ANATOMIC PATHOLOGY 1997

VOLUME TWO

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Printed in Hong Kong
01 00 99 98 97 5 4 3 2 1

◂ CHAPTER EIGHT ▸

MALIGNANT MESOTHELIOMA IN WOMEN

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Malignant mesothelioma, once a relatively rare disorder, now occurs in industrialized nations in epidemic proportions. The majority of cases are the result of the widespread use of asbestos prior to 1972, especially in the construction and shipbuilding industries. Because workers in these industries have traditionally been men, there is a striking gender bias in this disease. Nonetheless, mesotheliomas of both the pleura and peritoneum occur in women as well, although little information is available regarding the histopathologic features or the primary sites of such tumors. Furthermore, little is known regarding the types of asbestos exposure (if any) or the lung asbestos burdens in women compared with men.

In 1980, McDonald and McDonald reported on a survey of all fatal malignant mesothelial tumors in North America.[1] Among 557 mesotheliomas reported through the end of 1972, 162 (29%) occurred in women; of these, 99 (61%) were pleural in origin. The annual incidence of mesothelioma in 1972 was estimated to be 0.7 cases per million women aged 15 years and older, and evidence was presented that, in Canada, the rate of mesothelioma in women had remained somewhat constant over a 15-year period. A history of occupational exposure to asbestos was found in only 5% of the women in the study.

Hillerdal reviewed the literature on mesothelioma and found 4710 published cases through 1982.[2] Information regarding gender was available in 2867 of these cases, and 619 (22%) occurred in women. Among ten subsequent series of patients with mesothelioma, a total of 1601 tumors were reported, 342 (21%) of them in women.[3–12] Thus the percentage of women with mesothelioma has remained fairly constant worldwide over the past several decades.

In 1993, Dawson et al reviewed 177 cases of women with mesothelioma from the United Kingdom; this is the only large study dealing exclusively with mesothelioma in women.[13] The authors found little difference in tumor site or histologic type between men and women. Among those women for whom asbestos exposure information was available, 74 (80%) of 93 had a history of such exposure. Lung fibrosis was identified in 72 (47%) of 152 cases. A higher lung amphibole (crocidolite, amosite, and tremolite) burden than the mean burden in 31 female controls was found in 115 (98%) of 117 women tested.

From the perspective of differential diagnosis, special consideration must be given to papillary peritoneal tumors in women. Peritoneal mesotheliomas must be distinguished from primary and secondary serous papillary carcinomas of the peritoneum.[14,15] Furthermore, the well-differentiated papillary mesothelioma of the peritoneum is a special variant characterized by an indolent clinical course and prolonged survival.[16] Deciduoid peritoneal mesothelioma is another uncommon variant that affects young women.[17] Interestingly, in the Goldblum and Hart study, 13 women with diffuse malignant peritoneal mesotheliomas had no known history of asbestos exposure.[15]

The purpose of the present study is to review our experience with malignant mesothelioma in women, including clinical and histopathologic features as well as asbestos exposure. Mineral fiber analysis of lung tissue was performed in about one third of the cases. Patients with serous papillary carcinoma of the peritoneum were excluded.[18]

Materials and Methods

Among 770 patients with malignant mesothelioma from one of the authors' (VLR) files, 62 (8.0%) were women. All tumors were pathologically confirmed based on open or thoracoscopic biopsy, decortication, pneumonectomy, or autopsy specimens using previously described criteria.[19] Information regarding occupational or other exposures to asbestos was obtained by direct patient interview. Age, sex, and primary site of the mesothelioma (ie, pleura or peritoneum) were also recorded in each instance. The presence or absence of asbestosis or parietal pleural plaques was also noted in patients for whom such information was available. Criteria for the pathologic diagnosis of these conditions have been published previously.[20–22]

Among those women for whom asbestos exposure information was available, 74 (80%) of 93 had a history of such exposure. Lung fibrosis was identified in 72 (47%) of 152 cases. A higher

whom such information was available. Criteria for the pathologic diagnosis of these conditions have been published previously.[20–22]

H&E-stained sections of each tumor were reviewed. Immunohistochemical studies were performed using the avidin biotinylated complex technique on trypsinized sections. Antibodies employed included monoclonal antibodies against cytokeratins (AE_1/AE_3, Boehringer Mannheim, Indianapolis, Ind, and CAM 5.2, Becton Dickinson, San Jose, Calif) and Leu-M1 (CD-15, Becton Dickinson), and polyclonal antibodies against carcinoembryonic antigen (CEA; Dako, Carpinteria, Calif). Antibodies were localized using diaminobenzidine as the color reagent. Negative controls included normal rabbit serum and an irrelevant mouse monoclonal antibody. Positive controls were used with each study.

Formalin-fixed or paraffin-embedded peripheral lung parenchyma was available for analysis of tissue asbestos content in 20 of the 62 cases. Most of these were from autopsies where lung tissue was available for analysis, although some were from surgically resected specimens. In the other 42 cases, only tumor tissue was available or the amount of lung tissue sampled was insufficient for analysis. Lung tissue was processed for digestion using the sodium hypochlorite technique as previously described.[22] The residue was collected on 0.4-μm pore filters (Nuclepore Corp, Blasingame, Calif). For light microscopic analysis, the filter was mounted on a glass slide for asbestos body quantification. Filters were counted at a magnification of ×400, and only bodies with typical morphology and thin, translucent cores were counted as asbestos bodies.[23] Results were reported as asbestos bodies per gram of wet lung tissue (AB/g). The normal range for our laboratory is 0 to 20 AB/g, and the detection limit for a 0.3-g sample size is approximately 3 AB/g. For samples in which no asbestos bodies were detected, the value was recorded as less than the detection limit.

For scanning electron microscopic (SEM) analysis, the filter was mounted on a carbon stub with colloidal graphite, sputter-coated with gold or platinum, and examined in a JEOL JSM 6400 scanning electron microscope (JEOL Inc, Peabody, Mass) at a screen magnification of ×1000. Fibers 5 μm or greater in length were counted using a protocol in which 100 consecutive fields or 200 fibers were counted, whichever came first. Fibers were defined as particles with an aspect ratio (length to width) of at least 3:1 and roughly parallel sides. The concentration of fibers for each sample was calculated based on the fiber density (per mm^2) on the filter surface times the effective area of the filter, divided by the weight of the lung sample. The results are reported as total uncoated fibers 5 μm or greater in length per gram of wet lung (UF/g). The normal range for our laboratory is less than 440 to 13,000 UF/g (median, 3100 UF/g), and the detection limit for a 0.3-g sample size is approximately 440 UF/g. Uncoated fibers were detected in all samples analyzed.

Fiber types were determined using a combination of fiber morphology assessed by SEM and elemental composition assessed by energy dispersive x-ray analysis (EDXA). Fibers were classified as asbestos or nonasbestos mineral fibers as previously described.[22] Asbestos fibers were further classified as amosite, crocidolite, tremolite, anthophyllite, actinolite, or chrysotile. Amosite and crocidolite were grouped together as commercial amphiboles; tremolite, anthophyllite, and actinolite were grouped together as noncommercial amphiboles. Between 5 and 28 fibers were analyzed for each sample (mean, 14 fibers per sample). The proportion of each fiber type and the total uncoated fiber concentration were used to determine the tissue concentration of amosite and crocidolite; tremolite, anthophyllite, and actinolite; chrysotile; and nonasbestos mineral fibers for each case. For those where no fibers of a particular type were detected, the value was recorded as less than the detection limit for that fiber type.

Results

The demographic, pathologic, and exposure information for the 62 women with mesothelioma is summarized in ▸Table 8-1◂. The median age of the 61 patients for which this information was available was 59 years (range, 28–82 years). These values are similar to those previously reported for the overall series of mesothelioma in

►TABLE 8-1◄

Demographic, Pathologic, and Exposure Information for 62 Women With Mesothelioma

Case No.	Age	Exposure History/Occupation	Diagnosis
1	58	Spinner/winder/weaver, asbestos textile plant, 14 y; wife of insulator	B Pl
2	62	Wife of shipyard worker, 29 y	B Pl
3	28	Status postchemotherapy and radiation for Wilms' tumor	B Pl
4	52	Laundry worker, military institute	E Pl
5	57	Wife of shipyard worker	E Pl
6	NA	NA	Pe
7	45	Status postchemotherapy and radiation for lymphoma, 1977; wife of auto mechanic	E Pl
8	75	Wife of shipyard pipecoverer, 30 y	B Pl
9	41	Wife of merchant marine seaman, 4 y	E Pl
10	43	Schoolteacher	E Pl
11	58	Teacher's aide, 18 y	S Pl
12	38	Tugboat worker, 15 mo	E Pl
13	32	Daughter of insulator, 18 y; wife of insulator, 7 y	B Pl
14	68	Company nurse, Johns-Manville, 40 y	E Pl
15	44	Dry-cleaning plant assembler	E Pl
16	55	Household contact (asbestos worker)	S Pl
17	68	Homemaker; no known exposure	B Pl
18	71	Wife of insulator, 27 y	B Pl
19	31	Household contact (pipecoverer), 16 y	B Pl
20	66	Household contact (mother of pipefitter), 2.5 y	S Pl
21	61	Household contact (asbestos worker)	B Pl
22	69	Shipyard worker, 1 y	E Pl
23	48	Optical plant worker	E Pl
24	45	Elementary school student, 6 y	E Pe
25	71	Laborer on cleanup crew, iron works, 3.5 y	E Pl
26	38	Daughter of amosite asbestos plant worker	E Pl
27	68	Smoked Kent cigarettes	B Pl
28	70	Wife of construction worker	S Pl
29	49	Household contact (aunt of Case 13), 11 y; radiation for breast carcinoma, 4 y prior to diagnosis	B Pl
30	70	Homemaker; no known exposure	S Pl
31	65	Wife of shipyard worker	S Pe
32	65	Household contact (wife of plumber/pipefitter), 15 y	E Pl
33	73	Braider operator, Johns-Manville	B Pe
34	45	Daughter of insulator who died of mesothelioma	B Pl
35	31	Daughter of insulator, 10 y	E Pl
36	59	NA	E Pl
37	66	Smoked Kent cigarettes	E Pl
38	46	Daughter and wife of asbestos insulators, 30+ y	B Pl
39	41	Household contact (father and uncles), 18 y	B Pe
40	70	Smoked Kent cigarettes	S Pl
41	56	Household contact (daughter of machinist), 7 y	E Pl
42	48	Administrative assistant, polyurethane manufacturing plant	E Pl
43	61	Radiation therapy for breast cancer, 21 y prior to diagnosis	S Pl
44	82	Household contact (shipyard worker)	Pl
45	76	Household contact (asbestos worker), 5 y	E Pl
46	71	Radiation to pelvis, 50+ y prior to diagnosis	E Pe
47	74	Household contact (wife of insulator)	E Pl
48	46	Household contact (stepdaughter of shipyard worker), 6 y	E Pe
49	41	Household contact (daughter of tire presser), 13 y	B Pl
50	68	Household contact (wife of papermaker), 30 y	E Pl
51	53	Laborer, aluminum and chemical plants, 2 y	E Pl
52	52	NA	B Pe
53	77	Household contact (mother of steamfitter), 5 y	S Pl
54	55	Household contact (wife and daughter of shipyard and refinery workers), 30 y	E Pe
55	29	Household contact (father, cousin, uncle), 20 y	B Pl
56	78	Household contact (wife of shipyard worker), 30 y	E Pl
57	74	Household contact (wife of oil refinery worker), 27 y	E Pl
58	68	Household contact (wife of insulator), 25 y	E Pl
59	78	Shipyard worker, 2 y; household contact (wife of insulator), many years	E Pl
60	47	Aunt smoked Kent cigarettes	E Pl
61	81	Household contact (wife and mother of pipefitters/welders), 41 y	E Pl
62	71	Shipyard worker, 2 y	E Pl

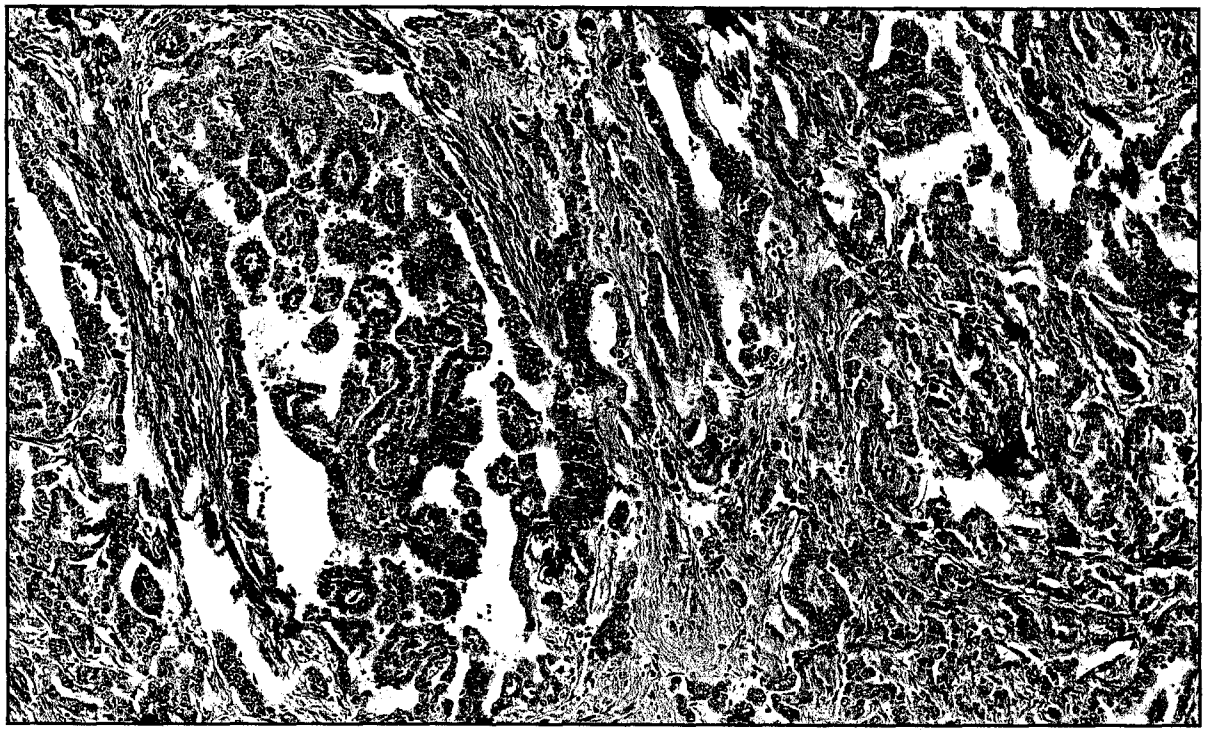
B, biphasic; Pl, pleural; E, epithelial; Pe, peritoneal; S, sarcomatoid; NA, not available.

men and women.[24,25] Fifty-three of the tumors arose in the pleura and nine in the peritoneum. The ratio of pleural to peritoneal tumors was 5.9:1 for women compared with 10.6:1 in men (unpublished data from the author's [VLR] series).

Twenty-nine (56%) of 52 pleural mesotheliomas in women were epithelial variants, including tubulopapillary and solid epithelial patterns ▸IMAGE 8-1◂. Nine tumors (17%) were sarcomatoid, including three with a predominantly desmoplastic pattern ▸IMAGE 8-2◂. The remaining 14 mesotheliomas (27%) were biphasic ▸IMAGE 8-3◂. The ratios of epithelial to biphasic to sarcomatoid tumors showed a greater proportion of epithelial mesotheliomas in women compared with men (56:27:17 for women vs 41:35:23 for men). Similar ratios were observed among the 9 peritoneal mesotheliomas in women (56:33:11). The proportion of epithelial peritoneal tumors was also increased compared with those occurring in men (49:46:5 for peritoneal tumors in men). In both sexes, purely sarcomatoid tumors were less common in the peritoneum than in the pleura. Only one of the peritoneal mesotheliomas in women was a purely sarcomatoid variant ▸IMAGE 8-4◂.

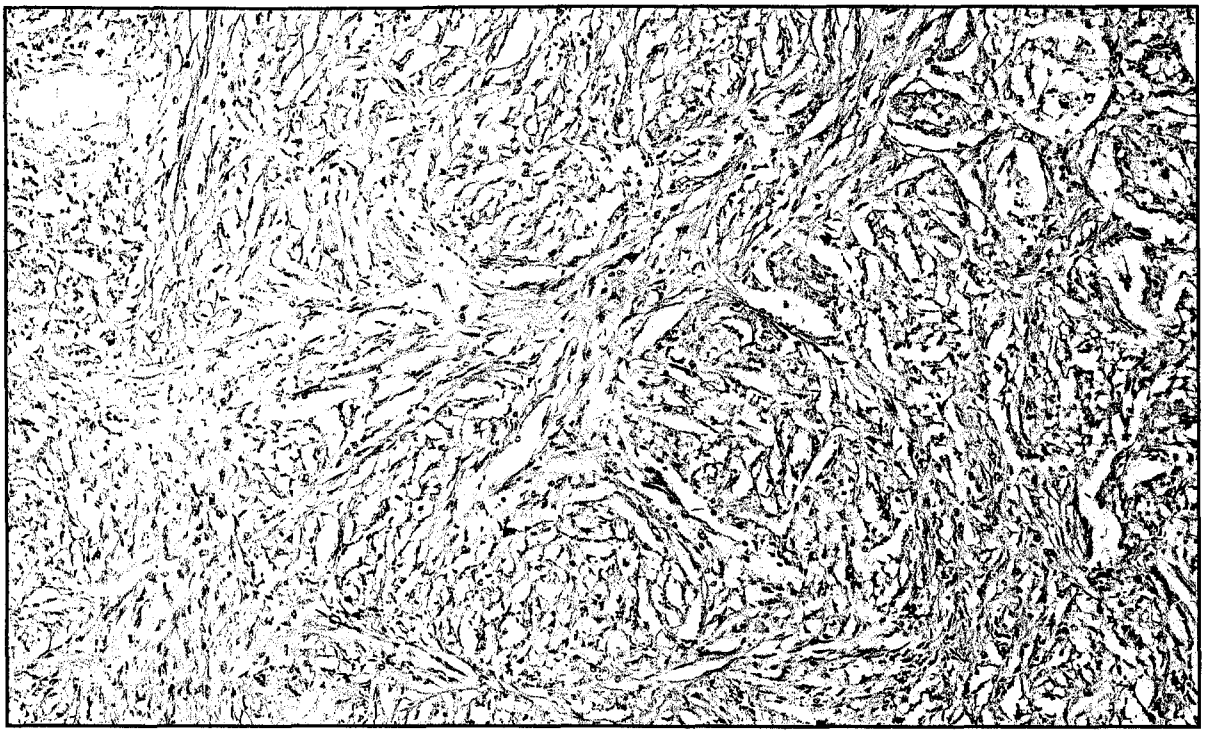
Ancillary evidence of asbestos exposure includes the findings of parietal pleural plaque formation or asbestosis in sections of lung parenchyma. Parietal pleural plaques ▸IMAGE 8-5◂ were noted in 13 (50%) of 26 patients for whom such information was available. Asbestosis ▸IMAGE 8-6◂ was present in 5 (16%) of 31 patients from whom lung tissue was obtained, and 4 of these were occupationally exposed to asbestos (see next section). These percentages for exposure in women are lower than those for men with mesothelioma (73% pleural plaques and 24% asbestosis) in the author's (VLR) series.

Results of immunohistochemical studies were available for 47 women ▸TABLE 8-2◂. Positive staining for cytokeratins was observed in 42 of 46 instances. The four that were keratin negative involved the use of polyclonal beef-muzzle keratin antibodies in sarcomatoid or biphasic tumors. The author (VLR) currently uses a monoclonal anti-keratin cocktail that includes AE_1/AE_3 and CAM



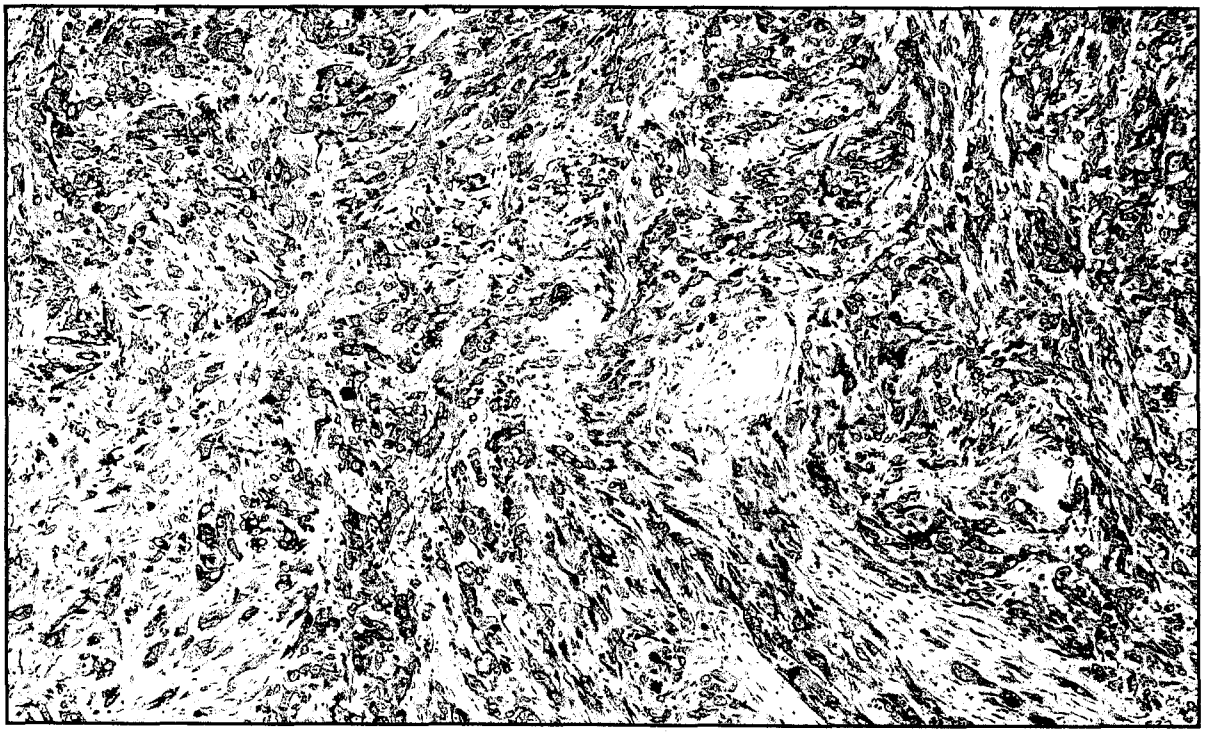
▸IMAGE 8-1◂

Case 60. Malignant mesothelioma showing a tubulopapillary pattern. (H&E, ×25)



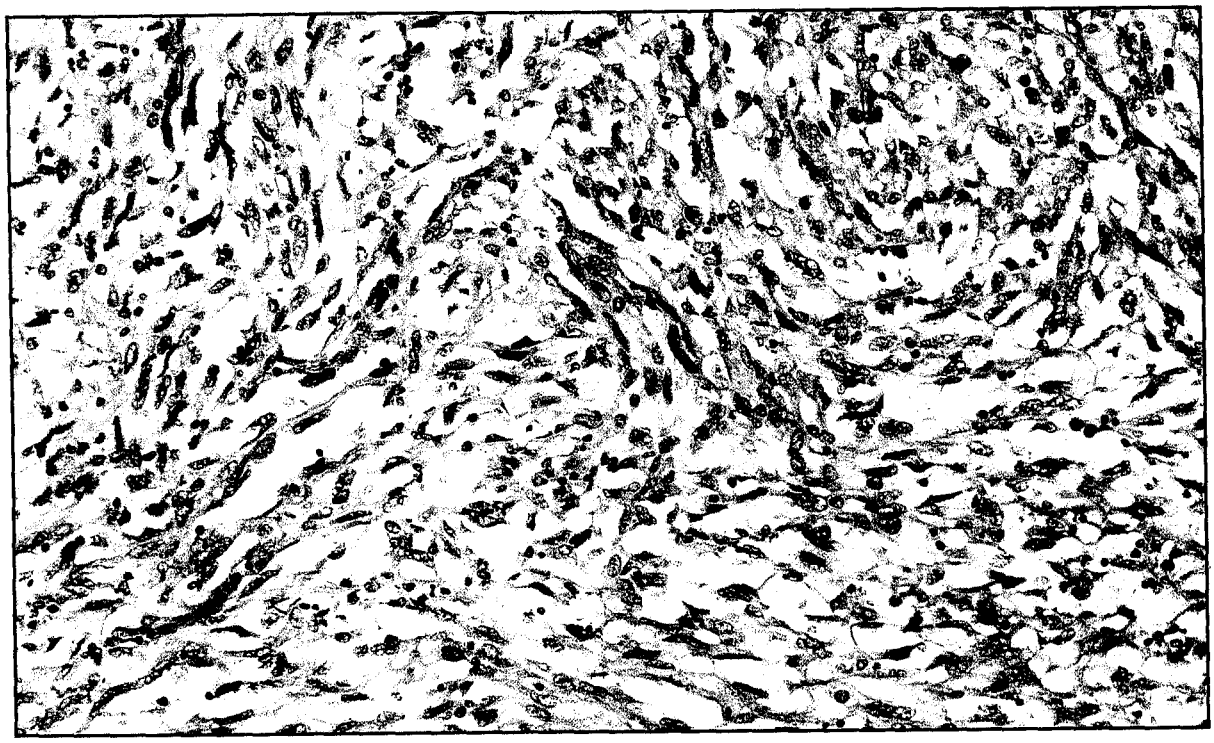
►IMAGE 8-2◄

Case 20. Malignant mesothelioma showing a desmoplastic pattern, consisting of thick collagen bundles arranged in a storiform pattern and separated by tumor cells with plump, often hyperchromatic, nuclei. (H&E, ×75)



►IMAGE 8-3◄

Case 55. Biphasic variant of malignant mesothelioma, showing predominantly epithelial morphology in the upper part of the field and a sarcomatoid pattern in the lower part. (Keratin immunoperoxidase, ×75)

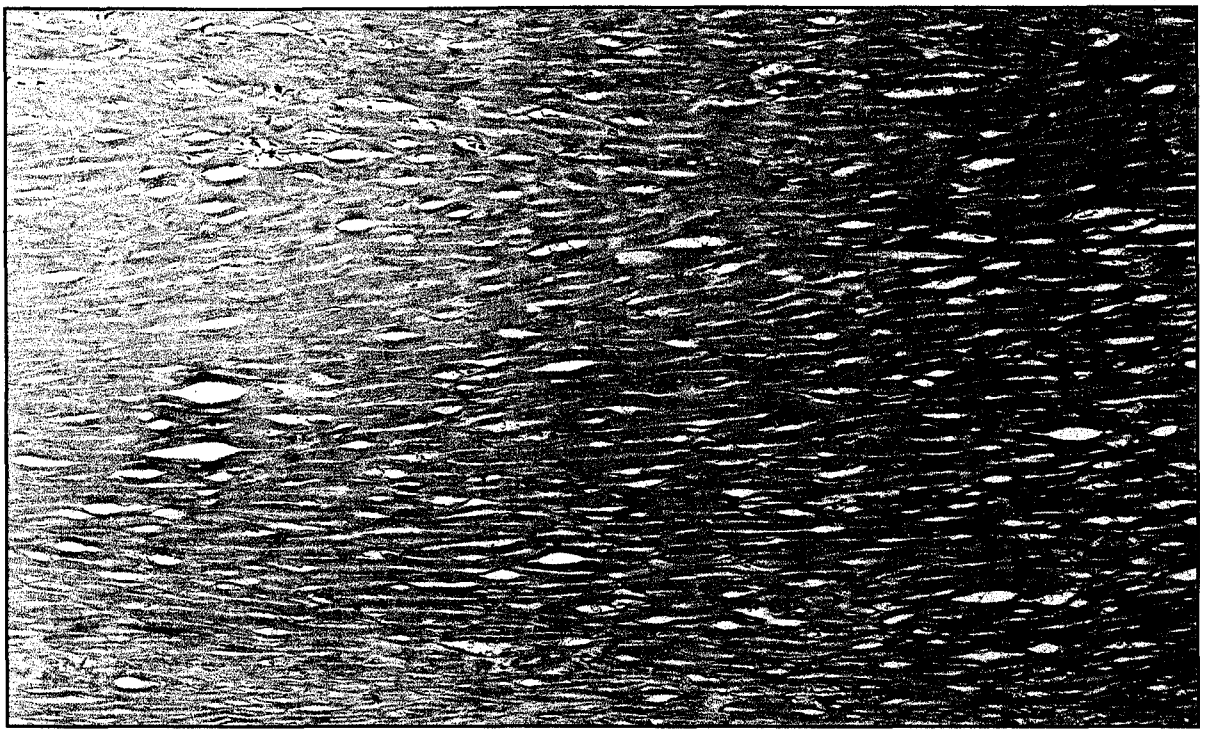


►IMAGE 8-4◄

Case 31. Sarcomatoid mesothelioma of the peritoneum showing a fibrosarcomatous pattern. (H&E, ×50)

►IMAGE 8-5◄

Case 1. Peribronchiolar fibrosis associated with asbestos bodies (upper left and right lower center). Note the multinucleate giant cell (right upper center). (H&E, ×100)



►IMAGE 8-6◄

Case 21. Parietal pleural plaque consisting of layers of acellular hyalinized collagen arranged in a "basket-weave" pattern. (H&E, ×25)

►TABLE 8-2◄

Immunohistochemical Findings in Women With Mesothelioma

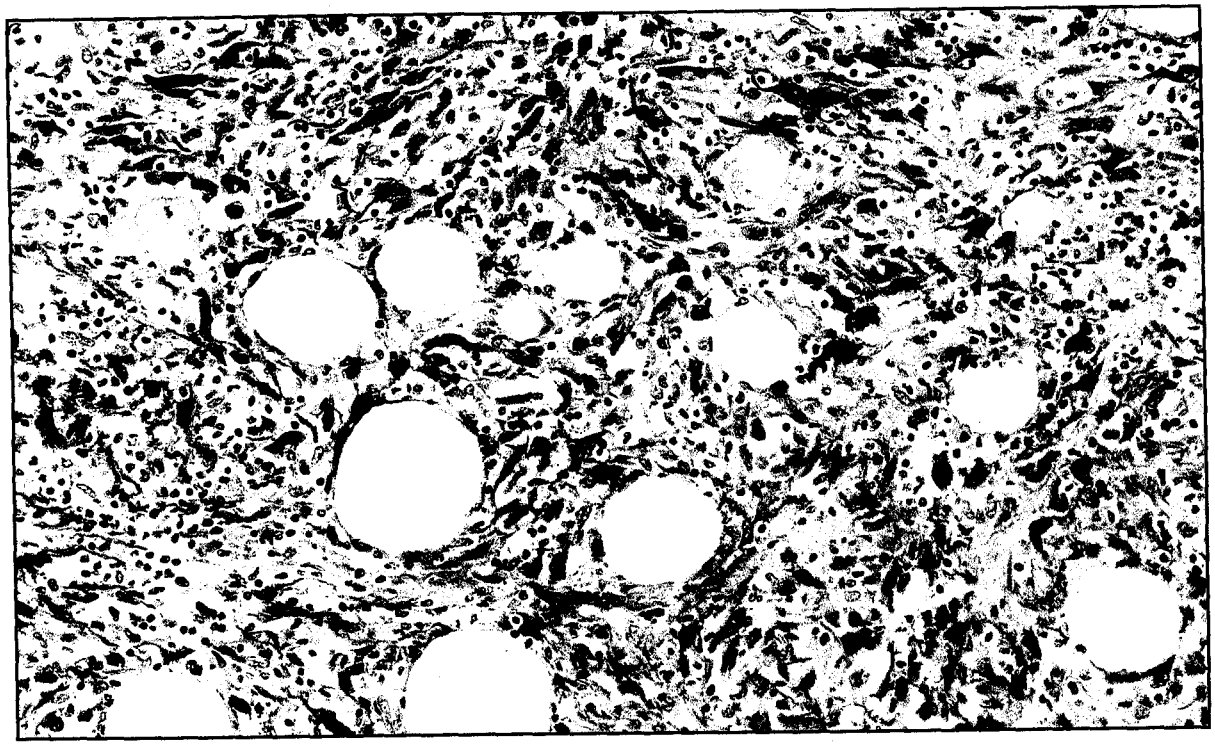
Antigen	No. of Cases (Positive/Total)*
Cytokeratins	42/46
Carcinoembryonic antigen (CEA)	1/46
Leu M-1 (CD15)	1/41
HBME-1	5/8

*Number of cases with positive staining over total number of cases for which staining with the indicated antibody was performed. See text for details regarding the antibodies used.

5.2. All mesotheliomas studied in women were keratin positive using this particular cocktail IMAGE 8-7. Forty-six tumors were stained using a polyclonal antibody against carcinoembryonic antigen; one stained focally positive. Similarly, one of 41 tumors stained focally positive for Leu M-1 (CD15). Eight tumors were stained using a monoclonal antibody raised specifically against mesothelial cells,[26] and five of these were positive ►IMAGE 8-8◄. In our experience, this antibody does not significantly stain the sarcomatoid component of mesotheliomas. Immunostaining for vimentin, epithelial membrane antigen, and B72.3 was performed in too few cases for meaningful interpretation. The overall immunohistochemical results were quite similar to those observed for mesotheliomas in men.[19]

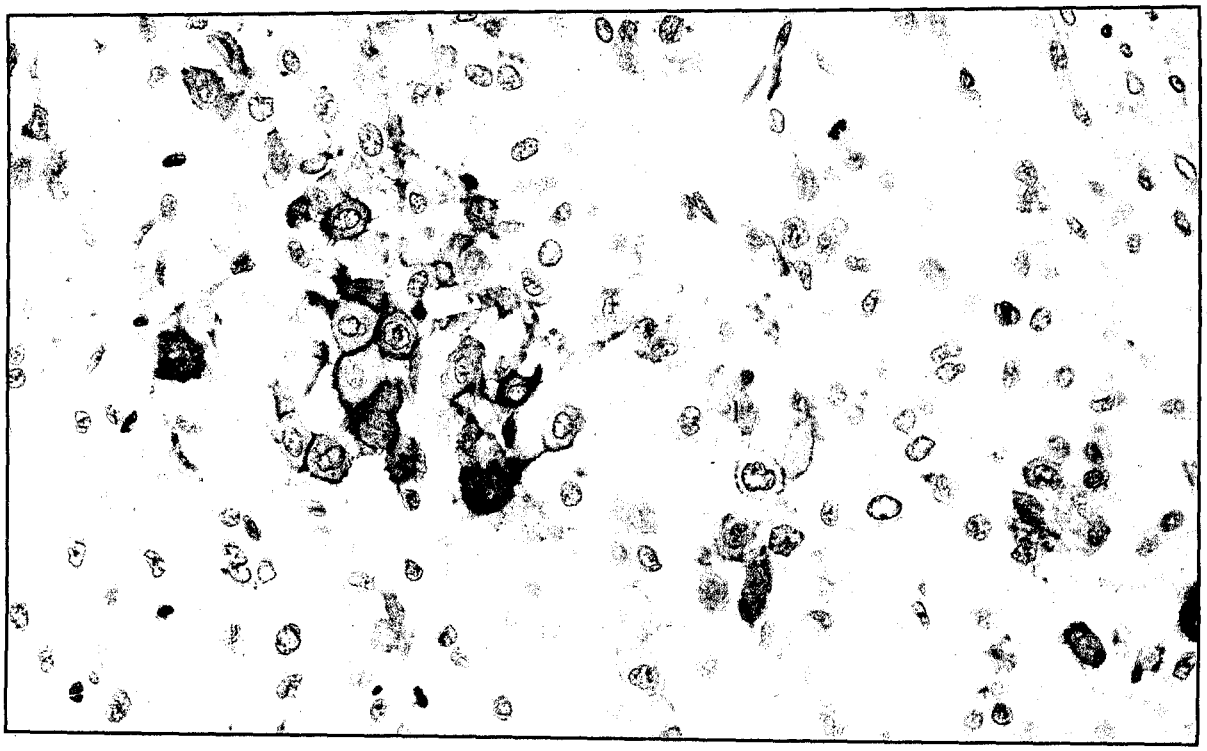
Exposure Information

Information regarding potential exposure to asbestos was available in 59 cases ►TABLE 8-1◄. Eleven women (19%) had an occupational exposure to asbestos. Three worked in shipyards for 1 to 2 years, and one worked on a tugboat for 15 months. Three patients worked at an asbestos manufacturing plant for 14 to more than 40 years (one as a braider; one as a spinner, winder, and weaver; and one as a company nurse). The other four patients were exposed to asbestos while employed at a power plant (13 years), as a laborer at an iron works (3.5 years), as a laborer at a



►IMAGE 8-7◄

Case 31. Sarcomatoid peritoneal mesothelioma showing keratin-positive spindle cells invading adipose tissue. (Keratin immunoperoxidase, ×50)



►IMAGE 8-8◄

Epithelial malignant mesothelioma stained with monoclonal antibody HBME-1, showing a predominantly membranous pattern of staining. (HBME-1 immunoperoxidase, ×100)

chemical plant (2 years), and at an optical manufacturing plant (no time available). Four of the women with occupational exposures also had pathologic asbestosis (Cases 1, 14, 25, and 33), and four had pleural plaques (Cases 25, 33, 51, and 59).

By far the most common form of exposure was through household contact with an asbestos worker, from asbestos brought home on the clothes of a worker living in the same household. Thirty-six (61%) of 59 women with mesothelioma were household contacts of asbestos workers. For 34 of these cases, this was the only identifiable exposure to asbestos. All gave a history of washing the work clothes in the household. The household contact was a husband in 22 cases, a father in 6, a husband and a father in 3, and a son in 2. There was one case each of contact through a husband and a son; a father and uncles; and a father, a cousin, and uncles. The household contacts' occupations were as follows: insulator (10 cases); shipyard worker (6 cases); pipefitter/welder (3 cases); oil refinery worker (2 cases); and steamfitter, papermaker, tire presser, machinist, construction worker, merchant marine seaman, auto mechanic, and asbestos plant manufacturer (1 case each). In 7 cases, the occupation of the household contact was not available. The duration of exposure for the household contact was known in 27 cases and ranged from 1.5 to 41 years (median, 17 years). Nine of the women in this group had parietal pleural plaques (Cases 2, 13, 18, 19, 21, 28, 44, 47, and 59), and two also had asbestosis (Cases 1 and 47). Three had peritoneal mesotheliomas (Cases 31, 39, and 48), and one patient's (Case 34) father died of mesothelioma.

The disease-producing potential of asbestos in buildings has stimulated considerable controversy.[27,28] In this regard, it is interesting to note that two of the women with pleural mesothelioma had potential exposure to asbestos as teachers within schools with friable asbestos-containing materials (Cases 10 and 11). One of these patients (Case 11) had pleural plaques, and tissue asbestos analysis was performed (see next section). An additional case was a 45-year-old woman with peritoneal mesothelioma (Case 24) whose only known exposure to asbestos was in an elementary school for 6 years as a child. Another potential exposure to asbestos on clothing occurred in a laundry worker at a military institute (Case 4). Three other cases had no known exposure to asbestos: One was a dry-cleaning plant assembler (Case 15) and two were homemakers (Cases 17 and 30).

Therapeutic radiation has been associated with the development of mesothelioma many years later,[19] and five patients gave a history of prior radiation. One (Case 3) had received radiation and chemotherapy for Wilms' tumor as a child.[29] Analysis of her lung tissue demonstrated an asbestos content no different from background. Another patient (Case 7) had received radiation and chemotherapy for lymphoma 7 years prior to the diagnosis of mesothelioma. She was also the wife of an asbestos-exposed individual. A third patient (Case 29) received radiation and chemotherapy for breast cancer 4 years prior to the diagnosis. This is a rather short latency for radiation-induced mesothelioma, and the patient also had exposure as a household contact. Analysis of her lung tissue disclosed considerably increased levels of asbestos. A fourth woman (Case 43) had received radiation therapy for breast cancer 21 years prior to the diagnosis of mesothelioma in the ipsilateral pleura, while a fifth (Case 46) with peritoneal mesothelioma had received pelvic radiation more than 50 years prior to the diagnosis. None of these patients had pleural plaques or asbestosis.

Studies have shown that there is no relationship between cigarette smoking and the subsequent development of mesothelioma.[30] However, a special case is Kent cigarettes, the Micronite filter of which contained crocidolite asbestos between 1952 and 1956. Talcott et al reported a striking incidence of mesothelioma among workers who manufactured the filters,[31] and Longo et al showed that substantial numbers of fibers were released when these cigarettes were smoked.[32] Nonetheless, there has been no convincing evidence to date of an increased risk of mesothelioma among individuals who smoked these cigarettes. One of the difficulties in such studies is that occupational exposure to asbestos is such a major factor in the causation of mesotheliomas in men that any effect due to low-

dose exposure from smoking Kent cigarettes is lost in epidemiologic studies. In contrast, occupational exposure is less prevalent in women, and therefore this group may be ideal for measuring the effects of low-dose exposure to cigarette smoke.

Smoking histories were obtained for the 62 women in this study ▸TABLE 8-3◂. Twenty-four were smokers or ex-smokers, and 19 were lifelong nonsmokers. Among the 24 smokers, three were too young (less than 12 years old in 1956) to have smoked during the Kent Micronite-filter era. Smoking histories were unavailable for 19 patients, but four of these were too young to have smoked Kents with Micronite filters. Three women actually reported a history of smoking Kents from 1952 to 1956, which is 14% (3/21) of those who were known to be smokers and were old enough to have smoked during the time in question. If one assumes that among the 15 women for whom smoking information was unavailable and who were old enough to have smoked during the relevant years, all were smokers and none smoked Kents from 1952 to 1956, then the percentage of women smoking Kents among those who smoked would be as low as 8% (3/36). In contrast, the market share for Kent Micronite filter cigarettes from 1952 to 1956 was less than 1%.[32] One other patient's only known exposure occurred when she lived for 10 years (including 1952–1956) with her aunt, who smoked Kent cigarettes. Analysis of lung fiber burden in this case was unremarkable. These data suggest an association between smoking Kent cigarettes with Micronite filters and the subsequent development of pleural mesothelioma among women. Our observations need to be confirmed in a larger population-based study, such as the Surveillance, Epidemiology and End Results (SEER) Program.[33]

▸TABLE 8-3◂

Smoking Histories in 43 Women With Mesothelioma*

Smoking Category	No. of Cases
Smokers/ex-smokers	24
Were old enough to have smoked Kent cigarettes with Micronite filters	21†
Smoked Kent cigarettes with Micronite filters	3
Lifelong nonsmokers	19

*Smoking histories were unavailable for 19 patients, 15 of whom were old enough to have smoked during the Kent Micronite-filter era.
†Micronite filters contained crocidolite asbestos between 1952 and 1956. Patients aged 12 years or older in 1956 were considered old enough to have conceivably smoked Kents during the time in question.

Fiber Analysis

Analysis of lung parenchyma for mineral fiber content was performed in 20 cases ▸TABLE 8-4◂. The median asbestos body count for 19 cases studied by light microscopy was 31 AB/g (range, 2.0–8200). The asbestos body count exceeded our normal range of 0 to 20 AB/g in 11 (58%) of 19 cases. SEM with fiber-type analysis was performed in 18 cases. Of these, 9 had an elevated level of commercial amphiboles (amosite or crocidolite) and 8 had an elevated content of noncommercial amphiboles (tremolite, actinolite, or anthophyllite). Chrysotile levels were outside our control range in 3 cases. An elevated fiber burden was detected in 14 (70%) of 20 cases.

Tissue for asbestos analysis was available for only two of the women with occupational exposures (Cases 1 and 12), and both demonstrated an elevated pulmonary asbestos burden. One (Case 1) was a spinner, winder, and weaver of chrysotile asbestos textiles, and she had a markedly increased chrysotile burden, including chrysotile asbestos bodies ▸IMAGE 8-9◂. This patient also had an elevated burden of amosite asbestos, probably derived from washing the clothing of her husband, an insulator. The other woman (Case 12) had a mildly elevated asbestos body count and increased levels of both commercial and noncommercial amphiboles.

Fiber burden analysis was performed on lung tissue from 13 women who were household contacts of asbestos workers, and 10 (77%) of these had an elevated tissue asbestos burden. The median asbestos body count for these 13 samples was 300 AB/g (range, 2–8200 AB/g) and exceeded the background range in 8 (62%) of 13

TABLE 8-4

Tissue Asbestos Content in 20 Women With Mesothelioma

Case No.	AB/g (LM)	UF/g	AC	TAA	Chrys	NAMF
1	5100	67,000	14,000	6700	33,500	26,800
2	8200	—	—	—	—	—
3	9.4	3900	—	—	—	—
5	2.0	24,300	<4860	9720	<4860	14,600
11	2.9	13,000	<870	4330	<870	8670
12	31	24,000	4800	4800	<2400	14,400
13	2330	17,000	5460	2430	1820	7300
15	64	6800	<680	5440	<680	1360
17	9.8	3300	<660	1980	<660	1320
18	300	4550	3250	<650	<650	1300
19	415	8490	450*	<1060	<1060	8490
20	29	45,000	<4500	<4500	<4500	45,000
29	1650	31,000	4650	1550	1550	23,250
32	590	23,900	2920*	7170	<2390	16,700
34	8.4	2920	<490	490	<490	2430
39	17	11,300	<660	1990	<660	9300
44	3.3	117,000	2280	9360	<4680	108,000
47	7480	40,000	34,000	4000	<2000	2000
55	5.0	4400	490	1960	<490	1960
60	—	4290	<310	1220	<310	3060
Controls†	20	12,700	<2540	2540	<2540	10,200

AB/g (LM), asbestos bodies per gram of wet lung tissue as determined by light microscopy; UF/g, uncoated fibers 5 μm or greater in length per gram of wet lung tissue as determined by scanning electron microscopy; AC, amosite or crocidolite (crocidolite detected only in Case 47); TAA, tremolite, actinolite, or anthophyllite; Chrys, chrysotile; NAMF, nonasbestos mineral fibers.

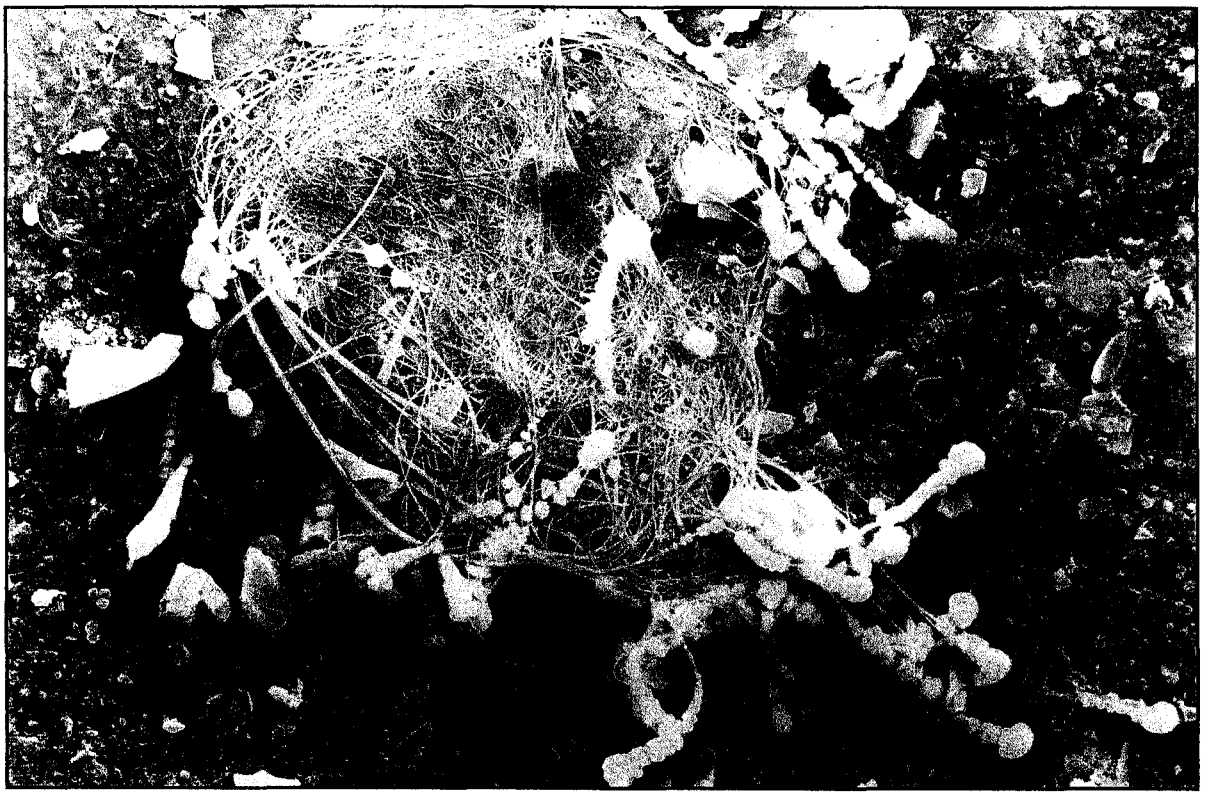
*Coated fibers only.

†Control values represent the upper limit of values identified in lung tissues from 19 male control cases as previously published.[22,49]

cases. Among the 12 samples for which SEM and EDXA were performed, commercial amphiboles were elevated in 7 cases, noncommercial amphiboles in 4 cases, and chrysotile in 2 cases. In one unique situation, both the woman (Case 18) and her husband presented with mesothelioma and pleural plaques; the husband also had asbestosis. Analysis of the husband's lung tissue demonstrated about 80 times as many asbestos bodies and 30 times as many uncoated fibers as those found in his wife's lungs.

Among the three patients exposed through household contact but without an elevated tissue asbestos burden, one was a 29-year-old woman (Case 55) with pleural mesothelioma who was exposed to dust on the clothes of her father, cousin, and uncles over a 20-year period. A single amosite fiber was detected by SEM, which is considered an ambiguous result (none expected in controls). Another patient was a 45-year-old woman (Case 34) with pleural mesothelioma who was exposed to dust on her father's clothes for 18 years; her father was an insulator who died of mesothelioma. The third patient was a 41-year-old woman (Case 39) with peritoneal mesothelioma who had been exposed to asbestos on the clothes of her father and uncles during the summers over a 20-year period.

Tissue asbestos analysis was performed in five additional cases. One patient (Case 11) was a teacher's aide for 18 years in a school with chrysotile-containing asbestos ceiling tile. This patient had a normal range asbestos body count but an increased tremolite (a known contaminant of chrysotile) burden by SEM/EDXA.[34] Another patient (Case 15) was a dry-cleaning



▸IMAGE 8-9◂

Case 1. Nuclepore filter with a cluster of chrysotile asbestos fibers isolated from the lungs. Free fiber ends appear to spin off the central mass like the arms of a spiral galaxy and have become coated to form numerous chrysotile asbestos bodies. (Reprinted with permission from Roggli.[50]) (Scanning electron microscopy, ×850)

plant assembler with an elevated asbestos body count and an increased tremolite burden; the source of tremolite exposure was not identified. A third patient (Case 3) was a 28-year-old woman with pleural mesothelioma who had received radiation and chemotherapy treatments for Wilms' tumor of the kidney at 4 years of age.[29] A fourth patient (Case 60) lived for 10 years with an aunt who smoked Kent cigarettes. A fifth patient (Case 17) had no known exposure to asbestos. The tissue asbestos burden in all three of these last cases was indistinguishable from background.

Nonasbestos mineral fibers were identified in all 18 cases in which SEM was performed. The fibers included talc, rutile, silica, aluminum silicates, and potassium aluminum silicates. Such fibers generally have low aspect (length to diameter) ratios, and there is no evidence that they play any role in the pathogenesis of mesothelioma.[35]

DISCUSSION

The pathologic features of malignant mesothelioma in women are similar to those observed in men. Pleural mesotheliomas outnumber peritoneal tumors in both sexes, although the proportion of peritoneal mesotheliomas is slightly higher in women. Epithelial variants predominate, and the percentage of epithelial types is slightly greater in women compared with men. The immunohistochemical features are also similar in both sexes: both epithelial and spindle cell components of the tumors stain positive for cytokeratins when a cocktail containing antibodies directed against both low and high molecular weight keratins is used. Fewer than 5% of mesotheliomas stain positive for CEA or Leu-M1, and such staining is usually focal.

Caution must be exercised in diagnosing epithelial variants of peritoneal mesothelioma in

women, as these may be confused with serous papillary carcinomas of the peritoneum. The distinction can usually be made based on careful attention to histologic, histochemical, immunohistochemical, and ultrastructural features. Budding or tufting is commonly seen in serous papillary carcinomas, as are numerous psammoma bodies. Intracellular mucin can be demonstrated with the periodic acid–Schiff stain in as many as half of papillary carcinomas, but only rarely in mesotheliomas. Staining with OC-125 is identified in more than 90% of serous papillary carcinomas, but in only 14% of mesotheliomas. Ultrastructurally, mesotheliomas possess long-surface microvilli that are often quite numerous, whereas the microvilli of serous papillary carcinomas are more sparse and tend to be stubby rather than long and slender.[18]

Ancillary histologic findings supportive of an asbestos etiology may be found in women but are somewhat less common. In our series of cases, pleural plaques were found in half of the women but in nearly three quarters of the men. Asbestosis was identified in 16% of the women with mesothelioma compared with 24% of men.

The exposure histories and results of tissue asbestos analysis in the women studied resulted in some interesting observations. A history of exposure to asbestos through household contact with an asbestos worker was found in 61% of our cases. This type of exposure was first reported as a cause of mesothelioma by Newhouse and Thompson in 1965,[36] and Anderson et al reported 5 cases of pleural mesothelioma in a study of 756 household contacts of asbestos factory workers in 1979.[37] Gibbs et al reported the results of tissue asbestos analysis in a series of 10 patients with mesothelioma who were household contacts of asbestos workers and found elevated counts beyond those of a reference population in 8 of the 10 cases.[38] These findings are almost identical to those presented here, in which an elevated tissue asbestos burden was noted in 10 (77%) of 13 of the household contacts with mesothelioma. One of the tumors (Case 31) was a sarcomatoid peritoneal mesothelioma. To our knowledge, this is the first case of peritoneal mesothelioma in a household contact in which an elevated pulmonary asbestos content has been demonstrated in support of an asbestos etiology.

A history of occupational exposure to asbestos was identified in 19% of our cases, and an elevated tissue asbestos burden was found in each of the two instances in which lung tissue was available for analysis. These findings differ from those reported by McDonald and McDonald[1] and by Dawson et al.[13] The former reported an occupational history of exposure to asbestos in only 5% of women with mesothelioma in North America. That study depended on occupational histories obtained by interviewing surviving relatives, and thus may have underestimated the actual prevalence of exposure. Furthermore, the reports were collected prior to 1980, and it is difficult to know how many might have been serous papillary carcinomas of the peritoneum misdiagnosed as mesothelioma. In the study by Dawson et al, occupational exposure to asbestos was identified in 51 (55%) of 93 cases for which information was available. This series contained a substantial number (20) of women who were exposed to asbestos during the manufacture of gas masks during World War II. Our cases are largely medicolegal referrals, and thus may not be representative of all mesotheliomas in women in the United States. Therefore, it is difficult to know the precise percentage of US women with mesothelioma who are occupationally exposed to asbestos.

Considerable scientific controversy and debate has surrounded the problem of how to manage the large amount of asbestos presently in place in public buildings in this country. One review of this subject noted that no cases of asbestos-related disease have been reported among individuals whose only known exposure was as occupants of buildings with friable asbestos-containing materials.[28] Contrary to this assertion, two cases of pleural mesothelioma have been reported in such a setting. Stein et al described a 54-year-old woman with pleural mesothelioma whose only known exposure to asbestos was as an office worker in a building with ceiling material composed of 70% amosite asbestos.[39] Amosite asbestos fibers were identified in samples of this patient's lung tissue. Roggli and

Longo described a 58-year-old woman with pleural mesothelioma, pleural plaques, and a work history including 18 years as a teacher's aide in a building containing tremolite-contaminated chrysotile in ceiling tiles. Analysis of pulmonary fiber burden demonstrated an elevated tremolite content in this patient.[34] The risk of this occurrence must be extremely low when one considers the rarity of this association and the large number of individuals with presumed exposure.

Some mesotheliomas have no demonstrable association with asbestos exposure.[40] In this regard, it is interesting that a history of therapeutic radiation to the site of subsequent mesothelioma development was reported in five of the patients in this study. One of these women had a brief period of only 4 years between the radiation and the diagnosis of mesothelioma but also had a strong history of household exposure and an elevated tissue asbestos content. We therefore believe that this case is asbestos related. The other four women received radiation from 7 to more than 50 years prior to the development of mesothelioma. The association between prior treatment for Wilms' tumor and subsequent development of mesothelioma, as seen in Case 3, has been reported by others as well.[41,42] The discovery of a Wilms' tumor suppressor gene and the identification of the gene product in a large proportion of mesotheliomas is fascinating[43] and may provide a lead in the study of familial or hereditary predisposition to mesothelioma. The association between prior radiation for breast cancer and subsequent development of mesothelioma, as seen in Case 43, has also been reported previously.[44]

The occurrence of familial mesothelioma suggests a genetic predisposition, as already noted. Three of our cases may be examples of genetic predisposition. Two patients (Cases 13 and 29) belonged to families in which mesothelioma occurred in the mother, daughter, aunt, and uncle. In another instance (Case 34), the father and daughter both developed mesothelioma. In the present series, a history of asbestos exposure and/or an elevated pulmonary asbestos fiber burden was present, which indicates that the genetic factor probably makes the individual more susceptible than usual to the effects of asbestos on the pleura.[45] If tumor suppressor genes are involved in such a predisposition, then a possible mechanism would be hereditary deletion of one copy of the suppressor gene, so that interaction of asbestos with mesothelial cells would inactivate or delete the single remaining copy.[46]

A history of asbestos exposure was elicited in 45 (76%) of 59 of our cases, and an abnormal tissue asbestos content was found in 14 (70%) of 20 cases. The main fiber type identified was commercial amphibole (mostly amosite), with noncommercial amphiboles (mostly tremolite) identified less frequently and chrysotile identified least. Recent studies have shown that as many as 58% of women with mesothelioma in Australia and 30% of women in France have a positive asbestos exposure history.[47,48] These observations have important implications for estimates of the background rate of mesothelioma. McDonald and McDonald estimated the background rate to be one to two cases per million population per year, based on the observed rates in women and the authors' finding that only 5% were occupationally exposed to asbestos.[1] However, if half of these women are exposed, the background estimate would be closer to one case per million per year. This would amount to an expected number of 250 mesotheliomas per year in the United States. The real number observed is 2200 cases per year, which implies that 89% ([2200 – 250]/2200) are asbestos related. In this regard, it is interesting that an elevated asbestos content was observed in 89% of cases for our entire series (both men and women).[49]

Summary

About 8% of our cases of mesothelioma occur in women, with a median age of 59 years. Our percentage is lower than other series reported in the literature because of the large number of occupationally exposed men referred to our laboratory. Tumor arose in the pleura in 86% of the women in our study, and the majority were epithelial. Pleural plaques were found in

half of the women for which this information was available, and asbestosis was found in only 16%. A history of exposure to asbestos was identified in three quarters of the women, more than half of whom were household contacts of asbestos workers. Occupational exposure to asbestos was identified in only 19% of patients. An elevated tissue asbestos burden was noted in 70% of women from whom lung tissue was available for analysis. The main fiber type identified was amosite, followed by tremolite and chrysotile. These findings and those from other countries suggest a need for reassessment of the background rate of mesothelioma in industrialized nations.

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