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EXHIBIT NO. 18
Betty Browning

EPIDEMIOLOGY OF PRIMARY MALIGNANT MESOTHELIAL TUMORS IN CANADA*

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All fatal malignant mesothelial tumors known to pathologists in Canada between 1959 and mid-1968 were registered. They numbered 165 (1 per million population per annum); two thirds were in males. Occupational and residential histories were obtained "blind" from relatives and friends of 90% of the cases and 2 matched control series. An association with definite or probable occupational exposure to asbestos was clearly demonstrated, but only 20% of male cases and one female case had any such contact. Almost all the excess was in the manufacture and industrial application of asbestos rather than in mining or milling. No association was found with lesser degrees of occupational exposure or residence in asbestos-mining areas, but there was a small excess of possible domestic exposures. The smoking histories in the mesothelial tumor and main control groups were almost identical and unlike those for cases of primary lung cancer.

EVIDENCE FOR AN ASSOCIATION BETWEEN MALIGNANT mesothelioma and asbestos exposure rests mainly on the remarkable concentration of cases reported by Wagner et al.[5] in the crocidolite mining areas of South Africa, the case-control studies of Elmes et al.[1] in Belfast, and Newhouse and Thompson[2] in London, and the considerable excess mortality due to this disease observed by Selikoff et al.[3] in American insulation workers. The survey described here was undertaken to obtain a more generally representative view of the problem in one of the 2 major chrysotile-producing countries of the world. Our aim has been to study all fatal cases known to have occurred in Canada since 1959.

METHOD

At the end of 1967 we wrote to the 423 members of either the Canadian Association of Pathologists or the Quebec Association of Laboratory Physicians inquiring whether they had seen any fatal cases of primary malignant tumors of the pleura or peritoneum diagnosed by autopsy or biopsy since 1959. In due course we obtained a reply from them all, and, if this was in the affirmative, a personal visit was made by one of us to review the records and to exclude cases which did not meet these criteria or about which the pathologist had serious doubt. In all, 165 cases were found; 113 were pleural, 45 peritoneal, 3 pleural and peritoneal, and 4 pericardial. The diagnosis was supported by autopsy in two thirds of the cases and by biopsy in the remainder. Later, we plan to have material from as many as possible reviewed by a panel of pathologists.

During the visit to the pathologist, 2 fatal control cases—one primary and one secondary lung cancer—were selected from the autopsy or biopsy records, matched for sex and, as closely as possible, for age and date of death. In 2 instances, no adequately matching case of primary lung cancer could be found. Two control series were chosen in order to examine 2 types of question. Primarily, we wished to know whether persons who had died from malignant mesothelial tumors had differed in their past exposure to asbestos and certain other materials from comparable persons in the general population. Comparability demanded that the control series should comprise persons matched with the cases for

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age, sex, date and place of death, and postmortem diagnostic procedure. To insure that information obtained from relatives would be of equal quality, it was important that the terminal illness should also be similar. Secondary lung cancer seemed to meet these criteria reasonably well and had the additional advantage that several primary cancer sites were included, but none were in the lung. A second main question was whether primary mesothelial tumors were related to tobacco smoking in the same way as primary lung cancer, and, for this reason, a matched series of cases of this disease was also selected.

A field survey was arranged in which investigators (doctors, public health nurses, and public health inspectors) sought out the relatives and friends of the deceased and completed a detailed questionnaire in English or French relating to occupation, residence, indirect household exposure to dust, family history, and smoking habits. Special emphasis was given to the occupational history. So far as possible, all employers or employing companies were listed with dates and a note made of the exact nature of the work done. The relative was then asked whether each job involved contact with wood, rubber, asbestos, cement, copper, nickel, or fiber glass. Finally, a check list was used, to inquire whether the subject had ever been employed in any of the following: locomotive repair shop; shipbuilding, overhauling, or breaking; installation of large boilers or steam pipes; insulation of domestic heating equipment; building—soundproofing, fireproofing, heat retention, assembling prefabricated buildings, and demolishing buildings; manufacture of brake linings or clutch plates; mining industry; textile industry; cement industry; dock or transport industry.

No interviewer knew to which group the case under investigation belonged, and the information recorded in the questionnaire was also coded blind. Questionnaires were completed for 447 (91%) of the 493 cases and controls.

Findings

The distribution of cases by province and year of death is shown in Table 1, and by age, sex, and site in Table 2. More cases were found in 1966 and 1967 than in previous years. Recent interest in these tumors may have contributed to this, and, as the records in some hospitals were poorer for the earlier years, memory may also have been a factor. With these points in mind, the true rate of increase is difficult to assess. During the 8 complete years, 1960–1967, the average annual incidence was 1.0 per million of population. The rate was appreciably higher in Quebec (1.5) than in Ontario (0.8) or in the rest of Canada (0.9), 1966 and 1967 again accounting for much of the difference. Three quarters of the cases were aged 50 or more at death, and males predominated by 2.4 to 1. Under 50, there was little difference in the sex distribution.

The case and 2 control series were very similar in age distribution and in the proportion of each for which the questionnaire was completed (Table 3). Table 4 shows the number of men aged 18 years or more who were occupationally exposed up to 10 years before death to asbestos and certain other materials in dust or vapor form. Whereas all 3

TABLE 1. Distribution of Cases by Year of Death and Province

Year	Ontario	Quebec	Other Provinces	Canada
1960	–	6	9	15
1961	1	6	3	10
1962	4	4	5	13
1963	9	3	7	19
1964	6	8	3	17
1965	7	7	5	19
1966	8	14	9	31
1967	6	13	6	25
1968 (1st half)	5	9	2	16
	46	70	49	165
Incidence/million/year 1960–1967	0.8	1.5	0.9	1.0

[illegible] Mesothelial [illegible]

[illegible]	Peritoneum		Pleura and peritoneum		Pericardium		[illegible]
	M	F	M	F	M	F	
[illegible]	1	[illegible]	1	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	1	1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	26	19	1	[illegible]	[illegible]	1	[illegible]
	45		2				

[illegible] exposed to wood dust [illegible] the mesothelial tumor [illegible] other materials [illegible] for asbestos. Men [illegible] asbestos [illegible] also to [illegible] especially [illegible] Table [illegible] these [illegible] part of the excess [illegible] excess [illegible] mesothelial tumor [illegible] control groups was [illegible] there was [illegible] of jobs [illegible] classified as "possible [illegible] occupation [illegible] was considered "[illegible] had any occupation [illegible] asbestos, there was [illegible] mesothelial tumor group and [illegible] possible [illegible] any lung cancer group.

The occupations [illegible] able exposure to asbestos [illegible] 5. Men employed [illegible] asbestos [illegible] facturing, the installation of [illegible] as insulators were responsible for [illegible] excess of cases [illegible] workers made little [illegible] and only [illegible] worked with asbestos [illegible] The time [illegible] death for all [illegible] cases [illegible] able [illegible] ranged from [illegible] and one woman who [illegible] less than [illegible] year [illegible] 20 and 38 years.

Materials other [illegible] further consideration [illegible] worked with more [illegible]

Table 2. Distribution by Age [illegible] Sex of Cases and Controls

[illegible]	Male			Female
[illegible]	Secondary lung cancer	Primary lung cancer	Mesothelial tumors	Secondary lung cancer
[illegible]	[illegible]	[illegible] (1)	[illegible]	[illegible]
[illegible]			[illegible]	
[illegible]	[illegible] (2)		4 (3)	[illegible]
[illegible]	6 (1)	2 (2)	5 (6)	[illegible]
[illegible]	[illegible] (11)	24 (20)	9 (8)	[illegible]
[illegible]	26 (2[illegible])	24 (23)	8 [illegible]	[illegible]
[illegible] 25	25 (3[illegible])	15 (33)	2 [illegible]	5 (1[illegible])
[illegible]	[illegible] (19)	17 (15)	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	5 [illegible]	[illegible]
[illegible]	10[illegible] (97)	107 (98)	57 (51)	[illegible]
[illegible]	5[illegible]	59	55.[illegible]	[illegible]
[illegible]	1[illegible]	[illegible].5	10.3	

[illegible] shown in parentheses [illegible]

TABLE 4. Occupational Exposure of Men to Certain Materials*

	Mesothelial tumors	Secondary lung cancer	Primary lung cancer
	(100 men)	(96 men)	(97 men)
Asbestos	20	3	4
Cement	17 (4)	9 (0)	8 (0)
Copper	6 (2)	1 (0)	1 (0)
Fiber glass	6 (3)	0	0
Nickel	5 (2)	0	0
Rubber	3 (1)	0	0
Wood	18 (1)	19 (0)	16 (0)
Total exposures recorded	75 (13)	32 (0)	29 (0)

* Definite or probable exposure to the substances named in dust or vapor form in men aged 18 or more. The number of men who were also definitely or probably exposed to asbestos is given in parentheses.

ing wood, for which there was evidently no difference between the 3 groups, 37 exposures to cement, copper, fiber glass, nickel, or rubber were recorded for the cases, of which 12 were in men definitely or probably exposed to asbestos. The 25 remaining exposures were in 19 men, and the comparable figures for the 2 control groups were 10 and 9, respectively. An analysis of these exposures is shown in Table 7, where it may be seen that the excess appeared to be in occupations involving contact with copper, nickel, fiber glass, or rubber (9:1:1) rather than with cement only, and seemed unrelated to possible exposure to asbestos. The relevant occupations of the 9 men in the mesothelial group were as follows: *copper:* lathe operator (2), munition manufacture, brass foundry; *nickel:* lathe operator (2), mine worker; *rubber:* tire manufacture, plantation work; *fiber glass:* municipal maintenance work, wood-caulking (ship).

Residential histories indicated that 45% of male cases and 38% of female cases had spent their childhood entirely in a rural area compared with 40% of males and 38% of females with secondary lung cancer, but the primary lung cancers were less often reared in rural areas (males 31%, females 28%). No difference was found between cases and both control groups after the age of 15 years. Excluding 5 cases (3 mine or mill workers and 2 textile workers) and one mine and mill worker in each control group, who lived in mining towns, only 3 men and 2 women had

TABLE 5. Distribution of Cases and Controls According to Their Occupational Exposure to Asbestos

Males	Mesothelial tumors		Secondary lung cancer		Primary lung cancer	
Exposure to asbestos	No.	%	No.	%	No.	%
Definite	11	20.0	1	3.1	1	4.1
Probable	9		2		3	
Possible	20	20.0	22	22.9	16	16.5
Unlikely	60	60.0	71	74.0	77	79.4
All*	100	100.0	96	100.0	97	100.0

Males: Distribution of definite and probable groups compared with possible and unlikely: $\chi^2 = 21.5$, 2 d.f., $P < 0.001$

Females	Mesothelial tumors		Secondary lung cancer		Primary lung cancer	
Exposure to asbestos	No.	%	No.	%	No.	%
Definite	1	2.0	—		—	
Probable	—		—		—	
Possible	—		1	1.9	—	
Unlikely	49	98.0	51	98.1	46	100.0
All*	50	100.0	52	100.0	46	100.0

* One child in each group dying under the age of 18 has been excluded.

TABLE 6. Distribution of Occupations Classified Under Definite or Probable Exposure to Asbestos

	Mesothelial tumors	Secondary lung cancer	Primary lung cancer
Asbestos mine or mill	3	1	1
Asbestos textile manufacture	4*	0	0
Brakelining installation	2	0	0
Insulation	5	0	0
Other occupations involving contact with insulation materials	5	2	3
Hardware store (handling asbestos sheet and pipe)	1	0	0
Filled gas masks with asbestos textile	1	0	0
TOTAL	21	3	4

* Includes one person who worked in brakelining manufacture.

ever lived within 20 miles of an asbestos mine. One of the 5 was a case, 3 had secondary lung cancer, and one had primary lung cancer.

The possibility of contact as a result of some other member of the family bringing home dusty clothes from occupations involving the use of asbestos was also examined. Excluding 7 persons (5 cases and one in each control group) who were occupationally exposed themselves (definitely or probably), there was one case in a female with definite home exposure and one male with probable home exposure. In addition to 5 persons (one case and 4 with primary lung cancer) who were possibly occupationally exposed to asbestos themselves, there were 26 persons with a possible home exposure: 14 cases, 6 with secondary lung cancer, and 6 with primary lung cancer. The category of possible home exposure was given in households where a person possibly exposed at work to asbestos brought home dusty clothes. Thus, excluding those persons with definite or probable occupational exposure, there were 15 persons with mesothelial tumors, 8 with secondary lung cancer, and 10 with primary lung cancer, who had had at least possible home exposure to asbestos dust.

The frequency of cancer reported in close relatives did not differ from that in the control groups. An analysis of cigarette smoking habits is shown in Table 8. In both males and females, persons in the primary lung cancer group had smoked considerably more than those in either the case or secondary lung cancer groups. The latter 2 groups had almost an identical distribution of smoking habits. The 20 men with definite or probable occupational exposure to asbestos showed no great difference in smoking habits from cases without occupational exposure.

DISCUSSION

Though our study is not directly comparable with those of Elmes et al.[1] in Belfast, and Newhouse and Thompson[2] in London, it seems fairly clear that the difference between cases and controls regarding asbestos exposure was less in our findings than in theirs. There are several possible explanations for this. The first is that our study was based on a national sample of cases derived from all parts of a very large country, whereas theirs were from 2 specific industrial areas, one a shipbuilding city and the other from a hospital close to a large asbestos factory. A second

TABLE 7. Occupational Exposure to Certain Materials of Men without Definite or Probable Exposure to Asbestos

	Mesothelial tumors	Secondary lung cancer	Primary lung cancer
Cement only	10 (5)	9 (6)	8 (2)
Copper, nickel, rubber, or fiber glass	9* (2)	1 (1)	1 (0)
	19 (7)	10 (7)	9 (2)

* Including three men also exposed to cement.
The number of men *possibly* exposed to asbestos is given in parentheses.

TABLE 8. Average Daily Number of Cigarettes Smoked

Cigarettes per day	Male				Female		
	Mesothelial tumors	Secondary lung cancer	Primary lung cancer	Mesothelial tumors with asbestos exposure	Mesothelial tumors	Secondary lung cancer	Primary lung cancer
Nil	21 *22*	19 *20*	4 *4*	2 *10*	29 *58*	36 *71*	21 *47*
10 or less	17 *18*	21 *22*	10 *11*	4 *20*	9 *18*	5 *10*	9 *20*
11–29	40 *41*	37 *39*	47 *50*	13 *65*	10 *20*	7 *14*	12 *27*
30 or more	19 *20*	18 *19*	34 *36*	1 *5*	2 *4*	3 *6*	3 *7*
TOTAL*	97 *100*	95 *100*	95 *100*	20 *100*	50 *100*	51 *100*	45 *100*

* Excluding 6 persons under 15 years of age and 6 men and 2 women whose smoking history was not recorded

possibility is that our series was diluted by cases which they would not have accepted. A third point is that we took great care to insure that the histories of case and control were collected and coded without knowledge of the group to which they belonged. This was not so stated in the Belfast survey and not possible in the study of Newhouse and Thompson. The findings of Selikoff et al.[3] are not comparable with ours since their investigation was based on an occupational group selected for its exposure to asbestos and not on a population sample.

It was not our aim to assess the role of asbestos in the etiology of primary lung cancer. Several studies have shown that occupational exposure may be associated with increased risk of this tumor, especially in smokers.[4] Since our series of primary lung cancer was selected to match the mesothelial cases in age, sex, and geographical distribution, it cannot be considered representative in itself. Nevertheless, it was probably sufficiently so for it to be worth noting that the history of exposure to asbestos was very similar to that for secondary lung cancer. Any contribution from asbestos in the causation of this series of primary lung cancers was, therefore, not apparent.

CONCLUSION

The findings from this national survey indicate that primary malignant mesothelial tumors are rare in Canada, and it is somewhat doubtful whether there has been a true increase in incidence since 1959. An association between these tumors and definite or probable occupational exposure to asbestos was clearly demonstrated, but only a minority of male cases (20%) and one female case had any such exposure. No difference was found between cases and the 2 control groups regarding lesser degrees of occupational exposure or residence in asbestos-mining areas, but, in 10% of the mesothelial tumors compared with 5% of the secondary lung cancer group, there was at least a possible domestic contact with asbestos dust.

Probably our most noteworthy finding was that almost all the excess in occupational exposure was in the manufacture and industrial application of asbestos rather than in mining or milling. Taken in conjunction with the results of other epidemiologic studies, this suggests either that chrysotile is less associated with mesothelial tumors than other forms of asbestos or that something in addition to asbestos is necessary. If there is an additional factor, our findings imply that it is not cigarette smoking.

Nine men with mesothelial tumors had worked in occupations unrelated to asbestos but involving contact with copper, nickel, rubber, or fiber glass compared with one in each of the control groups. The interpretation of this finding is doubtful.

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