

Malignant Mesothelioma: Global Incidence and Relationship with Asbestos

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Abstract: Mesothelioma incidence varies markedly from one country to another. The highest annual crude incidence rates (about 30 cases per million) are observed in Australia, Belgium, and Great Britain. A lot of data indicate a relationship between mesothelioma and asbestos. The hot areas for mesothelioma exactly correspond to the sites of industries with high asbestos use, such as shipbuilding and asbestos-cement industry. However, in many countries with high asbestos consumption, mesothelioma incidence is low. The reasons for this fact are not clear. The latency periods elapsing between first exposure to asbestos and development of mesothelioma are mostly longer than 40 yr. An inverse relationship exists between intensity of asbestos exposure and length of the latency period. Mesothelioma generally develops after long-time exposures to asbestos. Some recent studies show that the risk increases with the duration of exposure. Possible co-factors in the pathogenesis of asbestos-related mesothelioma include genetic predisposition, diets poor in fruit and vegetables, viruses, immune impairment, recurrent serosal inflammation. The study of co-morbidity in mesothelioma could give an insight into the pathogenesis of the tumor. While a levelling-off in mesothelioma incidence has been registered in some countries, a worsening of the epidemic is predictable in large parts of the world.

Key words: Mesothelioma, Asbestos, Latency period, Exposure duration, Co-factors, Co-morbidity, Recurrent inflammation, Pleural plaque

Incidence

Malignant mesothelioma remains a serious health problem for two reasons. Firstly, mesothelioma case burden is very relevant in various countries¹⁻⁶, and, second, the results of the therapies are very poor^{7, 8}.

The incidence of malignant mesothelioma shows marked variations from one country to another⁹ (Fig. 1, Table 1¹⁰⁻³⁷). For a large part of the world, data are not available or insufficient. Moreover, the sources of information are different. In few countries mesothelioma registries or cancer registries cover all the national territory, but in others only limited parts of the country are covered. In many countries, in which incidence data are not available, the incidence rates

are estimated on the basis of mortality data. In others, only estimates based on the experience of researchers and doctors operating in the country, are available. The consequence of this heterogeneity is that not all available data have the same degree of reliability.

The highest incidence rates are reported from, or estimated for, Australia^{10, 11}, Belgium³, and Great Britain¹². Annual crude incidence rates in such countries are around 30 cases per million. The studies conducted by Australian Mesothelioma Register represent an excellent example of mesothelioma monitoring and investigation. The annual Reports of the Australian Mesothelioma Register documented year by year the impressive rise in mesothelioma incidence that has occurred in Australia. Sixteen cases were notified in 1980, and 490 in 2000¹¹. In addition, the above Reports and the parallel publications reported the occupation of a

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Fig. 1. Estimated annual crude incidence rates of malignant mesothelioma in the world. ■ >20 cases per million; ■ 11–20 cases per million; ■ <11 cases per million; □ not available data.

majority of the patients with mesothelioma. However, in the more recent Report¹⁰, occupational data are not available for a high proportion, nearly 50%, of the registered cases. This is regrettable, since the relationship between occupation and mesothelioma in general requires to be furtherly investigated. Changing in risk groups has been emphasized already more than ten years ago³⁸. Moreover, before unsuspected or insufficiently explored occupations have only recently emerged as occupations at risk³⁹. Probably, many works at risk remain yet unrecognized.

Scarce data are available for Belgium. It has been estimated that about 300 mesothelioma cases are yearly diagnosed in the country³. This figure corresponds to a crude incidence rate of 29 cases per million.

In Great Britain the annual number of deaths from mesothelioma increased markedly among men in the period 1968–2001, and to a far less degree among women. Total mesothelioma deaths were 153 in 1968, and 1,848 in 2001¹². On the basis of these data one can estimate a crude incidence rate of about 30 cases per million. Mesothelioma mortality varies noticeably in the different parts of the country. The highest rates among men are observed in the areas, characterized in the past by high shipbuilding activity (West Durbantonsire, Barrow-in-Furness, Plymouth, Portsmouth, etc.)¹². The areas with the highest mortality rates among women are those, in which factories for the manufacture of asbestos products were located. As far as the mesothelioma risk in the various occupations is concerned, the highest proportional mortality rates were observed for metal plate

workers, vehicle body builders, plumbers and gasfitters, and carpenters¹².

A high incidence rate (about 23 cases per million) may also be estimated for The Netherlands. In such country the annual number of deaths from pleural mesothelioma among men increased from 61 in 1969 to 313 in 2001¹³. Among women the annual number of deaths varied between 8 and 43, with the highest figures having been observed around 1980 and around 1994.

A second group of countries includes a large portion of Europe (France, Germany, Italy, Scandinavian countries), and New Zealand⁹. Annual crude incidence rates of mesothelioma in this group are comprised between 11 and 20 cases per million. In the Scandinavian countries cancer registries cover all the national territory. In Denmark a cancer registry is active since 1943. In the period 1943–1993, 1,912 cases of malignant mesothelioma were registered¹⁷. In such period the incidence rate among men showed an increase of 12–13 times. Crude incidence rate is 13 cases per million. In Norway the incidence of pleural mesothelioma showed recently a marked increase. The age-adjusted incidence rate among men was 20.6 per million in the period 1990–1994, and 26.1 per million in the period 1995–1999¹⁵. In Sweden a cancer registry started in 1958. The incidence of pleural mesothelioma among men has increased from 1969 (15 cases) to 2001 (89 cases)¹³. The increase has occurred until 1989 and in the following years the rate has remained stable. Marked differences have been observed from one area to another, with rates strongly higher in the counties of

Table 1. Estimated incidence of mesothelioma in some countries

Country	IR	Main source of the data	References
Australia	30	Mesothelioma Registry	10, 11)
Great Britain	30	Mesothelioma Mortality Registry	12)
Belgium	29	Researchers estimates	3)
The Netherlands	23*	Mortality data	13)
Italy	17*	Mortality data	14)
Norway	16*	Cancer Registry	15)
New Zealand	15	Cancer Registry	16)
Denmark	13	Cancer Registry	17)
Germany	13	Various	18)
Sweden	12*	Cancer Registry	13)
France	10–13*	Mesothelioma Surveillance Program	19)
Finland	>10*	Cancer Registry	20)
Canada	9	Cancer Registry	21)
Cyprus	9	Researchers estimates	†)
United States	9*	SEER Program	22–24)
Hungary	8	Mesothelioma Registry	25)
Turkey	7.8	Researchers estimates	‡)
Croatia	7.4*	Cancer Registry	26, 27)
Japan	7	Mortality data	28)
Romania	6	Researchers estimates	3)
Austria	5.6*	Cancer Registry	29)
Poland	4*	Mortality data	30)
Slovakia	4	Researchers estimates	3)
Slovenia	4	Cancer Registry	31)
Spain	4*	Mortality data	32)
Estonia	3	Researchers estimates	3)
Israel	3	Cancer Registry	33)
Latvia	3	Researchers estimates	3)
Lithuania	3	Researchers estimates	3)
Macedonia	3	Researchers estimates	3)
Portugal	2–3	Researchers estimates	3)
Argentina	2.2*	Health Ministry Statistics	34)
Singapore	2	Cancer Registry	35)
South Korea	1–2	Cancer Registry	36)
Morocco	0.7	Researchers estimates	37)
Tunisia	0.6	Researchers estimates	37)

IR = estimated annual crude incidence rates per million; * = pleural mesotheliomas only; †) = Christodoulides G, personal communication; ‡) = Bariş Y, personal communication.

Gothenburg and Malmö, the sites of large shipyards⁴⁰). In Finland mesothelioma incidence has increased in the period 1960–1995⁴¹). Annual number of cases was lower than 10 in the 1960s, and it has increased in the following decades reaching the figure of 57 cases in 1989. In the early 1990s a reduction has been observed. At present, the annual number of pleural mesotheliomas is higher than 50 cases²⁰), with an incidence rate higher than 10 cases per million. In France a program for the mesothelioma surveillance was established in 1998¹⁹). Mesotheliomas are registered in 21 districts with a population of 16 millions. National incidence is estimated

on the basis of the data collected in the area included in the program. The estimated national cases ranged between 660 and 761 for 1998, and between 600 and 808 for 1999, after the method followed in computing. A crude incidence rate of 10–13 per million may be estimated on the basis of the above data. In Germany there is no cancer registries covering all the national territory¹⁸). An incidence of 1,094 cases has been estimated for 2004¹⁸). The incidence rates could be about 13 cases per million. In Italy mesothelioma registries have only recently been extended to all national territory⁴²). In Italy mortality from pleural cancer increased in the period

1970–1999. Age-adjusted death rate among men was 1.64 per 100,000 in the quinquennium 1970–1974, and 3.22 per 100,000 in the quinquennium 1995–1999¹⁴). The analysis of mortality rates from pleural cancer among men in the period 1988–1997 showed extreme variations from one province to another, passing from 3 per million in the Province of Isernia to 116 per million in the Province of Gorizia⁴³).

In New Zealand a cancer registry is active since 1980¹⁶). In the period 1997–2000 an annual mean of 60 cases has been registered. This corresponds to a crude incidence rate of 15 cases per million.

In a large group of countries annual crude incidence rates of mesothelioma are below 11 cases per million⁹). Such group includes different countries of Europe (Central and Eastern Europe, Ireland, Portugal, Spain), of North America (Canada, USA), South America (Argentina), Asia (Cyprus, Israel, Japan, Singapore, South Korea, Turkey), and Africa (Morocco, Tunisia). Mesothelioma epidemiology in Central and Eastern Europe has been for long time ill defined^{3, 44}). Also at present, data are not available for large countries, such Russia and Ukraine. Interestingly, marked differences in the incidence of pleural mesothelioma from one area to another have been observed in Croatia^{26, 27}). The age standardized incidence rate among men resident in the coastal area (26.6 per million), where shipyards and an asbestos-cement factory are located, was significantly higher than among men of inland area (6.9 per million).

Mortality from pleural cancer in Spain has recently been analyzed³²). Mortality rates in men increased from 0.40 per 100,000 in 1980 to 0.78 in 2001. The highest mortality rates were seen in the Barcelona Province, and in particular in Cerdanyola del Valles, where a large asbestos-cement factory was active since 1907.

In Canada crude mesothelioma incidence in the period 1988–1992 was around 9 cases per million, with rates significantly higher in Québec than in the remaining parts of the country²¹). In the United States, mesothelioma incidence in men has levelled-off after the mid 1990s^{22, 23}). This finding is based on the data collected by the Surveillance, Epidemiology, and End Results (SEER) program. Such program covers a limited portion of the US. Very marked variations have been observed among the areas monitored by SEER. In 1998 mesothelioma incidence ranged from 4.49 per million in Hawaii to 23.30 per million in Seattle (Puget Sound)²⁴). It remains doubtful, if the data obtained by SEER in about 15% of US population reflect or not the situation of the entire country.

In Asia the case of Japan is striking. While the mortality from mesothelioma has remained very low until early 1990s,

a dramatic increase has been reported in the following years. The annual number of deaths from mesothelioma was about 150 in 1991²), and 772 in 2001²⁸). In 2005, 911 deaths have been registered (Morinaga K, personal communication). In the past serious problems in the registration of deaths from mesothelioma have been encountered in Japan⁴⁵).

Mesothelioma and Asbestos

A body of evidence indicate a relationship between exposure to asbestos and development of mesothelioma. Analysis of asbestos consumption and mesothelioma incidence in various industrialized countries disclosed a significant correlation between the two variables^{46, 47}). A double-curve pattern may be observed in some countries: the curve of mesothelioma incidence mirrors the curve of the asbestos consumption, that has occurred some decades previously. Such pattern is seen, for instance, in the UK⁴⁸), as well as in Sweden⁴⁹), and Japan²⁸). At a national level, mesothelioma case distribution exactly reflects the location of using asbestos industries. Beside the above-mentioned examples of Croatia²⁷), Great Britain¹²), Spain³²), and Sweden⁴⁰), it should be quoted the situation of Italy. Mortality data for malignant tumors of the pleura among men in the period 1988–97⁴³), show variations of about 40 times from one Province to another. The Provinces with the highest standardized mortality rates (from 4 to 12 per 100,000) correspond perfectly to the areas, in which the largest shipyards and the largest asbestos-cement factory were located. At the opposite, many Provinces of Central and Southern Italy, scarcely or recently industrialized, had mortality rates comprised between 0.30 and 0.94 per 100,000.

The relationship between asbestos exposure and mesothelioma is also demonstrated by the strong differences in risk for mesothelioma in the various occupational groups^{12, 20, 40, 50}). Such risk is proportional to the intensity of exposure to asbestos the different categories had.

The low incidence of mesothelioma in some areas of the world seems to represent an exception to the rule asbestos-mesothelioma relationship. In the Bazhenovskoye area, Russian Federation, where the largest deposits of asbestos in the world are located, exposure was very heavy in the past. This is documented by the fact that in 1947 the prevalence of asbestosis among workers of the area, reached the value of 29.3%⁵¹). However, mesothelioma remained a relatively rare event, with eight cases diagnosed in a 23-yr period (1981–2003)⁵¹). In Thailand, asbestos has been used for more than 30 yr⁵²). In 1996, Thailand ranked second in the world for capita consumption of asbestos⁴⁶). However,

not only mesothelioma but also asbestos-related disease in general are practically unknown in the country⁵²). In Hong Kong, one of the largest ports in the world, a very low mesothelioma incidence (one case per million) has recently been reported⁵³). In South Korea, one of the most important shipbuilders in the world during the last decades, mesothelioma incidence is low with 40–50 cases per year³⁶). There are different possible explanations for the above exceptions: type of asbestos used, short periods of employment, low life expectancy, competitive causes of death, underdiagnosis, not sufficient latency periods elapsed, differences in susceptibility/resistance to the effects of asbestos (congenital or acquired) etc.. The idea that latency periods have not yet elapsed, seems to be mainly valid for the countries, in which industrialization is a relatively recent event. Contrary beliefs exist about the role of the different asbestos types in etiology of mesothelioma. After some researchers, increase and decline in US mesothelioma incidence are essentially attributable to increase and decline in the use of amphiboles²³). However, other authors, by analyzing asbestos fibers in lung, pleural plaques, and tumor tissue from mesothelioma patients, conclude that chrysotile has a major role⁵⁴).

Latency Period

It is currently stated that the time periods elapsing between first exposure to asbestos and diagnosis of mesothelioma are 20–40 yr. However, studies conducted on large mesothelioma series indicate that generally latency periods are longer. In 400 pleural mesotheliomas investigated in the Trieste-Monfalcone area, Northeastern Italy, the latency periods ranged between 14 and 75 yr (mean 48.8 yr, median 51)⁵⁵). In 301 mesotheliomas of the pleura and peritoneum, diagnosed in workers from the Devonport Naval Dockyards, UK, mean latency period was 48.5 yr⁵⁶). The discrepancy between these figures and those generally reported in the literature is not difficult to explain. Early studies on latency period regarded insulation workers, a category with very heavy exposure. Some data indicate that an inverse relationship exists between intensity of exposure to asbestos and length of the latency period. In the Trieste-Monfalcone study, insulation workers showed relatively short latency periods (range 28–32 yr, mean 29.6, median 29.0)⁵⁵). Among dock workers latency periods ranged between 25 and 60 yr (mean 36.2, median 31.5). Latency periods were longer among shipyard workers (range 14–72 yr, mean 49.1, median 51.5), among seafarers (range 35–75 yr, mean 55.9, median 56.0), and among women with history of domestic exposure

to asbestos (range 27–62 yr, mean 51.4, median 54.0). In the Devonport study⁵⁶), the trades with more heavy exposure had a mean latency period significantly shorter than trades less heavily exposed.

Duration of Exposure

The natural history of mesothelioma shows that the tumor may develop even after very short or very mild exposures to asbestos. This fact has received great emphasis. However, the role of exposure duration has been neglected. If short exposures are sufficient to induce mesothelioma, the tumor is mostly the consequence of long-time exposures. In the Trieste-Monfalcone series, 75% of the patients had been exposed for 20 yr or more, and 91% for 5 yr or more⁵⁷). Some recent studies clearly show the influence of exposure duration on mesothelioma risk. Ulvestad *et al.*⁵⁸) have analyzed the cancer incidence among workers of an asbestos-cement industry in Norway. No mesothelioma case was observed among people with less than 5 yr of employment. The standardized incidence ratio increased with duration of employment, being 34.8 among workers with 5–9 yr of employment, 51.3 among those with 10–14 yr, and 84.1 among workers with more than 15 yr of employment. Another study was conducted on Norwegian insulation workers⁵⁹). In such cohort there was also some indication of increasing risk with duration of employment, with a standardized incidence ratio of 17.6 among workers with 5–9 yr of employment, and a SIR of 46.3 among persons with 15–19 yr of employment. However, there was an apparent reduction of risk with 20 or more years of employment. Tessari *et al.*⁶⁰) investigated two cohorts of workers, employed in two plants manufacturing and repairing railway coaches in the Province of Padua, Italy. The standardized mortality ratio for pleural mesothelioma increased with the duration of employment. In a study on a cohort of asbestos textile workers in the Province of Turin, Italy, Pira *et al.*⁶¹) found increased standardized mortality rates with the duration of employment for peritoneal cancer, but not for pleural cancer.

Despite some inconsistencies, the data about the relationship between the duration of employment and risk of mesothelioma indicate that duration of exposure is important. This means that the critical event is not only the exposure of the first years, but, at least in a majority of cases, also the subsequent exposures. Such fact has not sufficiently been appreciated. On the other hand, the relevance of the subsequent exposures is also suggested by another order of considerations. In cases with very long latent period (60–

70 yr), it is scarcely plausible that the first steps of the neoplastic process have started at the time of early exposure, remaining latent for six-seven decades. The latent period represents the time period, in which contact with asbestos has occurred. Latent period does not correspond to the induction period, presumably shorter. The distinction between latency and induction period has been proposed both for cancer in general, as well as for mesothelioma pathogenesis⁶². We may assume that generally the carcinogenic effects of asbestos are neutralized by the defence mechanisms. In a majority of cases, mesothelioma develops only when a relatively high cumulative dose is reached, and/or surveillance system is impaired.

Co-factors

Small percentages of people exposed to asbestos develop mesothelioma⁵⁰. This indicates that factors other than asbestos play a role in the genesis of the tumor⁶³. A body of evidence suggest that individual differences in metabolic genes, involved in detoxification, might partly explain the difference in susceptibility to mesothelioma⁶⁴. The occurrence of more mesothelioma cases among members of the same family has attracted some attention^{65–68}. Generally, familial mesothelioma reported in the literature were asbestos-related. Familial mesothelioma affecting blood-related persons raises the question if a hereditary susceptibility to oncogenic effect of asbestos exists. When affected members of a family are not blood-related, the possibility has to be considered, that a series of factors family members share (from diet to exposure to electromagnetic fields at home, and to exposure to pets, etc.), have a synergistic effect with asbestos. The study of familial mesothelioma could give an insight into mesothelioma genesis.

Some studies suggest that dietary factors might influence the risk of mesothelioma^{69, 70}. Diets rich in fruit and vegetables seem to have a protective effect. In a study, a reduction of antioxidants (such as alpha-tocopherol and ascorbic acid) in the serum of patients with mesothelioma was found⁷¹.

A possible role of viruses has been proposed in the genesis of mesothelioma. In particular, a lot of researches were conducted on simian virus 40 and mesothelioma^{72–75}. Certain findings suggest that SV40 increases the risk of developing mesothelioma among people exposed to asbestos⁷³. However, some studies have challenged the reliability of the results obtained in this field⁷⁶.

Investigation on co-morbidity in mesothelioma has been proposed, as a way for the identification of co-factors⁶³.

The association of mesothelioma with other pathological conditions could allow a better knowledge of the background, on which mesothelioma develops. In particular, numerous studies have investigated the co-existence of mesothelioma with other primary malignancies^{77–80}. The association between mesothelioma and other cancers, such as non-Hodgkin lymphoma or hepatocellular carcinoma, could indicate a role of immune impairment in the genesis of mesothelioma^{78, 80}.

Very frequently mesothelioma does not develop on normal pleura, but on pleura affected by pleural plaques⁸¹. Pleural plaque is the effect of recurrent inflammatory and repair processes, occurring for decades. In a recent study, the presence of benign pleural disease appeared to increase the risk of peritoneal mesothelioma, but not the risk of pleural mesothelioma, beyond that attributable to the severity of exposure to asbestos⁸². Despite this “negative” finding, it is biologically plausible that an endless sequence of inflammatory episodes represents a condition predisposing to malignant evolution⁸³. The development of peritoneal mesothelioma in the course of familial Mediterranean fever⁸⁴, characterized by recurrent peritonitis, furtherly supports this idea. A clue comes also from animal pathology. Pericardial mesotheliomas have been observed among dogs (golden retrievers), affected by recurrent pericardial effusion⁸⁵.

Predictions

In many industrialized countries a great concern exists about the future trend of mesothelioma epidemic. Various studies have been devoted to the predictions in this field^{14, 45, 86–88}. Predictions are difficult, since during the last decades phenomena of opposite sign have occurred. World asbestos production has progressively increased since 1960, reaching its peak in the late 1970s⁸⁹. However, limitations in the use of asbestos began in some European countries in 1960s and 1970s. Therefore, it is legitimate to expect the effects of such reductions. In Italy asbestos was banned in 1992. However, some limitations in the use of the mineral were adopted in certain workplaces, such as shipyards and ports, in the late 1970s. It seems that the effects of the restrictions have already been observed in some countries, like Sweden⁴⁰, or in some sectors, such naval dockyard in the UK⁵⁶. In Japan, asbestos consumption was high in the last decades. In 1980 nearly 400,000 tons were used⁸⁹, and relevant amounts of the mineral were used until 2000. After some forecasts, a very high number of deaths from mesothelioma, is predicted in Japan in the next decades⁴⁵.

Concluding Remarks

Unfortunately for very large parts of the world, data on mesothelioma incidence/mortality are not available. This constitutes a serious obstacle in the progress of the knowledge on mesothelioma. Moreover, lack of data does not allow that a sufficient perception of the risk is reached. The countries that have banned the use of asbestos are growing. However, they represent a small minority in the world.

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