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Malignant Mesothelioma in Japan: Analysis of Registered Autopsy Cases

YOSHIHIRO MURAI
Department of Pathology
Faculty of Medicine
Toyama Medical and Pharmaceutical University
Toyama, Japan

ABSTRACT. In the *Annual of the Pathological Autopsy Cases in Japan*, issued by the Japanese Society of Pathology from 1958 to 1996, a total of 1,846 (0.17%) malignant mesothelioma cases (1,287 male, 558 female, 1 unknown) were registered among 1,056,259 autopsy cases. The frequency of mesothelioma (number of cases/total autopsy cases) was 0.10% (461/440,334) for the term 1958–1979, 0.18% (716/390,124) for 1980–1989, and 0.30% (669/225,801) for 1990–1996; the frequency of cases increased significantly over the time periods ($p < .0001$). Among 1,785 cases for which tumor sites were ascertained, there were 1,213 pleural mesothelioma (68.0%), 431 peritoneal (24.1%), 108 pericardial (6.1%), 6 tunica vaginalis testis (0.3%), and 28 "others" (1.6%). Histological cell type was noted in 598 cases; 245 (41.0%) were epithelial, 168 (28.1%) were biphasic, and 185 (30.9%) were sarcomatous. Seventy-three (0.007%) cases of malignant mesothelioma with asbestosis were found during the entire 39-y period. The frequency of those with asbestosis (number of cases/total autopsy cases) was 0.001% (5/440,334) for the term 1958–1979, 0.006% (27/390,124) for 1980–1989, and 0.018% (41/225,801) for 1990–1996; this increase over time was statistically significant ($p < .0001$). Researchers expect that cases of asbestos-related mesothelioma will increase in Japan in the future. Tumor sites and histological cell types of mesothelioma with asbestosis did not differ from those in individuals without asbestosis.
<Key words: asbestos, asbestosis, histological cell type, malignant mesothelioma>

MALIGNANT MESOTHELIOMA originates from serosal cells of the pleural, peritoneal, and pericardial cavities, and from the tunica vaginalis testis. Since Wagner et al.[1] reported mesotheliomas from asbestos exposure in South Africa in 1960, many researchers have subsequently confirmed his conclusions. In Japan, consumption of asbestos has increased markedly since World War II, and it is one of the leading consumers in the world.

Since 1958, autopsy cases in Japan have been registered in the *Annual of the Pathological Autopsy Cases in Japan* (hereinafter *Annual*) by the Japanese Society of Pathology. Baba[2] surveyed the annuals from 1974 through 1980 and reported that, although there were no pleural malignant mesotheliomas associated with asbestosis until 1977, there was 1 death in 1978, 3 in 1979, and 2 in 1980. His report suggests that the number of occupational pleural malignant mesotheliomas has begun to increase in Japan. In this study, we sought to extend the survey of the *Annuals* and to elucidate the features of malignant mesothelioma with asbestosis.

Materials and Method

The *Annuals of the Pathological Autopsy Cases in Japan* (years 1958–1996) by the Japanese Society of Pathology were used. Until the annual for 1996 was issued, a total of 1,846 (1,287 male, 558 female, 1 unknown) autopsy cases with malignant mesothelioma had been recorded among 1,056,259 autopsy cases. This documentation is a passive system for the recording of autopsy reports received from individual pathologists; no confirmatory reviews are provided. Tissue slides are not sent in and archived. Some diagnoses,

Table 1.—Frequency of Malignant Mesothelioma among Autopsy Cases

Years	Mesothelioma: Male	Female	Both	Total no. of autopsy cases	Percentage	No. autopsies	No. deaths	Autopsy rate (%)
1958–1959	13	8	21	19,356	0.11	10,638	23,299	45.7
1960–1964	44	17	61	68,039	0.09	43,254	98,839	43.8
1965–1969	61	38	96	104,736	0.09	77,274	165,791	46.6
1970–1974	90	43	133	112,905	0.12	89,465	240,446	37.2
1975–1979	97	53	150	135,298	0.11	117,910	329,676	35.8
1985–1989	278	137	415	197,249	0.21	180,895	682,369	26.5
1980–1984	210	90	301 (1)*	192,875	0.16	171,297	513,648	33.3
1990–1994	335	120	455	169,345	0.27	152,576	820,622	18.6
1995–1996	162	52	214	56,456	0.38	50,962	365,325	13.9
Overall	1,287	558	1,846 (1)*	1,056,259	0.17	894,221	3,240,015	27.6
1958–1979	302	159	461	440,334	0.10†	338,541	858,051	39.5
1980–1989	488	227	716 (1)*	390,124	0.18†	352,192	1,196,017	29.4
1990–1996	497	172	669	225,801	0.30†	203,538	1,185,947	17.2

*The number in parentheses is the case for whom sex was not known.
†$\chi^2 = 316.751$, $p < .0001$.

however, of mesothelioma have been confirmed by a panel or by consultation because mesothelioma is a difficult diagnosis.

The age, sex, clinical diagnosis, residence area, occupation, main pathological lesions, and some additional lesions are recorded in each *Annual*. Malignant mesotheliomas are regarded as the main pathological lesions, independent of tumor size. The space for the description of occupational history in the *Annual* is restricted in that only the main or most recent occupation is described. The life employment system has been relatively maintained in Japan.

The frequency of malignant mesotheliomas and those with asbestosis in autopsy cases in each of the three terms—1958–1979 (22 y), 1980–1989 (10 y), and 1990–1996 (7 y)—as well as the change over time, were examined. We used the Chi-square test for statistical evaluations.

Results

The frequency of malignant mesothelioma (number of cases/total number of autopsy cases) was 0.17% (1,846/1,056,259) for the entire 39-y period from 1958 to 1996 (Table 1). The comparison over the three periods revealed a significant increase in the frequency of mesothelioma, from 0.10% (461/440,334) in 1958–1979, to 0.18% (716/390,124) in 1980–1989, to 0.30% (669/225,801) in 1990–1996 ($\chi^2 = 316.751$, $p < .0001$).

The age and sex distributions are shown in Table 2. Seventy-four percent of all cases were between 50 y and 79 y of age, and the highest frequency of malignant mesothelioma was found in both sexes in the 60–69 y age range. There were 17 (0.9%) cases under the age of 19 y.

Among the 1,846 mesothelioma cases, occupational histories were not described for 651 of them. Special attention was not given to asbestos exposure in all mesothelioma cases. The occupations of 1,285 cases were categorized into four groups, relative to asbestos exposure: (1) definite, (2) probable or possible, (3) uncertain, or (4) unlikely (Table 3). Twenty-six cases in the definite group were employed in asbestos-processing plants. Among the 226 cases in the probable or possible group, 96 had worked in the construction industry, 33 had been shipyard workers, 31 metal workers, 24 electricians, 22 railroad workers, 17 pipefitters, and 3 boilermen. Company workers, farmers, and factory workers were included in the uncertain group. Some farmers held side jobs during the "leisure season" for farmers in Japan. On the other hand, there were many cases that belonged to the unlikely group, and asbestos exposure could not be identified only by their occupations. Housewives, schoolteachers, medical doctors, nurses, and clergy were included.

Tumor sites of 1,785 cases were noted in the *Annual* (Table 4). There were 1,213 (68.0%) pleural mesothe-

Table 2.—Age and Sex Distribution of Malignant Mesothelioma Cases

Age (y)	Male: n	%	Female: n	%	Total: n	%
0–9	8	0.6	3	0.5	11	0.6
10–19	4	0.3	2	0.4	6	0.3
20–29	33	2.6	16	2.9	49	2.7
30–39	50	3.9	20	3.6	70	3.8
40–49	149	11.6	53	9.5	202	11.0
50–59	298	23.2	112	20.1	410	22.2
60–69	374	29.1	170	30.5	544	29.5
70–79	275	21.4	129	23.1	404	21.9
80–89	92	7.2	49	8.8	141	7.7
≥ 90	2	0.2	4	0.7	6	0.3
Overall	1,285	100.0	558	100.0	1,843	100.0

Note: The ages of 2 cases and the sex of 1 case were not known.

Table 3.—Occupational Histories of Malignant Mesothelioma Cases

Occupational exposure to asbestos	No. of cases	Occupation
Definite	28	Worker in asbestos-processing plant (n = 26), asbestos insulation worker (n = 2)
Probable or possible	226	Worker in construction industry (n = 96), shipyard worker (n = 33), metal worker (n = 31), electrician (n = 24), railroad worker (n = 22), pipefitter (n = 17), boilerman (n = 3)
Uncertain	455	Company worker (n = 201), farmer (n = 79), factory worker (n = 46), driver (n = 36), self-employed shop (n = 24), miners (n = 9), shipman (n = 7), laundryman (n = 6), other (n = 47)
Unlikely	576	Housewife (n = 228), workers in food and drink service industry (n = 50), clerk (n = 47), school teacher (n = 39), public servant (n = 27), medical doctor (n = 11), worker in clothes-service industry (n = 8), nurse (n = 6), religionist (n = 6), student (n = 6), policeman (n = 6), other (n = 142)

liomas, 431 (24.1%) peritoneal mesotheliomas, and 108 (6.1%) pericardial mesotheliomas. Six (0.3%) mesotheliomas arose from the tunica vaginalis testis. Pleural mesotheliomas were predominant in both sexes; however, the frequency in males (72.7%) was higher than that in females (56.9%). On the contrary, the frequency of peritoneal mesothelioma in females (35.3%) was higher than that in males (19.3%). The male to female ratio for each tumor site was also calculated and appears in Table 4. The ratios (male/female) of the pleural and peritoneal mesotheliomas were 3.0 and 1.3, respectively.

Histological cell types of 598 mesotheliomas were ascertained in the *Annual*, and there were 245 (41.0%) epithelial, 168 (28.1%) biphasic, and 185 (30.9%) sarcomatous types (Table 5). The frequency of epithelial cell type in peritoneal mesothelioma (52.4%) was higher than those in the other tumor sites.

Of all 1,846 mesothelioma cases, 73 cases were accompanied with asbestosis (Table 6). The prevalence of asbestosis was higher among mesothelioma cases (3.95%; 73/1846) than in the overall data system (0.05%; 525/1056,259). The first peritoneal and pleural mesotheliomas with asbestosis were found in 1976 and in 1978, respectively. The frequency of malignant mesotheliomas with asbestosis (number of cases/total autopsy cases) was 0.001% (5/440,334) for the term 1958–1979, 0.006% (27/390,124) for 1980–1989, and 0.018% (41/225,801) for 1990–1996. There was a significant increase during all three periods (χ^2 = 62.582, p < .0001). The tumor sites were ascertained in 71 cases, and there were 50 (70.4%) pleural and 18 (25.4%) peritoneal mesotheliomas. Histological cell types of mesotheliomas with asbestosis were obtained in 40 cases. The epithelial cell type was predominant (18 cases [45.0%]); the next most-frequent cell type was biphasic (12 cases [25.0%]), followed by sarcomatous (10 cases [30.0%]).

Discussion

Takahashi et al.[3] reported that recent mesothelioma incidence among the 10 Western countries and Japan ranged between 5 (Japan) and 25 (Australia), with a median of 15 per one million per year (United States). They speculated that the asbestos consumption curve for Japan in past years lagged behind that for Western countries, and that the cumulative exposure effect has not yet reached the level that can be expected from other countries. In autopsy cases, the frequency (0.17%) of mesothelioma in this survey (1958–1996) was also lower than that of Western countries.[4,5] Hartmann and Schutze[4] reported 106 cases of pleural mesothelioma among 33,500 autopsy cases (0.32%) from 1957 to 1987 in Germany. Giarelli et al.[5] reported 170 cases of malig-

Table 4.—Tumor Sites of Malignant Mesothelioma

Site	Male		Female		Total		
	n	%	n	%	n	%	Male:Female
Pleura	906	72.7	306	56.9	1,213*	68.0	3.0
Peritoneum	241	19.3	190	35.3	431	24.1	1.3
Pericardium	76	6.1	32	5.9	108	6.1	2.4
Tunica vaginalis testis	6	0.5	—	—	6	0.3	—
Pleura and peritoneum	8	0.6	1	0.2	9	0.5	8.0
Pleura and pericardium	5	0.4	2	0.4	7	0.4	2.5
Mediastinum	4	0.3	7	1.3	11	0.6	0.6
Diaphragm	1	0.1	—	—	1	0.1	—
Overall	1,247	100.0	538	100.0	1,785	100.0	2.3

*The sex of 1 pleural case was not known.

Table 5.—Histological Cell Type of Malignant Mesotheliomas

Site	Epithelial		Biphasic		Sarcomatous		Total	
	n	%	*n*	%	*n*	%	*n*	%
Pleura	155	37.4	115	27.8	144	34.8	414	100.0
Peritoneum	66	52.4	37	29.4	23	18.3	126	100.0
Pericardium	18	48.6	10	27.0	9	24.3	37	100.0
Other	6	28.6	6	28.6	9	42.9	21	100.0
Overall	245	41.0	168	28.1	185	30.9	598	100.0

Table 6.—Description of Malignant Mesotheliomas Accompanied by Asbestosis

Year	No. of cases/ total cases autopsied	Percentage
	Frequency	
1958–1979	5/ 440,334	0.001*
1980–1989	27/ 390,124	0.007*
1990–1996	41/ 225,801	0.018*
1958–1996	73/1,056,259	0.007

Site	No. of cases	Percentage
	Tumor site	
Pleura	50	70.4
Peritoneum	18	25.4
Pleura and peritoneum	2	2.8
Mediastinum	1	1.4
Overall	71	100.0

Cell type	No. of cases	Percentage
	Histological cell type	
Epithelial	18	45.0
Biphasic	12	25.0
Sarcomatous	10	30.0
Overall	40	100.0

*$\chi^2 = 62.582$, $p < .0001$

nant pleural mesothelioma among 40,826 autopsy cases (0.42%) during the period 1968–1987 in Italy. Compared with Western countries, there would be a time lag in the increase of mesotheliomas in Japan. The frequency for the term 1990–1996 (i.e., 0.3%) from Japanese autopsies was three times higher than that for 1958–1979 (i.e., 0.1%). Present consumption of asbestos in Japan remains high, and we expect that asbestos-related mesotheliomas will increase in the future.

In our study, the most common site of mesothelioma was pleura, followed by peritoneum, and pericardium. Mesothelioma of the tunica vaginalis testis was very rare. Hillerdal[6] reviewed 4,710 cases of mesothelioma, and 88.8% of the cases were pleural in origin, 9.6% were peritoneal, 0.6% were pleural and peritoneal, 0.7% were pericardial, 0.2% were in the tunica vaginalis testis, and 0.1% occurred at an undetermined site. The frequency (68.0%) of pleural mesothelioma in Japan is relatively low. Perhaps asbestos-related mesothelioma may occur most frequently in pleura; therefore, it may reflect the different cumulative exposure effect between Japan and Western countries. This speculation is supported by the fact that pleural mesothelioma is more common in males than females. Males have more opportunities to be exposed to asbestos by virtue of their occupations. However, in the cases of malignant mesothelioma with asbestosis, the frequency of pleural mesothelioma is not so different from those without asbestosis. The frequency of peritoneal cases in asbestos-related mesotheliomas may be higher in those with asbestosis (i.e., highly exposed asbestos cases) than in the cases with lower asbestos exposure, because a certain quantity of asbestos fibers may need to reach the peritoneum.

Mesotheliomas are commonly diagnosed between the ages of 50 y and 79 y. In our study, however, there were a few cases under 19 y of age. Special attention should be given to childhood mesothelioma, whether or not it is diagnosed correctly. In the 22 childhood cases Fraire et al.[7] reviewed, 45% of them were accepted as mesothelioma, and 14% were of "doubtful or uncertain nature." In the remaining 41%, the diagnosis of mesothelioma was rejected. Given that the diagnosis of mesothelioma in recent years has become more accurate as a result of the development of immunohistochemical staining, investigators must accumulate more data concerning mesothelioma and its relationship with asbestos exposure. A few childhood mesothelioma patients were reportedly exposed to asbestos; however, most cases had no such exposure.[7] It is said that asbestos-related mesothelioma needs a long latency period from the beginning of the asbestos exposure to the time the tumor is manifested. Therefore, the existence of childhood mesothelioma may be one reason why researchers do not attribute all mesotheliomas to asbestos exposure.

The most common etiologic factor of mesothelioma is asbestos. Other factors reported are erionite,[8] radiation,[9] chronic inflammation,[10] among others.[11] Investigators confirmed by animal experiment that SV40 virus caused mesothelioma in the hamster.[12] McDonald and McDonald[13] reported that in approximately one-half of the male mesothelioma cases, no potential for occupational asbestos exposure could be identified. Other researchers have reported various percentages (i.e., 0–87%) of cases for which asbestos exposure was not documented.[14] In our earlier report,[15] we evaluated asbestos body counts in the lungs of 27 malignant mesothelioma cases, and approximately one-half of mesothelioma cases had counts of more than 1.51 asbestos bodies per 5 gram wet lung tissue, thus indicating occupational asbestos exposure. In the current study, the frequency of the patients who were clearly identified as having asbestos exposure was not very high. However, we note that all occupational records related to asbestos exposure have not been described in

the *Annuals*. In addition, the absence of proof of asbestos exposure does not constitute a lack of probability that the epidemic of mesothelioma in Japan has resulted from asbestos. One must consider that asbestos-induced malignant mesotheliomas may result from nonoccupational exposure to asbestos. It is reported that bystander and consumer exposures are the "third wave" of asbestos disease playing out now.[16]

Three main histological types are recognized in mesothelioma: (1) epithelial, (2) sarcomatous, and (3) biphasic. Hillerdal[6] reported that the epithelial type (50%) was the most common in 829 pleural mesothelioma cases; the next most-frequent type was biphasic (34%), followed by sarcomatous (16%). Roggli et al.[17] reported the following histological cell types from 200 cases of malignant pleural mesothelioma: epithelial (40%), biphasic (37%), and sarcomatous (23%). In our survey, the histological type that occurred most frequently (41.0%) was epithelial; however, the frequency of biphasic (28.1%) and sarcomatous (30.9%) cell types was the opposite of that reported by Roggli et al.[17]

Whether specific histological cell types of mesotheliomas are related to asbestos exposure remains uncertain. Magner and McDonald[18] suggested that mixed mesothelial tumors were specifically associated with asbestos exposure. Leigh et al.[19] reported there was a significant correlation in lung fiber content with cell type from epithelial (i.e., low fiber content) through mixed to sarcomatous (i.e., high fiber content). However, Hirsh et al.[20] reported that the proportion of epithelial mesothelioma type in the group with definite past asbestos exposure was higher than that in the group that was unexposed to asbestos. On the other hand, Wright and Sherwin[21] concluded that their data did not support the hypothesis that any specific histological type of mesothelioma is especially related to asbestos exposure. Although only mesotheliomas with asbestosis were selected in this study, our data support the conclusion posited by Wright and Sherwin.[21]

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Requests for reprints should be sent to Dr. Yoshihiro Mural, Department of Pathology, Faculty of Medicine, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama, 930-0194 Japan.

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