Malignant mesothelioma in women

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Abstract

Background Malignant mesothelioma reportedly shows different epidemiology and pathology in females, and a proportion are believed to arise spontaneously.

Methods One hundred and seventy seven cases of malignant mesothelioma in females were reviewed, examined by histochemistry and immunohistochemistry, assessed for asbestosis and lung fibre burden by transmission electron microscopy with energy dispersive x ray analysis, and compared with 31 female controls.

Results Two of one hundred and three cases tested for carcinoembryonic antigen were positive and were excluded from further analysis. Tumour cases showed increased amphibole burdens; in those in whom exposure information was known, 74 (80%) of 93 patients had a history of exposure to asbestos. Seventy two (47%) of 152 patients had lung fibrosis. Tumour site and histological type were little different from those reported in adult males. Mixed type histological pattern, lung fibrosis, and peritoneal site were associated with heavier lung asbestos burdens, but not exclusively. Thirty five (30%) of 117 patients had amphibole burdens of less than 2×10^6 fibres/g; the sites affected and the histological pattern of tumours in this group were similar to those in cases with amphibole fibre counts of $\geq 2 \times 10^6$ /g lung. A higher lung amphibole burden than the mean burden in control females was found in 115 (98%) of 117 patients tested.

Conclusions The pathology of malignant mesothelioma appears to be similar in women and in men, and in cases associated and unassociated with asbestos.

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Malignant mesothelioma in females is well recognised, although there has been only one exclusively female series (of 52 cases) previously reported.¹ Published material indicates that it is 2-10 times less common in females,^{2,3} although in populations which have little or no exposure to asbestos the incidence is more equal.⁴ The static incidence rate of malignant mesothelioma in females compared with the rising incidence in males (related to the use of asbestos in industry) has led to suggestions that a significant proportion of the tumours in women are "spontaneously occurring" and unrelated to asbestos

exposure. The proportion of cases of malignant mesothelioma with a history of occupational exposure to asbestos is less in women than in men, varying from 5.4% in women and 40% in men in Quebec⁵ to 17% in women and 82% in men in Norway.⁶ Occupational histories may overestimate or underestimate exposure to asbestos depending on the types of cases involved and the rigour of the investigations. Mineralogical evaluation of lung tissues is extremely helpful in verifying or refuting the accuracy of occupational exposures. To date there have been few published data in female cases of malignant mesothelioma.

The proportion of cases of malignant mesothelioma affecting the peritoneum is reported to be greater in females,^{7,8} ranging from 15% in females and 7% in males in a review of 4710 cases,⁹ to 39% in North American females and 22% in males.¹⁰ However, a UK series of 246 cases showed almost identical site distributions in both sexes.¹¹ Histological subtyping showed no significant differences between males and females in two UK series,^{12,13} but one study of pleural tumours showed the epithelial type to represent a greater proportion in females (76%) than males (37%),¹⁴ and this preponderance of epithelial type was also seen in a Canadian study (females 59%; males 39%).¹⁵ Differential exposure to different types of amphiboles has been proposed to explain these differences, but again with little or no corroboration by mineral analysis of lung fibre burdens.

In this study of 177 women we examined the histopathology of malignant mesothelioma and measured the mineral fibre content of their lungs by transmission electron microscopy (TEM) with energy dispersive x ray analysis using an "EDAX" machine. The lung fibre counts were compared with those in 31 female controls. To the best of our knowledge this is the largest series reported.

The objectives of the study were to determine the site and histological profile of malignant mesothelioma in females, to correlate the lung mineral fibre content with the type of exposure to asbestos, and to investigate the possibility of a subpopulation within the female gender of malignant mesothelioma unrelated to asbestos exposure.

Methods

MATERIALS

All available pathological, occupational and mineralogical data on 177 female cases classified as malignant mesothelioma in the files of

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this unit over the period 1963–1990 were reviewed (during this period 1184 male cases were classified). The cases were largely referred as wet lung/tumour tissue or as slides or blocks, often for histological confirmation of diagnosis. Twenty six cases had no tumour tissue or slides for review; these cases were originally classified by Dr JC Wagner and his record of histological pattern was used for our analysis. Of the remaining 151 cases, 22% had six or more histological slides or blocks available for study, 63% had three or more, and 85% had two or more. Thirty one women from five series of consecutive post mortem examinations on patients with no known history of exposure to dusts, and no mesothelioma or lung cancer, from Exeter, Liverpool, Belfast, Dublin, and Cardiff, were used as controls. These were, of necessity, unmatched.

STUDY DESIGN

Histological slides of each tumour were stained with haematoxylin and eosin and examined and, where possible, the tumour was stained for glycogen (PAS) and neutral mucin (PASD). Immunohistochemistry was performed to detect cytokeratin and carcinoembryonic antigen by peroxidase conjugated avidin biotin staining (Broad spectrum keratin "CKKES" and CEA "CKCES," Diagnostic Products Corporation, Los Angeles, USA). Malignant mesotheliomas were assigned to epithelial, spindle (connective tissue, sarcomatoid) or mixed histological subtypes. Background lung was stained with haematoxylin/van Gieson where possible, and fibrosis was assessed and graded according to the method of Hinson *et al.*¹⁶ A search for asbestos bodies was carried out on conventionally stained 5 µm sections.

TEM was performed according to the method of Pooley and Clark.¹⁷ Briefly, non-tumorous lung was digested in 40% potassium hydroxide, washed, and ashed in an atmosphere of oxygen. Digested lung residues were filtered on to Millipore filters and carbon coated; 100–200 fibres were individually identified by energy dispersive x ray analysis and the proportions of each different fibre type in the digest were calculated. Fibre length and diameter were measured directly from the screen at a magnification of $\times 20\,000$.

Exposure to asbestos was classified according to Zielhuis¹⁸ into (1a) direct occupational exposure; (1b) indirect occupational exposure—for example, workers in the vicinity of asbestos contaminated work situations; (2)

paraoccupational exposure—for example, the wives of men working with asbestos; (3) neighbourhood exposure—for example, people living in the vicinity of asbestos mines or processing factories; (4) exposure in ambient air; (5) no known exposure.

Results

AGE

The mean age for the 102 cases of malignant mesothelioma of known age was 60.5 (range 18–89) years and for the 31 controls was 68 (range 30–93) years.

HISTOLOGY AND SITE (TABLE 1)

Review of the stained slides of the 151 cases for which tumour tissue was available showed evidence of malignant mesothelioma in all cases. Two of one hundred and three cases (2%) tested for carcinoembryonic antigen were positive and were excluded from further analysis.

Of the remaining 175 cases, 125 (71%) were positive, tumours were pleural (mean age 62 years), 29 (17%) were peritoneal (mean age 56 years), and 21 were of unknown site. The histological profile for tumours of known histology was 54% epithelial, 33% mixed, 13% spindle.

Of the 131 tumours stained for glycogen and mucin, 45 (34%) were positive for glycogen (37% of epithelial tumours and 23.5% of spindle tumours) and none for mucin. Psammoma bodies were seen in five (3%) of 175 cases (three pleural and two peritoneal, three of epithelial and two of mixed type).

Of 101 tumours analysed for cytokeratin, 90 (89%) were positive. Cytokeratin was more common in epithelial (51 of 53) than spindle (11 of 15) tumours; 28 of 33 mixed tumours were positive for cytokeratin, and in the 25 cases in which both elements were included in the section stained both elements were positive in 14 and the epithelial element only in 11.

MINERAL ANALYSIS OF CASES AND CONTROLS (TABLE 2)

Of the cases of malignant mesothelioma, 98% had lung amphibole counts greater than the mean count in the controls; 78% of all cases of malignant mesothelioma had lung amphibole counts greater than 1×10^6 fibres/g dried lung and 89% of these had lung amphibole counts greater than 2×10^6 fibres/g dried lung.

Of the 105 tumours of known site from which lung tissue was examined by TEM, the

Table 1 Histological pattern of mesotheliomas according to site and amphibole burden

Category	n	Histological type (%)			
		Epithelial	Mixed	Connective tissue	Unknown type
All	175*	48	30	12	10
Pleural	125	51	33	14	2
Peritoneal	29	59	24	10	7
<2 × 10 ⁶ amphiboles/g	35	57	17	20	6
≥2 × 10 ⁶ amphiboles/g	82	39	32	12	17

*Two cases positive for carcinoembryonic antigen excluded.

Table 2 Lung fibre burdens ($\times 10^6$ fibres/g lung) in controls and patients with mesothelioma according to site, expressed as geometric mean (range)

Lung fibres	Control (n = 31)	Mesothelioma		
		All (n = 117) *	Pleural (n = 98)	Peritoneal (n = 7)
Total amphiboles	0.04 (0-1.0)	10.1 (0-2888)	7.3 (0.10-2888)	221 (1.3-2353)
Crocidolite	0.02 (0-0.50)	5.1 (0-2888)	3.4 (0-2888)	175 (0-2353)
Amosite	0.02 (0-0.50)	0.09 (0-2420)	0.09 (0-2420)	1.1 (0-12.8)
Tremolite	0.02 (0-0.80)	0.03 (0-120)	0.03 (0-120)	0.11 (0-1.6)
Chrysotile	4.4 (0-20.1)	7.1 (0-2506)	6.7 (0-2506)	1.1 (3.2-49.2)
Total fibres	10.5 (0-83.1)	77.5 (1.2-3105)	67.6 (1.2-3105)	365 (25.2-2370)

*12 cases of unknown site.

peritoneal group showed a higher amphibole burden than the pleural group. One hundred and one cases of known histological type underwent TEM; the highest amphibole burdens were seen in those cases exhibiting the mixed pattern, with those of spindle pattern showing the lightest burdens.

The site and histological profile of the group with total amphibole counts of $<2 \times 10^6$ fibres/g dried lung differed little from those with amphibole counts of $\geq 2 \times 10^6$ fibres/g dried lung (table 1), apart from the slight preponderance of mixed histological pattern in those with heavier fibre burdens.

Six specimens contained only amosite as their amphibole burden. One specimen, from a Turkish peasant girl from the western part of central Anatolia, contained high levels of tremolite and erionite. Twenty eight cases contained over 30×10^6 fibres/g lung tissue of chrysotile; all but four of these also contained over 2×10^6 amphibole fibres/g dried lung. Traces of amphiboles (from 0.4 to 1.8×10^6 amphibole fibres/g dried lung) were found in the remaining four cases with high chrysotile counts.

There were too few cases to permit an assessment of the influence of any one fibre type on site or pattern, independently of other fibre types.

ASBESTOS BODIES

One hundred and thirty three cases were assessed by light microscopy for the presence of asbestos bodies in background lung; 70

(53%) were positive. In the 49 specimens positive for asbestos bodies that subsequently underwent examination by TEM, the lowest total amphibole count was 2.2×10^6 fibres/g dried lung tissue. On the other hand, in the 63 specimens with no asbestos bodies, 50 subsequently underwent TEM and 23 of these had total amphibole counts over 2×10^6 fibres/g dried lung tissue.

FIBROSIS (TABLE 3)

Fibrosis was graded in background lung for 152 cases and 31 controls. No fibrosis was found in 26 controls, four showed grade 1 fibrosis, and one control (with cryptogenic fibrosing alveolitis) had grade 4 fibrosis. More severe fibrosis in patients with malignant mesothelioma was associated with increasing amphibole and total fibre counts, an increase in peritoneal site in relation to pleural site, and an increase in mixed histological type over epithelial and spindle types. The three cases with grade 4 fibrosis had a mean age at death of 46.5 years (14 years younger than the malignant mesothelioma patients as a whole).

OCCUPATIONAL EXPOSURE HISTORY

Occupational/exposure history, classified according to Zielhuis, is given in table 4. All those peritoneal tumours for which exposure information was available were in the occupationally exposed group (group 1a). The paraoccupational group (group 2) showed an increase in the proportion of tumours of mixed type (and to a lesser extent of those of

Table 3 Site of mesothelioma, histological pattern and lung fibre burden ($\times 10^6$ fibres/g lung expressed as geometric mean (range)) according to lung fibrosis grade

	Fibrosis grade				
	0	1	2	3	4
Site and pattern:					
n	80	34	25	10	3
Pleural (%)	66 (83)	27 (79)	22 (88)	5 (50)	0
Peritoneal (%)	6 (8)	4 (12)	3 (12)	3 (30)	3 (100)
Unknown site	8	3	0	2	0
Epithelial (%)	39 (49)	16 (47)	12 (48)	3 (3)	1 (33)
Mixed (%)	20 (25)	13 (38)	7 (28)	4 (40)	2 (67)
Connective tissue (%)	11 (14)	3 (9)	5 (20)	0	0
Unknown pattern	10	2	1	3	0
Mineral analysis:					
n	61	24	23	8	0
Total amphiboles	3.9 (0.10-2888)	16.2 (0.50-823)	33.2 (0.20-2420)	112 (0.50-2353)	-
Crocidolite	2.0 (0-2888)	8.0 (0-823)	13.8 (0-1693)	105 (0-2353)	-
Amosite	0.06 (0-7.9)	0.11 (0-2.2)	0.21 (0-2420)	0.05 (0-16.2)	-
Tremolite	0.02 (0-7.0)	0.07 (0-120)	0.05 (0-41.0)	2.8 (0-20.6)	-
Chrysotile	6.4 (0-1118)	10.4 (0-2506)	6.0 (0-344)	25.2 (0-1541)	-
Total fibres	50.6 (1.2-3105)	93.0 (7.3-2566)	119 (5.9-2444)	402 (17.40-2377)	-

Table 4 Site of mesothelioma, histological pattern and lung fibre burden ($\times 10^6$ fibres/g expressed as geometric mean (range)) according to type of exposure

	Exposure group (Zielhuis)					
	1a Direct occupational	1b Indirect occupational	2 Domestic	3 Neighbourhood	4 Ambient air	5 No known exposure
Site and pattern:						
n	38	13	15	6	2	19
Pleural (%)	27 (71)	11 (85)	14 (93)	5 (83)	1 (50)	16 (84)
Peritoneal (%)	5 (13)	0	0	0	0	0
Unknown site	6	2	1	1	1	3
Epithelial (%)	16 (42)	5 (38)	4 (27)	4 (67)	1 (50)	9 (47)
Mixed (%)	8 (21)	5 (38)	7 (47)	2 (33)	0	5 (26)
Connective tissue (%)	4 (11)	1 (8)	3 (20)	0	1 (50)	3 (16)
Unknown pattern	10	2	1	0	1	2
Mineral analysis:						
n	34	12	14	2	2	14
Total amphiboles	27.0 (0.10–2420)	6.3 (0.50–28.3)	4.9 (0–251)	2.0 (0.80–5.1)	11.0 (1.0–120)	1.3 (0.20–107)
Crocidolite	13.9 (0–1542)	5.2 (0.50–28.3)	1.9 (0–251)	2.0 (0.80–5.1)	0.29 (0.09–0.90)	0.57 (0–101)
Amosite	0.12 (0–2420)	0.25 (0–4.6)	0.22 (0–6.1)	0	0.03 (0.01–0.10)	0.21 (0–4.6)
Tremolite	0.02 (0–41.0)	0	0.20 (0–29.3)	0	39.3 (12.8–120)	0.04 (0–1.8)
Chrysotile	5.9 (0–1541)	16.9 (0–1118)	12.7 (0–2506)	8.5 (8.2–8.9)	0.47 (0.15–1.5)	3.9 (0–135)
Total fibres	108 (7.3–2444)	72.1 (18.3–1529)	64.1 (5.6–2566)	15.7 (14.6–16.9)	81.5 (6.6–1006)	22.9 (1.2–194)

spindle type), with a reduction in the proportion of epithelial type. The lowest mean age of death was seen in the neighbourhood exposure group (48.5 years), again 12 years younger than the malignant mesothelioma group of patients as a whole.

Measurements of 78 cases with exposure information showed the heaviest amphibole burden in those cases with direct occupational exposure. Only one of the 14 cases with no history of exposure had lung containing no amphiboles, and four of the 14 had total amphibole counts of $\geq 2 \times 10^6$ fibres/g dried lung tissue.

Discussion

The interpretation of the results of the histological and mineralogical data provided by this study must be tempered by the knowledge that it is a referred population, and therefore not completely representative of any community over the period studied. It is also heavily biased by the inclusion of groups such as wartime dockyard and gas mask workers, who suffered very heavy exposure to asbestos. The study is further restricted by deficiencies in the amount of material available for study, and in the completeness of exposure data and other information for which we were dependent on our referring bodies. These limitations notwithstanding, the study provides the largest database of malignant mesothelioma in females yet reported.

HISTOLOGICAL DIAGNOSIS

It is not surprising that review of the tumour histology confirmed appearances consistent with the diagnosis of malignant mesothelioma, since all cases were seen by at least one pathologist from this unit with considerable experience in the diagnosis of malignant mesothelioma before classification in our files. The diagnosis of malignant mesothelioma is further supported by the absence of neutral mucin¹⁹ and carcinoembryonic antigen^{20–22} in those tested.

Our finding of 89% positivity for cytoker-

atin is similar to reported data.²³ The preferential finding of positivity in the epithelial component in those of mixed histological pattern has also been reported by Montag *et al*²⁴ and Corson and Pinkus.²⁵

SITE AND HISTOLOGICAL SUBTYPE

Despite the referred nature of the series, the histological profile of our cases for each site and overall mirrors those given in the literature review of Hillerdal⁹ and is not strikingly different from those in other reported series (table 5). The predominance of the epithelial pattern in women with pleural malignant mesothelioma reported by the Mayo Clinic¹⁴ does not seem to be reflected in our study.

The suggestion in one series³⁰ that all cases of malignant mesothelioma occurring in patients with no history of exposure are of epithelial pattern is not borne out by our finding of 47% epithelial:26% mixed:16% spindle pattern in 19 cases in Zielhuis group 5 (table 4).

The higher amphibole burden found in patients with peritoneal tumours (table 2) is similar to the findings of McDonald *et al* in North America³¹ and those of Wagner *et al* in East London asbestos factory workers.³²

The reason for the high proportion of peritoneal malignant mesotheliomas in females in the literature is uncertain. If the peritoneal site is indeed favoured only after the development of asbestosis, it would seem to represent an excess in a gender with usually less heavy non-occupational exposure to asbestos. It may be that, despite care in the histological diagnosis, researchers have included tumours mimicking malignant mesothelioma (such as tumours of the extraovarian Mullerian system or endosalpingosis)^{33,34} that are unique to women. If this were the case, a large TEM study of peritoneal cases would be expected to show a dual population—those true cases of malignant mesotheliomas, probably also with related asbestosis, would have high asbestos burdens while cases of endosalpingosis would have counts similar to those of controls. Unfortunately, only seven of our 29

Table 5 Histological pattern according to site, and comparison with published material

Site	Source (ref)	n	Sex	Epithelial (%)	Mixed (%)	Spindle (%)
Overall	Present study*	158	F	54	33	13
	Literature review ⁹	922	Both	52	33	15
	Canada ²⁶	65	Both	46	25	23
	Belfast ¹³	184	Both	34	42	24
	Canada ¹⁵	32	F	59	35	6
Pleural		67	M	39	25	36
	Present study*	122	F	52	34	14
	Literature review ⁹	829	Both	50	34	16
	London ²⁷	115	NS	52	26	22
	UK ²⁸	23	F	48	39	13
		61	M	38	29	33
	Mayo Clinic ¹⁴	21	F	76	14	10
Peritoneal		71	M	37	38	25
	Present study*	27	F	63	26	11
	Literature review ⁹	75	Both	60	31	9
	USA ²⁹	82	Both	75	22	2

NS—not stated.

*Cases of unknown pattern excluded.

peritoneal cases had lung tissue available for TEM but, of these, six contained amphibole counts over 100×10^6 fibres/g dried lung. The other case, a worker in an aircraft factory said to be occupationally exposed to asbestos, had 1.3×10^6 amphibole fibres and 9.1×10^6 chrysotile fibres/g dried lung.

FIBROSIS

Most of our cases of malignant mesothelioma (73%) had grade 1 fibrosis or less, which is consistent with reports of malignant mesothelioma developing in dockyard workers at lower fibre burdens and grades of asbestosis than in those dockers with pulmonary carcinoma.³⁵ The study of East London asbestos factory workers also showed that malignant mesothelioma was associated with lower mean fibre burdens than was asbestosis alone.³²

Our study shows that increasing fibrosis is associated with peritoneal site ($p < 0.001$) and increasing amphibole burden, and this is again similar to the study of the asbestos factory workers³² and also to a study of asbestos related deaths in the UK in 1977.³⁶

In our study (table 3) 13 (68%) of 19 peritoneal cases had fibrosis compared with 54 (45%) of 120 pleural cases; overall, 72 (47%) of the 152 patients in our series had fibrosis. Browne and Smither¹² found that 28% of peritoneal cases and 22% of pleural cases had asbestosis; the higher incidence of fibrosis in our cases may reflect higher lung fibre burdens. Other studies, however, do show a higher incidence of asbestosis in malignant mesothelioma; Kannerstein and Churg found asbestosis in 74% of their series of peritoneal malignant mesothelioma,²⁹ 52% of 65 Canadian cases of pleural malignant mesothelioma were affected²⁶ and 46% of a series of 37 pleural cases.³⁷

MINERAL ANALYSIS BY TEM

The high mean amphibole burdens may reflect the high proportion of patients with a history of exposure to asbestos (74 of 93 of those with known history) and the heavy exposures of a large number of the cases. Twenty one of our women were gas mask workers; a further seven (of unclassified ex-

posure) represented seven of the eight highest total amphibole burdens in our study (each in excess of 1000×10^6 fibres/g dried lung). As one might expect, studies of occupational groups of workers have shown higher amphibole burdens—for example, gas mask workers,³⁸ asbestos process workers,³² cement workers,³⁹ and textile workers⁴⁰—than were found in a more general survey of patients with malignant mesothelioma.⁴¹

Only five of 14 patients with no history of exposure were found to have amphibole counts equal to or less than the highest counts in the control series, while four had counts of $\geq 2 \times 10^6$ fibres/g dried lung tissue, indicating that occasionally unrecognised exposures occur. These apparent anomalies indicate the inherent unreliability of exposure history and add weight to the recommendation that TEM of lung fibre burdens should be performed in assessing disease association with asbestos exposures.²⁸

Of the patients tested in this series, 98% showed amphibole burdens greater than the mean for the female controls. No amphiboles were detected in 2% of patients compared with 63% of controls. This is similar to the findings in a previous UK study of malignant mesothelioma in 1976, which found 5% of cases with no amphiboles compared with 20% of controls (males and females).⁴² In this series, 35 (30%) of 117 female patients had amphibole levels lower than 2×10^6 fibres/g dried lung, and these might be considered spontaneously arising tumours. The use of the TEM lung fibre count to define spontaneously arising malignant mesothelioma is difficult and arbitrary, however, because studies of control populations occasionally show counts in the region of 2×10^6 amphiboles/g dried lung.

Five of our cases with lung fibre counts below 2×10^6 amphiboles/g dried lung had levels of chrysotile higher than the highest control (highest control 20.1×10^6 chrysotile fibres/g dried lung; five cases 21.5 – 111.7×10^6 chrysotile fibres/g dried lung). There were no cases with a high chrysotile count that did not have contaminating amphiboles, so no cases of malignant mesothelioma could be attributed with certainty to the presence of

chrysotile alone. In control males, levels of up to 50×10^6 chrysotile fibres/g dried lung are not infrequently encountered. Epidemiologically there have been few cases of malignant mesothelioma associated with pure chrysotile exposure, and these have been attributed to contaminating amphiboles.^{5 43-45}

The two cases with no amphiboles and a chrysotile count similar to control values add to the small number of reports of cases of malignant mesothelioma shown by electron microscopic fibre analysis to have no amphiboles and low chrysotile burden,^{28 36 42} and support the hypothesis that some cases of malignant mesothelioma are not associated with exposure to asbestos. A number of possible alternative aetiologies have been proposed.⁴⁶

This study shows the usefulness of mineral analysis of lung tissues in assessing whether a case of malignant mesothelioma is likely to have been caused by asbestos exposure. The similarity of clinical and pathological features of malignant mesothelioma in women with high and low amphibole burdens indicates that these features alone are not likely to be useful in identifying the spontaneously arising tumour.

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