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Asbestos Exposure in Malignant Mesothelioma of the Pleura: A Survey of 557 Cases

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Abstract: A series of 557 malignant mesotheliomas of the pleura diagnosed in the Trieste-Monfalcone area, Italy, in the period 1968-2000 were reviewed. The series included 492 men and 65 women, aged between 32 and 93 years (median age 69 years). Necropsy findings were available in 456 cases (82%). Occupational histories were obtained from the patients themselves or from their relatives by personal or telephone interviews. Routine lung sections were examined for asbestos bodies in 442 cases. In 109 cases isolation and counting of asbestos bodies were performed. A majority of people had histories of working in the shipyards. Asbestos bodies were observed in lung sections in 67% of the cases. Lung asbestos body burdens after isolation ranged between 20 bodies and about 10 millions of bodies/g dried tissue. Latency periods (time intervals between first exposure to asbestos and death) ranged between 14 and 75 years (mean 48.8 years, median 51.0). Latency periods among insulators and dock workers were shorter than among the other categories. High asbestos consumption occurred in many countries in the 1960s and in the 1970s. The data on latency periods obtained in the present study suggest that a world mesothelioma epidemic has to be expected in the coming decades.

Key words: Asbestos, Mesothelioma, Pleura, Asbestos bodies, Shipbuilding, Latency periods, Diagnosis, Necropsy

Introduction

A few years ago, malignant mesothelioma was considered as a very rare entity. At present, it is estimated that about 10,000 new cases of mesothelioma, are diagnosed annually in some industrialized countries (North America, Western and Northern Europe, Japan, and Australia)[1].

During the last four decades, numerous studies on malignant mesothelioma have been conducted[2, 3]. However, the natural history of this tumor remains for various aspects ill defined or scarcely known. In particular, topics that deserve further investigation include the proportion of cases attributable to asbestos, the spectrum of the population at risk, the lenght of the latency periods, the impact of mild exposures to asbestos, and the role of co-factors in the development of the tumor.

In the present study a series of 557 malignant pleural mesotheliomas observed in the Trieste-Monfalcone area, were reviewed, with particular attention toward the characteristics of asbestos exposure in these cases.

The Trieste-Monfalcone area is a small coastal district, located in northeastern Italy, with a total population of about 300,000. This area is the site of large shipyards. Studies begun in the early 1970s showed that a large majority of the mesotheliomas diagnosed in this district, were attributable to asbestos exposure occurred in the shipyards[4, 5].

Materials and Methods

The cases analyzed in the present study were diagnosed

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in the period 1968-2000. In particular, the series included all the cases diagnosed at the Laboratory of Pathological Anatomy, Hospital of Monfalcone, in the period October 1979–October 2000, and a large majority of the cases diagnosed at the Trieste University during the period 1968-2000. The diagnosis was based on (or confirmed by) necropsy in 456 cases. In the remaining cases, the pathological diagnosis was made on pleuroscopy or surgery material (97 cases), or on cytological findings (4 cases). Lifetime occupational data were obtained from the patients themselves or from their relatives by personal or telephone interviews. When occupational data were encountered difficult to interpret, specific enquiries were conducted: people who had worked at the same workplace during the same years were traced and interviewed in order to ascertain whether or not asbestos exposure has occurred.

Routine lung sections obtained at necropsy, were examined for asbestos bodies in 442 cases. In 109 cases isolation and quantitation of asbestos bodies were performed after chemical digestion of lung tissue, using the Smith-Naylor method[6]; the lung samples were obtained from the right base unless it was largely involved by the tumor.

In 133 necropsy cases the thoracic cavities were carefully examined for the presence of pleural plaques. These were classified into three groups: (1) small, (2) moderate, and (3) large, based upon their size. Class 1 included the cases with small plaques (1–4 cm in major diameter); class 2 comprised plaques larger than 4 cm in major diameter, but not involving a majority of a hemithorax; class 3 corresponded to cases with plaques involving the majority of a hemithorax.

Results

The series included 492 men, aged between 32 and 93 years (mean 68.6, median 69.0), and 65 women, aged between 40 and 89 years (mean 70.1, median 73.0) (Table 1). A large majority of the male patients had worked in shipbuilding (Table 2). Twenty-one women had histories of asbestos exposure at home, having cleaned the work clothes of their

Table 1. Sex and age distribution in 557 cases of malignant pleural mesothelioma, Trieste-Monfalcone area, 1968–2000

Age groups (years)	No. of men	%	No. of women	%	Total	%
30–34	1	0.2	0	0	1	0.2
35–39	1	0.2	0	0	1	0.2
40–44	2	0.4	2	3.1	4	0.7
45–49	11	2.2	2	3.1	13	2.3
50–54	37	7.5	2	3.1	39	7.0
55–59	52	10.6	4	6.2	56	10.1
60–64	54	11.0	7	10.8	61	11.0
65–69	96	19.5	10	15.4	106	19.0
70–74	84	17.1	15	23.1	99	17.8
75–79	81	16.5	10	15.4	91	16.3
80–84	47	9.6	7	10.8	54	9.7
85–89	20	4.1	6	9.2	26	4.7
90–94	6	1.2	0	0	6	1.1

Table 2. Occupational data in 557 cases of malignant pleural mesothelioma, Trieste-Monfalcone area, 1968–2000

Exposure type	No. of men	%	No. of women	%	Total	%
Shipbuilding industry	314	63.8	5	7.7	319	57.3
Other industries	35	7.1	12	18.5	47	8.4
Navy and merchant marine	43	8.7	0	0	43	7.7
Other	33	6.7	5	7.7	38	6.8
Domestic exposure	0	0	21	32.3	21	3.8
Dock	18	3.7	0	0	18	3.2
Insulation	6	1.2	0	0	6	1.1
Insufficient data	43	8.7	22	33.8	65	11.7

family members employed in workplaces polluted by asbestos. For a relevant portion of the female patients, sufficient occupational and social data could not be obtained. Some unusual types of occupational exposure are listed in the Table 3. The duration of the asbestos exposure could be calculated for 348 cases (Table 4). About 80% of the patients had their first exposure before 1950 (Table 5). The latency periods, defined as time intervals elapsed between first exposure to asbestos and death, were calculated in 380 cases (Table 6). In about 75% of the cases latency periods were longer than 40 years. Marked differences in latency periods were observed from one occupational category to another (Table 7).

Asbestos bodies were found on routine lung sections in 67% of the cases. The prevalence of positive findings varied strongly after the type and the intensity of exposure (Table 8). The amounts of asbestos bodies after isolation ranged between 20 bodies and about 10 millions of bodies per gram of dried tissue. Even asbestos body burdens showed marked variations after the occupation (Table 9). Pleural plaques were observed in a majority of the necropsy cases, specifically investigated on this aspect (Table 10).

Table 3. Some unusual types of occupational exposure to asbestos in 557 cases of malignant pleural mesothelioma, Trieste-Monfalcone area, 1968–2000

Occupation	No. of cases
Bakery and pastry worker	5*
Storeman	3
Municipal water dept. worker	2
Recycling of canvas sacks worker	2
Truck driver	2
Asbestos company agent	1
Jute factory worker	1
Movie projectionist	1
Rag sorter worker	1
Rubber shoe factory worker	1
Telephone technician	1
Tiler	1
Wittenoom (Australia) crocidolite mine worker	1

*Two patients had possible additional types of exposure.

Discussion

Asbestos is universally considered as the principal (or from the practical point of view the unique) etiologic factor in the genesis of mesothelioma[2]. Nevertheless, extreme variations exist in the proportion of cases recognized as

Table 4. Duration of exposure to asbestos in 348 cases of malignant pleural mesothelioma, Trieste-Monfalcone area, 1968–2000

Duration (years)	No. of men	%	No. of women	%	Total	%
<1	2	0.6	0	0	2	0.6
1–4	22	6.8	0	0	22	6.3
5–9	28	8.6	4	17.4	32	9.2
10–19	29	8.9	2	8.7	30	8.9
20–29	50	15.4	7	30.4	57	16.4
30–39	110	33.8	8	34.8	118	33.9
40–49	81	24.9	2	8.7	83	23.9
50–59	3	0.9	0	0	3	0.9

Table 5. First exposure to asbestos in 394 cases of malignant pleural mesothelioma, Trieste-Monfalcone area, 1968–2000

Calendar years	No. of men	%	No. of women	%	Total	%
1910–19	8	2.2	0	0.0	8	2.0
1920–29	70	19.0	4	16.0	74	18.8
1930–39	125	33.9	7	28.0	132	33.5
1940–49	85	23.0	10	40.0	95	24.1
1950–59	43	11.7	2	8.0	45	11.4
1960–69	36	9.8	2	8.0	38	9.6
1970–79	2	0.5	0	0	2	0.5

Table 6. Latency periods (years) in 380 cases of malignant pleural mesothelioma, Trieste-Monfalcone area, 1968–2000

Years	No. of men	%	No. of women	%	Total	%
10–19	1	0.3	0	0.0	1	0.3
20–29	23	6.5	2	8.3	25	6.6
30–39	61	17.1	1	4.2	62	16.3
40–49	80	22.5	4	16.7	84	22.1
50–59	134	37.6	14	58.3	148	38.9
60–69	49	13.8	3	12.5	52	13.7
70–79	8	2.2	0	0.0	8	2.1

Table 7. Latency periods (years) in 380 cases of malignant pleural mesothelioma by category of exposure, Trieste-Monfalcone area, 1968–2000

Category	No. of cases	Range	Mean	St. dev.	Median
Shipbuilding	263	14–72	49.3	10.8	52.0
Other industries	35	28–69	46.5	9.8	49.0
Navy and merchant marine	33	35–75	56.3	9.3	56.0
Other	18	28–65	45.4	10.5	43.5
Dock workers	14	25–60	36.3	11.6	31.5
Domestic exposure	12	27–62	51.8	11.1	56.0
Insulation	5	28–32	29.6	1.5	29.0
Total	380	14–75	48.8	11.3	51.0

Table 8. Presence of asbestos bodies in routine lung sections in 442 malignant pleural mesotheliomas by category of exposure, Trieste-Monfalcone area, 1968–2000

Category	No. of cases	% of positive findings
Shipbuilding	266	77.4
Other industries	37	54.1
Naval and merchant marine	35	51.4
Other	29	37.9
Domestic exposure	20	35.0
Dock	17	88.2
Insulation	6	83.3
Insufficient data	32	50.0
Total	442	67.4

asbestos-related. In fact heavy difficulties are sometimes encountered in obtaining complete occupational data as well as in establishing if a given work implied contacts with asbestos. Not rarely the workplace, in which the patient has been employed, has been closed since various decades and it is very hard to determine if asbestos was present there. In a recent study performed on malignant pleural mesothelioma in Spain (Provinces of Barcelona and Cadiz)[7], a positive occupational history was observed in 62% of the cases. In an investigation performed in northern Italy (Romagna), the percentage of cases attributable to asbestos on the basis of the available occupational data was only 45%[8]. In another series, investigated in the Varese area, northern Italy, extremely low numbers of cases (12%) were considered as due to occupational exposure to asbestos[9]. On the contrary, the proportion of asbestos-related tumors in the present series, was higher than 90%.

The main feature of the Trieste-Monfalcone series, was the very high prevalence of people employed in "naval" work, including shipbuilding and ship repair, maritime trades, and dock work. In fact, among men, about 85% of the cases, for which occupational data were available, were classifiable as naval. Among these, a large majority of patients had worked in shipbuilding. There is no question about the relevance of asbestos exposure, occurred in the past in the shipyards[10]. This fact has been documented by a lot of studies during the last four decades, and the binomial shipyard-mesothelioma has become one of the most typical characteristics in the mesothelioma epidemiology[4, 11]. Even the maritime trades may have not trivial exposure to asbestos and, consequently, may to be at risk for asbestos-related mesothelioma. This is a more recent acquisition, corroborated by numerous data[12, 13]. Regarding dock work, this occupation does not automatically mean an exposure to asbestos.

Table 9. Lung asbestos body counts in 109 cases of malignant pleural mesothelioma by category of exposure, Trieste-Monfalcone area, 1968–2000

		Asbestos bodies × 1,000/g dried tissue (% of cases)			
Category	No. of cases	<1	1–10	10–100	>100
Shipbuilding	84	11.9	38.1	34.5	15.5
Other industries	8	50.0	37.5	12.5	0.0
Domestic exposure	7	57.1	42.9	0.0	0.0
Insulation	4	25.0	25.0	25.0	25.0
Navy and merchant marine	3	0.0	100.0	0.0	0.0
Other	3	66.7	33.3	0.0	0.0
Total	109	19.3	39.4	28.4	12.8

Table 10. Pleural plaques in 133 necropsy cases of malignant pleural mesothelioma by category of exposure, Trieste-Monfalcone area, 1968–2000

Category	Absent	Class 1	Class 2	Class 3	Total
Shipbuilding	11	15	33	37	96
Domestic exposure	4	5	3	0	12
Other industries	2	2	4	1	9
Other	1	3	1	1	6
Insulation	0	1	1	2	4
Navy and merchant marine	1	1	1	1	4
Insufficient data	0	0	1	1	2
Total	19 (14.3%)	27 (20.3%)	44 (33.1%)	43 (32.3%)	133 (100%)

However, the dock workers of the present series had been employed in the port of Trieste, where a very heavy asbestos exposure has been documented by previous investigations[14].

Generally, the classification of a given mesothelioma as “asbestos-related” or “not asbestos-related”, is based on occupational as well as on the environmental and social data. In a relatively low number of series, the exposure was evaluated and quantitated by investigating objective signs of exposure[15]. Data on lung asbestos body content were available in a high percentage of the present cases. This was essentially due to the fact that necropsies had been performed in a high number of cases. A dramatic decline in the necropsy rate has been reported from numerous countries[16–18]. Such decline did not involve the Trieste-Monfalcone area in the period we considered. On the contrary, the annual number of necropsies performed at the Trieste University showed a very marked increase in the 1970s, and it remained high in the following decades[12]. This high necropsy rate has undoubtedly been a critical factor in allowing the identification of mesotheliomas as well as in documenting the relationship of the tumor with asbestos. The progress in immunohistochemistry has produced marked improvement in the pathological diagnosis of mesothelioma[19]. Nevertheless, such a diagnosis remains not rarely difficult both on the side of differentiating primary versus secondary malignancies, as well as on the side of separation between benign and malignant[20]. The necropsy findings offer a firm basis for a reliable diagnosis.

In the present series many works were encountered, difficult to define in terms of asbestos exposure. Specific enquiries were necessary to ascertain that these occupations implied contacts with asbestos. The availability of objective signs confirming asbestos exposure was of particular relevance in these occupations.

Previous investigations conducted in Monfalcone area showed that asbestos exposure in this district did not remain confined to the workplaces[10]. Even the family members of the workers exposed to asbestos, were involved, throughout contacts with the work clothes, polluted by asbestos dust. In particular, in a series of women with histories of such domestic exposure, 51% showed pleural plaques at necropsy[10]. In the present mesothelioma series, at least 21 cases could be attributed to the cleaning of work clothes at home. However, environmental exposure to asbestos, a relevant factor in various series[2, 21–24], was not documented in the present cases.

In a large majority of the present cases, the exposure to asbestos began before 1950. The mesothelioma epidemic observed in the Trieste-Monfalcone area during the last decades is mainly the effect of very old exposures, mostly occurred in the 1930s. The latency periods in this series were exceedingly high when compared with those currently reported in the literature[25]. In addition, we confirm that substantial differences in latency periods exist after the type and the intensity of the exposure. In general, there was an inverse relationship between intensity of exposure and duration of the latency period. However, it is surprising that shipyard workers, generally exposed at high degrees, showed very long latency periods.

The duration of the latency periods represents a critical point in predicting the future trend in world mesothelioma epidemic. If the latency periods are longer than 40 years in a majority of cases, then the effects of the exposure occurred in the 1960s and in the 1970s, remain to be seen. The world production of asbestos showed a dramatic increase after 1960[26, 27], passing from about 2.2 millions of tons in 1960 to 5.1 millions in 1978. As far as shipbuilding is concerned, naval production showed a strong increase in the above decades[28, 29]. Such an increase was spectacular in Japan, where annual tons passed from 561,000 in 1955 to 11,000,000 in 1971; the number of completed ships in the above period passed from 158 to 992. In Europe the big shipbuilders were U. K., West Germany, and after 1962 Sweden, with annual tons generally comprised between 1,000,000 and 1,500,000. Other European countries, although less important in total production, showed a marked increase in the 1960s. In particular, in Spain, the annual tons passed from 51,000 in 1955 to 830,000 in 1971, and the number of completed ships from 23 to 161.

The first signs of the new mesothelioma epidemic predictable for the next decades have already been registered. It is significant for instance that during the last few years the annual number of mesothelioma in Japan has increased four times[30, 31]. Peximistic forecasts have been proposed for the future trend of the mesothelioma incidence[18, 32]. The data observed in the Trieste-Monfalcone area do not allow less heavy predictions.

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