms, deaths reflect incidence quite closely. The trend in Canada by date of death is presented in Fig. 1, using three-year moving averages. Ascertainment was begun in 1967 and some of the increase before then was probably due to incomplete case finding for the earlier period. After 1969, the trends separate as that for males continues to rise and for females, to fall back. Although the average annual incidence for the period between 1966 and 75, based on the population for 1971, was considerably higher in Quebec than in other parts of Canada, the incidence of accepted cases differed little in the three regions (Table 1). In the U. S. A., the rates for males were highest in the Pacific and Mid-Atlantic regions: review by the pathology panel reduced that in the Mid-Atlantic. Rates for females were not related to those for males.

Work Histories

Analysis of probability of occupational exposure to asbestos for patients and controls during the period up to 10 years before death is presented in Table 2. Results based on the four centers gave similar rates for

* Canadian Tumour Reference Centre, National Cancer Association of Canada at University of Ottawa, Ontario. UICC Mesothelioma Panel, at Barnert Memorial Hospital, Paterson, New Jersey.

TABLE 1. Annual Incidence of Malignant Mesothelioma per Million Population by Age, Sex, and Geographic Region and the Result of Review by Pathology Panel

	Male						Female					
	Incidence (per mill)			Total number of cases	Pathology panel		Incidence (per mill)			Total number of cases	Pathology panel	
	15–44 years	45 years and over	15 years and over		Number reviewed	Accepted (%)	15–44 years	45 years and over	15 years and over		Number reviewed	Accepted (%)
Canada (1966–75): Provinces												
Ontario	0.7	5.7	2.6	71	60	83	0.4	2.2	1.1	31	20	60
Quebec	1.2	12.0	4.9	103	83	55	0.8	4.7	2.2	49	32	53
Rest	0.4	3.0	2.2	58	49	76	0.2	1.3	0.7	19	18	61
TOTAL	0.8	7.0	3.0	232	192	69	0.4	2.5	1.3	98	70	57
U. S. A. (1972): Census regions												
New England and South-Atlantic	0.5	5.4	2.5	36	20	100	0.1	0.9	0.4	7	3	100
Mid-Atlantic	0.1	8.0	3.6	46	29	69	0.1	1.3	0.7	10	7	57
Northeast Central	0.2	6.0	2.6	35	27	82	0.0	2.9	1.3	19	17	82
Northwest, Southeast, Southwest Central and Mountain	0.2	4.3	1.8	35	21	71	0.3	1.1	0.6	13	14	67
Pacific	0.0	10.3	4.0	37	28	93	0.0	1.7	0.7	7	4	75
TOTAL	0.2	6.5	2.7	189	125	74	0.1	1.6	0.8	56	45	69

definite and unlikely exposure, and for the two intermediate categories taken together. Asbestos exposure for both subjects and controls was considerably more frequently recorded in the U. S. A. than in Canada. In Canada, 45.9% of subjects and 18.9% of controls had worked in occupation groups A–E and, in the U. S. A., 64.8% of subjects and 27.0% of controls (Table 3). The five groups were ranked according to the ratio of subjects to controls and made mutually exclusive by entering each man only once, in the highest group for which he qualified. Relative risks[6] were calculated for both countries combined, by comparing each group in turn with the two groups F and G taken together. Insulation carried by far the greater risk (RR = 46.0), followed by asbestos production and manufacture (RR = 6.1), and the heating trades other than insulation (RR = 4.4). After exclusion of men known to have worked in insulation or heating trades, an elevated risk still remained for those who worked in shipyards (RR =2.8) and construction (RR = 2.6). In all, 49 cases involved men who had worked in shipyards, including 29 who were insulators

TABLE 2. Distribution (%) of 185 Canadian and 159 U. S. Male Case-Control Pairs According to the Probability of Occupational Asbestos Exposure as Classified in Four Centers*

	Asbestos exposure								Case-control difference for definite and probable exposures
	Definite		Probable		Possible		Unlikely		
Center*	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	
Canada (1960–72)									
1	11.9	1.1	43.8	31.4	4.3	2.7	40.0	64.9	23.2
2	11.9	1.1	20.5	14.6	21.1	15.7	46.5	68.6	16.7
3	13.5	2.7	29.7	21.1	18.9	20.5	37.8	55.7	19.4
4	11.9	1.1	22.7	13.0	22.7	27.6	42.7	58.4	20.5
U. S. A. (1972)									
1	18.2	3.8	51.6	35.2	3.8	1.9	26.4	59.1	30.8
2	18.9	3.8	31.4	18.7	20.8	18.6	28.9	58.9	27.8
3	24.5	6.3	34.0	19.5	16.4	19.5	25.1	54.1	32.7
4	18.9	3.8	33.3	15.1	22.6	27.0	25.2	54.1	33.3

* Centers: (1) Environmental Sciences Laboratory, Mount Sinai School of Medicine, New York; (2) Gesondsheitsorganisatie TNO, den Haag, the Netherlands; (3) Department of Epidemiology and Health, McGill University, Montreal, Canada; (4) TUC Centenary Institute of Occupational Health, London School of Hygiene and Tropical Medicine, London, England.

TABLE 3. Employment in Occupational Groups A–G* Ten or More Years Before Death for 344 Male Cases and Their Matched Controls (Canada, 1960–72; U. S. A., 1972)

Occupational group	Jobs		Men		Relative risk
	Cases	Controls	Cases	Controls	
A. Insulation	27	1	27	1	46.0
B. Asbestos production and manufacture			25	7	6.1
Mining and milling (chrysotile)	4	2			
Manufacture	12	2			
Asbestos cement products	3	2			
Factory using asbestos	7	1			
C. Heating trades (excl. insulation)			70	27	4.4
Job necessitating heat-protective clothing	11	7			
Installing or repairing furnaces or boilers	28	9			
Steamfitter	5	2			
Boiler maker	2	1			
Plumbing and heating	23	8			
Welder	14	8			
D. Shipyards	49	17	21	13	2.8
E. Construction industry			45	30	2.6
Building trades	59	36			
Building demolition	3	2			
Painting	13	3			
Sheetrock spackling	1	0			
F. Other listed jobs (excl. men in groups A–E)			55	90	1
G. None of the above			101	176	
TOTAL			344	344	

* Men are listed once only in the group ranked highest; see text for definition of groups.

or pipe or boiler fitters. The remaining 20 men comprised 7 electricians, 4 metal workers, 2 painters, 2 ship fitters, 1 carpenter, and 4 whose jobs were not specified. For subjects briefly exposed to crocidolite asbestos, the interval between first exposure and death from mesothelioma was 25–35 years;[9,10,15] risks were therefore recalculated for this period. This slightly increased the relative risk from 2.6 to 3.2 for heating trades, and from 1.6 to 2.0 for work in shipyards.

The distribution of occupations for 156 cases and matched controls in group F, excluding those who qualified for groups A–E (188) is shown in Table 4. There were small excesses of some occupations but none in the larger groups—notably garage, maintenance, and transport work. Among other occupations (unlisted—Group G), an excess was found only in horticulture (4 to 0) and railway work (5 to 2).

Work with asbestos was recorded for only 2 female subjects. One woman had sewed amosite blankets for naval insulation and the other packed gasmasks, probably with crocidolite (a substantial quantity was found in lung tissue at autopsy). However, 42 subjects and 26 controls had been employed outside the home, 20 through 40 years before death, in work of an industrial nature.

Home Exposure

Two male and 6 female subjects but no matched control had been exposed at home to the dusty clothing of an asbestos worker; 2 controls were so exposed and the paired cases were not ($\chi^2 = 3.03$, 1 DF, $P = 0.08$). Of the 8 subjects, 5 had been ex-

TABLE 4. Employment in Other Listed Jobs of the 156 Male Cases Who Had Not Worked in Occupational Groups A–E and Their Matched Controls*

Occupation	Cases	Controls
Garage	11	12
Factory making rubber products	3	1
Maintenance man or building superintendent	13	13
Oil or chemical refinery	3	2
Carpentry	9	8
Factory making plastic products	0	3
Paint factory	2	1
Lathing	2	1
Dry cleaning	1	0
Sheet metal	1	3
Transport industry	15	22
Paper factory	3	4
TOTAL	156	156

* See text for definition of groups.

TABLE 5. Occupational Group and Site of Tumor in Male Cases and Controls

Occupational group*	Pleura†				Peritoneum†			
	Cases		Controls		Cases		Controls	
By group								
A. Insulation	11	10.9%	1	2.3%	16	29.1%	0	2.5%
B. Asbestos production and manufacture	18		5		7		2	
C. Heating trades (excl. A)	61	44.2%	21	20.4%	9	24.1%	6	20.3%
D. Shipyards (excl. A, C)	20		11		1		2	
E. Construction (excl. A, C, D)	36		22		9		8	
A–E	146	55.1%	60	22.6%	42	53.2%	18	22.8%
All other	119	44.9%	205	77.4%	37	46.8%	61	77.2%
TOTAL	265	100%	265	100%	79	100%	79	100%

* See text for definitions.
† Pleura includes pericardial tumors and peritoneum includes tumors of both peritoneum and pleura.

posed in childhood and the remaining 3 plus 2 controls as adults. In 3 cases and for 1 control, the clothing was that of a Quebec chrysotile production worker and, in 5 cases and for 1 control, an employee engaged in insulation or factory work. In the U. S. A. survey, an additional question was asked about exposure to asbestos in work or hobbies in the home. Among the 156 men who had not worked in occupational Groups A–E, and their matched controls, affirmative answers were given for 5 cases and 2 controls.

Neighborhood Exposure

Excluding those with occupational or domestic exposure, no subject, but 2 controls, had lived within 20 miles of a Canadian chrysotile mine. In the U. S. A., 1 subject and 2 controls had lived within 20 miles of a chrysotile mine in California. The places of residence of women were examined for the period 20 through 40 years before death. Of 96 case-control pairs in Canada, 19 subjects and 21 controls had lived only in rural areas; of 50 case-control pairs in the U. S. A., 5 subjects and 10 controls had done so. In Canada, 67 subjects and 66 controls, and in the U. S. A., 15 subjects and 13 controls, had lived in urban areas only.

Site of Tumor and Occupation

Of 265 male subjects with pleural tumors, 55.1% had worked in one of the occupational Groups A to E, compared with 22.6% of their matched controls (Table 5). The corresponding percentages of 79 males with peritoneal tumors and their matched controls were similar, 53.2% and 22.8%, respectively. However, 29.1% of peritoneal cases and 10.9% of pleural cases, compared with 2.3% and 2.5% in the respective control groups, had worked as insulators or in asbestos factories.

Other Materials

Relative risks in male case-control pairs are shown in Table 6 for exposure to dust from fiberglass, cement, rubber, copper, nickel, and wood. Only for fiberglass was the relative risk increased; after allowing for exposure to asbestos, this fell to 1.62 (95% confidence limits, 0.75 and 3.53, respectively).

Seventeen subjects and 12 controls had lived for 20 through 40 years before death within 20 miles of reported zeolite deposits[22] in Western U. S. A. A paired analysis gave a relative risk of 1.83, reduced to 1.60 (75% confidence limits, 0.58 and 4.93, respectively) when allowance was made for occupational exposure to asbestos.

Smoking

Findings concerning cigarette smoking habits were similar to those previously reported.[12,13] No association with mesothelioma was found for male cases. Female subjects tended to be rather heavier smokers than controls, perhaps related to the higher proportion employed outside the home. Overall, it seems improbable that tobacco smoking is an etiologic factor of any importance in this disease.

Discussion

The list of occupations provided by the Environmental Sciences Laboratory, Mount Sinai School of Medicine, proved a satisfactory method of classifying occupations thought to entail asbestos exposure. With minor modifications, the list could improve the comparability of case-control surveys in different regions and countries. Greater discrimination was achieved between cases and controls by selecting occupations reported to have been associated with mesothelioma than by assigning probabilities of asbestos exposure

to all occupations listed. It is reassuring however that, when the latter method was used, the order of difference between cases and controls remained similar.

The very high relative risk in insulators bears out the results of earlier cohort studies.[20,21] Chrysotile has been used for insulation in the U. S. A. since the beginning of the century. Amosite, introduced in the 1930s and employed extensively for marine construction in the World War II,[20] became the predominant fiber for insulation in the 1950s.[5] Insulators who died in 1972 were thus exposed to amosite as well as chrysotile some 25–35 or more years before a mesothelial tumor developed. Since the observed risk of mesothelioma has been high after work with amosite only[21] but not with chrysotile only,[16] circumstances tend to incriminate the amosite component.

In subjects who had done insulation and asbestos processing work, a high proportion of the tumors were peritoneal. This was also true of two large series of insulators,[20,21] amosite factory workers,[21] crocidolite gasmask workers,[9,10,15] and factory workers exposed to crocidolite, amosite, and chrysotile.[18] This contrasts with the pattern in chrysotile miners and millers, among whom all cases so far observed have been pleural.[15,16] However, the principal difference between chrysotile production workers and persons exposed to mixed mineral types of asbestos in processing or application lies in the absolute level of risk. Of 4,247 deaths among chrysotile miners and millers, 0.3% were due to mesothelioma[16] compared with 8–16% in the other groups mentioned.[10,15,18] It remains uncertain however whether the risk continues to be low when chrysotile is processed. Two relatively small studies of factory workers[7,24] suggest that this may be so and, in the present survey, no increase in risk was found in garage workers, certainly exposed to chrysotile from brake linings.[19]

Borow *et al.* reported 72 cases of mesothelioma, 58 in employees of a large asbestos factory in New Jersey.[2] Chrysotile only was manufactured from 1918 until the mid-1930s when crocidolite was introduced for production of large asbestos cement pipe and amosite for some other products. The first case of mesothelioma occurred in 1951 and there were 3 more cases before 1960. In the first half of the 1960s, the number of cases had increased by a factor of 8 and in the second half, by a factor of 20. There was only 1 case of mesothelioma in the large female work force employed in the textile department in which chrysotile only was used. This contrasts with the 8.9% death rate from mesothelioma reported by Newhouse for workers in a textile factory in which chrysotile, crodicolite, and amosite were used.[18]

TABLE 6. Exposure to Certain Materials in Male Case-Control Pairs

Exposed to:	Case only	Control only	Both	Neither	Relative risk	95% Confidence limits
Fibre glass	27	12	3	302	2.25	1.14, 4.44
Cement	43	38	7	256	1.13	0.73, 1.75
Rubber	15	25	4	300	0.60	0.32, 1.14
Copper	36	35	6	267	1.03	0.65, 1.64
Nickel	18	13	1	312	1.38	0.68, 1.40
Wood	62	63	19	200	0.98	0.69, 1.40

The association of mesothelioma with exposure to asbestos-contaminated clothing in the home was again confirmed. Cases have not been found in the neighborhood of the Quebec chrysotile mines and mills in our studies or in those of Theriault and Grand-Bois,[23] but, as the number of cases among the workers themselves was few, this is not surprising. The absence of mesothelioma in the neighborhood of the New Jersey amosite factory is more reassuring evidence.[8]

In 1972, our inquiry from all North American pathologists yielded a total of 274 fatal cases of mesothelioma. From detailed analysis of data available for California, we concluded elsewhere[17] that our survey probably underestimated the true incidence by about 30%. On the other hand, this is balanced by an almost similar proportion of cases rejected by the pathology panels. It has been argued[4,25] that very intensive questioning is needed, preferably while the subject is still alive, in order to elicit a full history of asbestos exposure in cases of mesothelioma. While this may be true, the same argument would apply, of course, to the controls, but perhaps to a lesser degree. In case-control studies of the type described here, the proportion attributable to asbestos exposure may therefore be somewhat underestimated. The upward trend in incidence in the male population seen in Canada is likely to be paralleled in the U. S. A. and, if due to the increased use of asbestos, will continue to rise for 20 to 30 years at least, because of the long latency period. The proportion of all cases attributable to asbestos must also therefore be expected to increase. Even so, the recent estimate from the National Institutes of Health[3] of a yearly average for the next 30–35 years of 10,000 deaths from mesothelioma in the U. S. A., due to asbestos alone, is not supported by our findings.

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