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Clinical Study on Mesothelioma in Japan: Relevance to Occupational Asbestos Exposure

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Background *In 2003, the number of deaths due to malignant mesothelioma in Japan was 878; however, only 85 cases of mesothelioma due to asbestos exposure were authorized for compensation. The reasons for this discrepancy require evaluation.*
Method *We examined medical records, X-rays, and pathology results to evaluate mesothelioma cases in Japan between 2003 and 2005; used a questionnaire to identify occupational and environmental histories, and determined the concentration of asbestos fibers in pathology specimens.*
Results *We identified 442 definite cases of malignant mesothelioma with a median age of 68 years. There were 316 malignant mesothelioma cases with occupational asbestos exposure, 12 cases with neighborhood exposure and 5 cases with likely domestic exposure. Most (78%) of the 87 cases exceeded 1,000 asbestos particles per gram of dry lung tissue.*
Conclusion *We conclude that 79.2% of cases of mesothelioma in Japan in recent years were caused by asbestos exposure.* Am. J. Ind. Med. 53:1081–1087, 2010.

***KEY WORDS:** mesothelioma; pleural plaques; exposure; asbestos particles; Helsinki criteria*

BACKGROUND

Until 1994, the International Classification of Diagnosis (ICD)-9 classified death due to mesothelioma and other causes of death together, and, therefore, statistics on only mesothelioma could not be obtained. After 1995, when ICD-10 was implemented and deaths due to mesothelioma were reclassified, statistics regarding incidents of death due to mesothelioma could be obtained in Japan, permitting a better understanding of this type of tumor. In 1995, the number of deaths was 500, increasing to 878 cases in 2003 and 1,050 in 2006. In Europe and America, 80% of the cases of mesothelioma are attributed to asbestos exposure; however, in Japan, only 85 cases of mesothelioma due to asbestos exposure were authorized to receive worker's compensation insurance during the 2003 fiscal year. We sought to clarify the cause of this disparity between the number of deaths and the number of compensation-authorized cases of malignant mesothelioma. There are reports [Kishimoto, 1992; Kishimoto et al., 2004] on mesothelioma and asbestos exposure from specific regions in Japan; however, there has not yet been any large-scale investigation targeting the whole nation. Accordingly, from 2003 to 2005 we conducted a 3-year nationwide study targeting 2,742 incidences of death due to mesothelioma. In addition to the relationship between asbestos exposure and mesothelioma, we investigated the diagnosis of mesothelioma in Japan.

METHODS

We reviewed all the cases in which the cause of death was diagnosed as mesothelioma based on "ICD CD46" in the demographic statistics from 2003 to 2005 and obtained

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detailed information on the clinical diagnosis, and occupational asbestos exposure for those cases.

Families that provided a letter of consent were given a questionnaire to obtain the occupational and residential histories. We also re-examined the diagnosis of mesothelioma itself based on review of medical records, radiology films, and pathology reports. We obtained cellular and pathological tissue samples and tumor tissues from the medical institutions that issued the death certificates. One radiologist and two pulmonologists re-examined the data, looking for the presence or absence of asbestos exposure based on chest images or based on the classification of pleural mesothelioma by the International Mesothelioma Interest Group (IMIG). Two pathologists reviewed the tissue and cell samples and tried to provide a definitive diagnosis.

We determined the presence or absence of asbestos exposure based on entries in the clinical records and also the family questionnaire investigation results (asbestos question sheet regarding occupational history). We investigated if the attending physician made entries regarding the occupational history in the clinical records for the incidents of death in 2004 and 2005. We define the lifetime as the time at which diagnosis was determined until the time of death.

For the cases in which excised lungs or autopsied lungs were provided by the medical institutions, we measured the number of asbestos particles in the tumor-free portion of the pulmonary tissue using the method by Kohyama [2008] at the Okayama Rosai Hospital. More specifically, the lung tissue was dehydrated at 100°C, and after accurately determining the dry weight, the tissue was dissected into small pieces and dissolved in sodium hypochlorite solution. After centrifugation at 10,000 rpm for 10 min, the supernatant was removed and the pellet was re-suspended in a new solution to total 50 ml in volume. The asbestos particles were collected on a 0.45-μm Millipore filter membrane using vacuum suction filtration and fixed with acetone on the filter membrane. The asbestos particles were counted under a phase contrast microscope and expressed as the number per gram of dry weight of lung tissue.

We used the student's test to determine the difference in the average value, and the χ^2 test to compare between two groups. Furthermore, we used the Kaplan–Meier method to compute the lifetime using the date of diagnosis as the starting point, and used the Logrank test to compare lifetimes.

RESULTS

Among the targeted 2,742 cases (878 cases in 2003, 953 in 2004, and 911 in 2005), we obtained familial consent from 956 cases (454 cases in 2003, 260 in 2004, and 242 in 2005). In the investigation of deaths in 2003, which was conducted immediately following the so-called Kubota Shock, during which the neighborhood exposure to asbestos induced more than 100 cases of mesothelioma in 2005 and public attention was focused on workplace asbestos exposure, familial consent was obtained in 51.7% of deaths. However, in 2004 and 2005, the percent decreased to 27.3% and 26.6%, respectively. From among the 956 cases in which consent was received, we obtained clinical records, medical treatment information, etc., from the medical institutions that issued the death certificates for 541 cases (56.6%), including 235 cases in 2003, 145 in 2004, and 161 in 2006 as indicated in Table I. From the information for the 541 cases provided by the medical institutions, there were 442 cases (81.7%) in which definitive diagnosis was obtained based on tissue samples. There were 49 cases (9.1%) in which only speculative clinical diagnosis was made based on data such as imaging and the concentration of hyaluronic acid in the pleural fluid, or definitive diagnosis could not be made pathologically or histologically, which were labeled as "suspected" as in Table I.

Regarding the site of mesothelioma, there were 418 cases of pleural mesothelioma (372 confirmed diagnoses and 46 suspected cases); 68 cases of peritoneal mesothelioma (65 confirmed diagnoses and three suspected cases); 3 confirmed diagnoses of pericardial mesothelioma; and 2 confirmed diagnoses of mesothelioma of the tunica vaginalis. However, 50 cases (9.2%) were determined to be diseases other than mesothelioma. In 20 of the 50 cases, lung cancer was diagnosed based on the tissue and cell samples from the autopsies carried out at the medical institutions. Furthermore, we made a comprehensive judgment considering the results from the imaging viewpoint, tissue pathology viewpoint, tumor markers, etc., and found 18 cases that were more likely lung cancer than mesothelioma and were labeled as "suspected lung cancer." Among the other 12 cases, there were 6 cases of ovarian cancer, 1 case of malignant lymphoma, 1 case of renal cancer, and other cases that were thought to be from malignant tumors such as 1 case of a solitary fibrous tumor, and 3 cases of benign asbestos pleurisy (fibrous pleurisy) that were diagnosed as mesothelioma.

TABLE I. Number of Japanese That Died of Malignant Mesothelioma From 2003 to 2005

	2003	2004	2005	Total
Population vital statistics	878	953	911	2,742
Consent from bereaved family	454	260	242	956
Information provided by hospitals	235	145	161	541
Mesothelioma	182	125	135	442
Suspected mesothelioma	26	8	15	49
Other diseases	27	12	11	50

TABLE II. Background of Patients With Mesothelioma and s/o Mesothelioma

	Confirmed mesothelioma		Suspected cases	
	Pleura	Peritoneum	Pleura	Peritoneum
No. of cases	372	65	46	3
Median age (range)	68 (38–94)	63 (16–89)	80 (54–97)	78 (59–86)
Gender				
Male	320	46	32	2
Female	52	19	14	1

Age and Gender

When comparing the background factors for the cases of mesothelioma and suspected mesothelioma, the median age for confirmed diagnosis of pleural mesothelioma was 68, and the median age for suspected mesothelioma was 80. Those cases with suspected mesothelioma were at a significantly advanced age as shown in Table II. Also, for peritoneal mesothelioma, the median age for confirmed diagnosis was 63, and 78 for suspected cases. Furthermore, there were 320 male and 52 female (6.2:1 males/females) cases of confirmed pleural mesothelioma and 32 male and 14 female (2.3:1 males/females) cases of suspected mesothelioma. On the other hand, there were 46 male and 19 female (2.2:1 males/females) confirmed cases of peritoneal mesothelioma, two male and one female case of suspected mesothelioma with there was no discernable difference in the gender groups.

Diagnostic Method

Among the 361 of 442 cases (81.7%) where the basis of diagnosis was clear, definitive diagnosis was made based on tissue analysis as indicated in Table III. The method for gathering tissue samples for the diagnosis of pleural mesothelioma cases was video-assisted thoracoscopic biopsy. This method was used for 116 cases. Cases were diagnosed based on not only video assisted thoracoscopic surgery (VATS) under general anesthesia but also with thoracoscopic surgery under local anesthesia. Subsequently, there were 106 cases of needle biopsy based diagnosis, 71 cases of thoracotomy-based diagnosis, and 11 cases where the autopsy was the first pathological diagnosis obtained.

Most cases (n = 37) of peritoneal mesothelioma were diagnosed based on laparotomy; nine cases diagnosed following laparoscopic biopsy, and four cases diagnosed based on needle biopsy. Furthermore, there were 45 cases of pleural mesothelioma and 11 cases peritoneal mesothelioma diagnosed only based on pleural fluid and ascites cell analysis. In the diagnoses based on histological analysis, there were 329 of 353 cases (93.2%) in which the presence or absence of immunostaining confirmed the diagnosis, whereas among the 56 cases of cytological examination based diagnosis less than half of the cases, 23 cases, were confirmed diagnoses (41.1%).

Tissue Type

Among the 442 cases of definitively diagnosed mesothelioma, only 305 cases (69.0%) had the cell type identified in the clinical records. There were 163 epitheliod cases (53.4%), 70 biphasic cases (23.0%), and 62 sarcomatoid cases (20.3%) [Inai, 2005].

History of Asbestos Exposure in the Workplace

There were 421 (95.2%) cases in which the presence or absence of the occupational history could be investigated based on the clinical records and the family questionnaires. Among those cases, 316 cases (75.1%) were suspected to

TABLE III. Diagnostic Procedures for Mesothelioma

	Pleura	Peritoneum	Total[a]	Immunohistochemical[b] staining
Cases	372	65	442	352/409 (86.1%)
Histological diagnosis	304	52	361	329/353 (93.2%)
Open lung and peritoneum	71	37	113	102/106 (96.2%)
Video assisted thoracoscopical biopsy	116	9	125	112/125 (89.6%)
Needle biopsy	106	4	110	105/110 (95.5%)
Autopsy	11	2	13	10/12 (83.3%)
Cytological examination	45	11	56	23/56 (41.1%)
Unknown	23	2	25	

[a]Includes a total of five cases of peritoneal and tunica vaginal mesothelioma.
[b]Denominator represents cases in which immunostaining method was employed.

have had exposure to asbestos including indirect or direct exposure as stipulated in their occupational histories. Furthermore, based on the questionnaire responses from the families, there were eight cases in which patients resided in the vicinity of the old Kubota Kanzaki factory in Amagasaki city in Japan. There were four additional cases of patients who resided in the neighborhood of an asbestos product manufacturing plant or a shipyard, totaling 12 cases of suspected neighborhood asbestos exposure. There were also five cases of occupational history in which family members were exposed to asbestos, which implied likely domestic asbestos exposure. As a result, we conclude that there were 333 cases (79.1%) of suspected asbestos exposure.

From the 188 cases of suspected occupational asbestos exposure, we identified the occupation histories of 165 cases (87.8%) based on the family questionnaires, and we concluded that the occupation histories of no more than 51 cases (27.1%) were recorded into the clinical records by the attending physician. In other words, despite the diagnosis of mesothelioma, we found that those clinicians did not obtain detailed occupational histories in many cases.

The occupational histories of the 316 cases of suspected occupational asbestos exposure are shown in Table IV. For cases in which there was the possibility of asbestos exposure in pursuing multiple occupations, the investigation selected the occupation in which the patient worked the longest. There were 69 construction workers, which makes up the largest group, 45 shipyard workers, 30 electricians, 28 steel and other manufacturing workers, 22 auto manufacturers or maintenance workers, 21 plumbers, 20 asbestos product manufacturers, and 16 wrecking crew workers and concrete product workers. There were 9 cases (27.2%) of asbestos product manufacturing workers, who were exposed to high concentrations of asbestos, among the 33 cases of peritoneal mesothelioma indicating a feature that denotes high frequency of occurrence in this occupation.

Exposure Period and Incubation Period

We investigated the exposure period, date, age, and latency period of the 316 cases of suspected occupational asbestos exposure. We examined the exposure period and incubation time for only the cases that had clinical record entries or responses by the families. The median asbestos exposure period for peritoneal mesothelioma is 20 years and the mean value is 21.7 years. For pleural mesothelioma, the median is 29 years and the mean value is 26.4 years. The latency period, which is considered to be from the first exposure to asbestos to the onset of mesothelioma, for pleural mesothelioma is a median of 41 years and an average value of 42.5 years. For peritoneum mesothelioma, the median is 41 years and the average value is 43.0 years. The median for all types of mesothelioma is 41 years, and the average value is 42.4 years. We confirmed that mesothelioma expressed itself after 40 years or more from the first exposure.

Pleura Plaque

We investigated 353 cases of the 442 cases of definitively diagnosed mesothelioma based on chest X-rays or chest CT scans, The scans were provided by the medical institutions targeting the presence of pleural plaque that was considered to be specific to asbestos exposure. We found 144 cases (40.8%) of pleural plaque. In 64 of the 144 cases (44.4%), there was calcification accompanying the pleural plaque. However, there was no statistically significant correlation found between the location of the mesothelioma and the frequency at which the pleural plaque occurred. Furthermore,

TABLE IV. Frequency of Cases Regarding Occupational Histories of Asbestos Exposure

	Pleura	Peritoneum	Pericardium	Tunica vaginalis	Total
Construction worker	65	3		1	69
Shipyard worker	40	4	1		45
Electrician	27	3			30
Steel industrial worker	25	2		1	28
Automobile manufacturer	21	1			22
Plumber	18	2	1		21
Asbestos products manufacturer	11	9			20
Wrecking crew	16				16
Cement product worker	10	1			11
Machinist	7	2			9
Warehouse worker	5	3			8
Chemical industrial worker	6		1		7
Glass maker	4				4
Others	23	3			26
Total	278	33	3	2	316

there were 316 suspected cases from the 442 cases of occupational exposure to asbestos, and among the 270 cases of the 316 cases where chest imaging was provided, 129 cases (47.8%) of pleural plaque were confirmed. In 14 of 86 cases (16.3%) in which occupational exposure to asbestos could not be confirmed, pleural plaque was confirmed. Among the 17 suspected cases of non-occupational exposure to asbestos (exposure to the neighborhood or in the home), 3 cases of pleural plaque were confirmed in which the patient was in the vicinity of the asbestos plant, a family member was working in a shipyard or engaged in plumbing as indicated in the residential history.

Asbestos Particles

We were able to measure the asbestos particles in the lungs of 40 of the pleural mesothelioma cases and 47 of the peritoneal mesothelioma cases based on the excised or autopsied lungs provided by the medical institutions. Table V shows an analysis of the number of asbestos particles and where they were found. We were able to confirm based on the Helsinki Criteria [Consensus Report, 1997], the standard for occupational exposure to asbestos, that there were 37 cases (78.7%) in which there were 1,000 particles or more of asbestos/1 g of dry lung tissue detected and 21 cases (44.7%) in which 5,000 particles or more were detected. There were a total of three unclear cases of asbestos exposure, two cases of pleural mesothelioma, and one case of peritoneal mesothelioma. Despite that pleural plaque could not be identified based on the images, the presence of more than 1,000 particles of asbestos was confirmed but these cases are thought to be mesothelioma due to asbestos exposure. Furthermore, although pleural plaque could not be confirmed, there were six cases where over 5,000 particles of asbestos were detected. We believe that we cannot make a determination on asbestos exposure based solely on the presence or absence of pleural plaque.

Asbestos Exposure and Mesothelioma

From the 442 cases in which mesothelioma was diagnosed based on pathology out of the 541 cases in this investigation, we found that there are 316 cases (71.5%) who had suspected asbestos exposure based on the occupational histories. There were 12 other cases of suspected exposure due to the neighborhood environment, and 5 cases of exposure in the home. Furthermore, another 14 cases had pleural plaques in the radiography while asbestos exposure could not be positively determined from the clinical history and the 3 other cases in which more than 1,000 asbestos particles/1 g of dry lung tissue were detected. While asbestos exposure could not be confirmed from the clinical history or pleural plaque. We determined these 17 cases also as positive asbestos exposure. Accordingly, we concluded based on these examinations that the above 350 cases (79.2%) out of the 442 cases of pathologically diagnosed mesothelioma were caused by asbestos exposure.

TABLE V. Number of Asbestos Particles

No. of asbestos particles[a]	Pleura	Peritoneum	Total
<999	10	0	10
1,000–4,999	15	1	16
>5,000	15	6	21
Total	40	7	47

[a]Per 1 g of dry lung tissue.

DISCUSSION

Among the 2,742 deaths from malignant mesothelioma based on vital statistics recorded over the 3-year period from 2003 to 2005, we targeted 956 cases in which family consent was obtained for a retrospective investigation and clarified the exposure histories of these mesothelioma cases. Among the 541 cases in which data gathering such as clinical records was possible, we confirmed the pathological diagnosis of 81.7%. We found that 372 cases originated from the pleura, 65 cases from the peritoneum, 3 cases from the pericardium, and 2 cases from the tunica vaginalis. In over 80% of the cases a definitive diagnosis was made based on histological diagnosis including immunostaining. On the other hand, in 56 cases where diagnosis was made based on cytological examination, immunocytochemical staining was positive only in 41.1% of the cases, and this brings to light the problem of diagnostic accuracy.

Currently in Japan, if mesothelioma is diagnosed the patient can receive aid through workman's compensation insurance or the asbestos health damage relief law. Although there is recognition of the improvement in diagnosis accuracy, it is clear that in the 3-year period from 2003 to 2005 the immunostaining method was not always reliable in the diagnosis of mesothelioma. In other words, in a case where diagnosis is made based only on cell examination, there may be a problem in discriminating between fibrous pleurisy (reactive mesothelial cells) [Kradin and Mark, 2006; Lyons-Boudreax et al., 2008] and lung cancer. For that reason, we found 9.2% in our examination to be diagnosed as other than mesothelioma such as lung cancer or ovarian cancer, as a result of comprehensive judgment on reviewing autopsy results, clinical records, images, etc. Because HE staining only or cell examination only was used for diagnosis in many cases, when we performed immunostaining, we were able to diagnose definitively not only lung cancer and ovarian cancer but also fibrous pleurisy (benign asbestos pleurisy). It was reported [Ordonez, 2003, 2006, 2007; Kushitani et al., 2008] that immunostaining is indispensable in a pathological

diagnosis of mesothelioma in order to distinguish pleural mesothelioma from lung cancer accompanying cancerous pleurisy, etc. Or in order to distinguish peritoneal mesothelioma from ovarian cancer accompanying cancerous pleurisy, etc. Furthermore, a definitive diagnosis could not be made based on the pathology in 9.1%. The reasons that a definitive diagnosis could not be reached were that the disease advanced rapidly and a detailed examination could not be performed, or although the attending physician recommended tests to diagnose suspected cases of mesothelioma, because the patient was of advanced age either the patient or the family requested not to have invasive tests done. Taking these conditions into consideration, pressing for improvement in the diagnostic accuracy in the diagnosis of mesothelioma is a paramount problem.

Among the 541 cases in this investigation, 442 cases were diagnosed with mesothelioma based on pathology and, among those cases, 71.5% were suspected to be exposed to asbestos based on the occupational history. The types of occupation that were common were construction work, working in a shipyard, electricians, steel products, and other manufacturing work. From 1950 and later, we understand that asbestos was used in these types of occupations, and asbestos was imported into Japan in large quantities for these types of work. We identified that these occupations frequently appear in high-risk groups. Seventeen other cases of non-occupational exposure to asbestos were suspected (12 cases suspected based on residential histories, and 5 cases were thought to be exposure in the home). On the other hand, 40.8% of cases with pleural plaque were confirmed from the 353 cases where the medical institutions provided chest images. Furthermore, among the 47 cases in which the asbestos particles were found in the lungs, 78.7% were found to have more than 1,000 particles/1 g of dry weight lung tissue. There were a total of 79.2% that had occupational or residential histories indicating asbestos exposure, images indicating the existence of pleural plaque, or measurements of the asbestos particles in the lungs and any of these would imply asbestos exposure. Based on the analysis done on these various types of data, 79.2% of the 442 cases were found to have asbestos exposure as the cause of mesothelioma. Furthermore, by examining the origin of the mesothelioma based on the occupations, the cases in which the occupational histories indicated asbestos product manufacturing work, where the patient would be exposed to high concentrations of asbestos, had high levels of asbestos particles in the lungs and were characteristic of the peritoneal mesothelioma cases, which comprise a large number of the cases.

Since 1950 the amount of asbestos used in Japan increased and reached its peak in 1974 at 350,000 tons. After that a trend appeared that showed a decrease in asbestos use until its ban in September 2006. For that reason, compared to Australia, England, and Belgium the amount used and the period of usage are high [Kohyama and Hoshino, 2008]. However, the frequency of occurrence of mesothelioma in the three countries was 30/1,000,000 people, and in Japan the occurrence rate was 7/1,000,000 people [Bianchi and Bianchi, 2007] but currently it is 9/1,000,000 people. Based on the current investigation, if we consider that in Japan the incubation period from the first time the patient was exposed to asbestos to the occurrence of mesothelioma is 43 years, based on the report by Murayama et al. [2006], we must expect two- to threefold the number of new patients in Japan. However, despite having a history of asbestos exposure, in no more than 27.1% of the cases was the occupational history entered in the clinical records. The importance and the repercussions of obtaining and recording the occupational history must be instilled in the clinicians who examine patients of asbestos-related diseases.

CONCLUSIONS

Among 442 cases of definite malignant mesothelioma, between 2003 and 2005, in Japan, 316 cases were exposed to occupational asbestos exposure; 12 cases had neighborhood exposure; and 5 cases had domestic exposure. We conclude that 79% of Japanese mesothelioma cases have been caused by asbestos exposure in recent years.

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