

Epidemiology of peritoneal mesothelioma: a review

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The epidemiology of peritoneal mesothelioma is complicated by possible geographic and temporal variations in diagnostic practices. The incidence rates in industrialized countries range between 0.5 and three cases per million in men and between 0.2 and two cases per million in women. Exposure to asbestos is the main known cause of peritoneal mesothelioma. Results on peritoneal mesothelioma have been reported for 34 cohorts exposed to asbestos, among which a strong correlation was present between the percentages of deaths from pleural and peritoneal mesothelioma (correlation coefficient 0.8, $P < 0.0001$). Studies of workers exposed only or predominantly to chrysotile asbestos resulted in a lower proportion of total deaths from peritoneal mesothelioma than studies of workers exposed to amphibole or mixed type of asbestos. Cases of peritoneal mesothelioma have also been reported following exposure to erionite and Thorotrast, providing further evidence of common etiological factors with the pleural form of the disease. The role of other suspected risk factors, such as simian virus 40 infection and genetic predisposition, is unclear at present. Control of asbestos exposure remains the main approach to prevent peritoneal mesothelioma.

Key words: asbestos, epidemiology, peritoneal mesothelioma, thorotrast

Introduction

The peritoneum is the second most frequent site of origin of mesothelioma, after the pleura. In developed countries, malignant mesothelioma (International Classification of Diseases for Oncology–Morphology codes 9050–9055) is the most frequent malignant neoplasm of the peritoneum [1]. Symptoms of peritoneal mesothelioma are unspecific, the most frequent being increased abdominal girth, pain and weight loss [2]; usually diagnosis occurs late. Treatment includes the combination of debulking surgery and i.p. chemotherapy. Survival remains poor; in the USA Surveillance, Epidemiology and End Results (SEER) cancer registry data median survival is 10 months and relative 5-year survival is 16% [3], however, in selected clinical series a longer survival (median >50 months) has been reported [2]. Although asbestos has been known for several decades to cause peritoneal mesothelioma, in addition to the pleural form of the disease [4], no detailed review of the epidemiological features of this disease has been published recently.

descriptive epidemiology

The descriptive epidemiology of peritoneal mesothelioma is complicated by temporal and geographic variability in diagnostic criteria. In addition, low sensitivity and low specificity of the diagnosis are important concerns, since

mesothelioma of the peritoneum can be misdiagnosed as a neoplasm originating from other abdominal organs, notably adenocarcinoma from the ovary, and vice versa [5, 6]. Furthermore, sensitivity and specificity of the diagnosis may vary by place and time, thus complicating geographic and temporal analyses of the occurrence of the disease. Furthermore, given the strong association between asbestos and mesothelioma, knowledge of previous exposure might influence diagnostic accuracy; if this is the case, a diagnosis of peritoneal mesothelioma would be more frequently made for a patient with recognized past asbestos exposure than for a patient with a similar clinical presentation but without history of asbestos exposure.

The consequences of these potential biases are difficult to assess. Although it is likely that occurrence of peritoneal mesothelioma is underestimated in most populations, overestimation might occur in circumstances of recognized asbestos exposure. In general, caution should be used in the interpretation of the available data on the incidence and mortality from this disease.

Recent international data on the incidence of peritoneal mesothelioma are available from Eurocim, a collaboration of European population-based cancer registries [7], and from the SEER program of the United States [3]. Only sparse data are available from the other countries. Figure 1 reports the most recent data from selected nationwide European cancer registries and the SEER registries; at this level of aggregation, age-standardized incidence rates among men range from 0.5 to about three cases per million population. However, higher rates

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are reported in smaller areas with widespread past use of asbestos, such as the harbor city of Genoa, Italy (age-standardized rate in men in 1995, 5.5 per million). In most populations, rates among women are in the range 0.2–2 per million and are lower than in men; although in some countries, such as Sweden, rates are comparable in the two sexes. A correlation in incidence rates exists between the two sexes (correlation coefficient of 1991–1995 rates on the basis of 41 European and nine USA populations covered by cancer registry, 0.41; $P = 0.003$).

Figure 2 shows the temporal trend in peritoneal mesothelioma incidence among men in selected countries [3, 7]. Rates between 1971 and 1995 remained stable in Sweden and United States (SEER), while they have increased in countries such as Denmark and Scotland. The analysis of age-specific rates provides a deeper insight in the pattern of disease incidence, but it is feasible only in populations with a large enough number of cases to provide meaningful results. Figure 3 shows such rates in England during 1971–1995 (men only); a birth cohort effect is indicated, with the highest rates experienced by men born between 1920 and 1930. A decline in the last time periods is apparent among young men, indicating that the overall incidence might decline in the future. Age- and time-specific trends in women cannot be adequately studied because of random variability.

In an analysis of 50 European and USA populations [3, 7], the incidence rates of peritoneal mesothelioma in men were one order of magnitude lower than those of pleural mesothelioma. Rates of peritoneal mesothelioma among men showed only

a modest correlation with that of the pleural form of the disease (Figure 4). A comparable analysis among women resulted in an even weaker correlation (correlation coefficient 0.14, P value 0.32). The modest correlation between peritoneal and pleural mesothelioma rates can be explained by differences in risk factors (e.g. circumstances of exposure to asbestos), but can also derive from bias in diagnostic and registration procedures.

exposure to asbestos

Data on the occurrence of peritoneal mesothelioma have been reported for 34 cohort studies of workers exposed to asbestos and asbestosis patients. The characteristics and key results of these cohorts are summarized in Table 1. A formal analysis of observed versus expected deaths (or cases) was presented in only few studies, because of difficulties in obtaining reliable reference rates. In order to provide some comparison between the cohorts, we used the proportion of peritoneal mesothelioma deaths over the total number of death as a measure of risk. This approach ignores differences in the age structure of the different study populations as well as temporal changes in the underlying rates. However, it is a relatively good indicator of the effect of an important determinant of the disease.

No peritoneal mesothelioma deaths were reported in 14 of the 34 studies; only two of these studies, however, comprised >1000 deaths, thus providing a reasonable power to detect a risk [13, 33]. The proportion over total deaths ranged in most of the remaining studies between 1/1000 and 1/100 (Table 1), with the

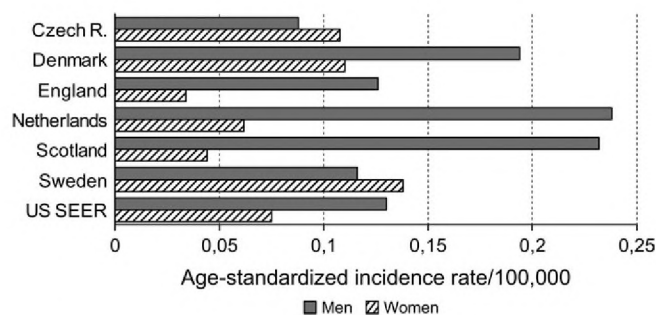
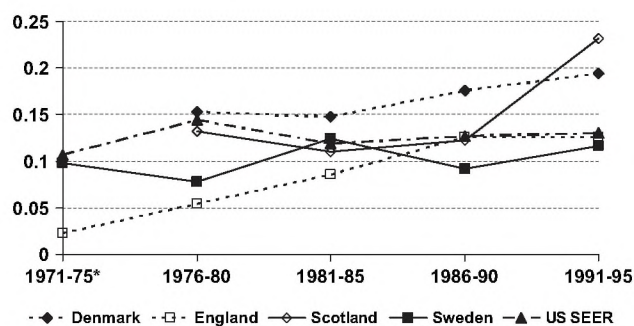


Figure 1. Incidence of peritoneal mesothelioma in selected countries (1991–1995).



* 1973–1975 for US SEER

Figure 2. Temporal trend in the incidence of peritoneal mesothelioma in selected countries (men).

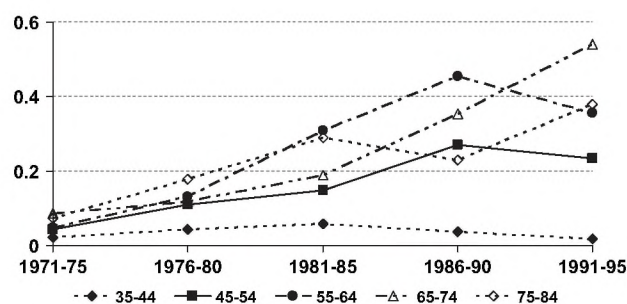


Figure 3. Age- and calendar time-specific incidence rates of peritoneal mesothelioma in England (men).

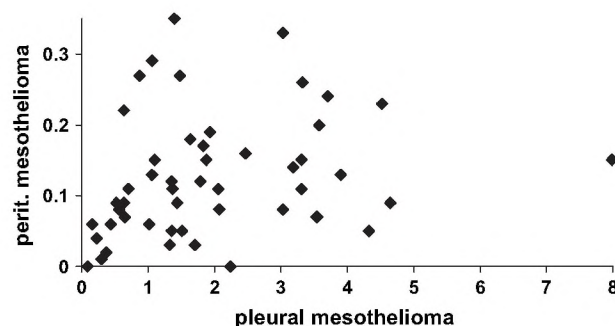


Figure 4. Correlation of peritoneal and pleural mesothelioma incidence rates among men, 1991–1995 (41 European and nine surveillance, epidemiology and end results populations).

Table 1. Characteristics and results on peritoneal mesothelioma of cohorts of workers exposed to asbestos and of asbestosis patients

n	Exposure circumstance	Fiber type	Country	Period employment	Sex	Size	Evidence	TD	PIMD	PeMD	LC SMR	Reference
1	Gas mask manufacture	Cr	UK	1938–1945	F	578	MR	166	13	4	1.94	[8]
2	Gas mask manufacture	Ch	UK	1939	F	570	DC	177	1	0	1.25	[9]
3	Gas mask manufacture	Cr	UK	1939	F	757	DC	219	3	2	2.10	[9]
4	Textile product manufacture	P Ch	United States	1938–1958	M	4137	DC	1392	10	4	NA	[10]
5	Cement workers	P Ch	UK	1936–1977	M	1592	DC	351	2	0	0.93	[11]
6	Cement workers	Mixed	Canada	1955–1959	M	535	DC	108	11	8	4.90	[12]
7	Friction product manufacture	Ch	United States	1939–1958	M	3641	DC	1267	0	0	1.49	[13]
8	Insulation manufacture	Am	UK	1945–1978	M	4820	DC	333	4	1	1.96	[14]
9	Railroad repair workers	Mixed	Sweden	1939–1980	M	3442	DC	925	5	0	1.16	[15]
10	Textile product manufacture	P Ch	UK	1933–1974	M	3211	DC	1113	10	1	1.32	[16]
11	Cement workers	P Ch	Sweden	1943–1976	M	1216	DC	220	0	0	1.23	[17]
12	Shipyard workers	Mixed	United States	1950–1969	M	5191	CR	668	8	0	1.09	[18]
13	Cement workers	Mixed	France	1940–1977	M	1506	DC	206	3	1	2.17	[19]
14	Mixed exposure	P Ch	Poland	1945–1985	M	2403	DC	527	1	0	1.41	[20]
15	Mixed exposure	Mixed	Germany	1930–1974	PM	3070	DC	185	6	0	1.44	[21]
16	Various product manufacture	Am	United States	1941–1945	M	820	BE	593	8	9	4.97	[22]
17	Cement workers	Ch	UK	1941–1983	MF	2167	DC	486	1	0	0.97	[23]
18	Cement workers	P Ch	United States	1937–1970	M	6931	BE	2143	9	1	NA	[24]
19	Vermiculite miners	Tre-Act	United States	1970–1981	M	569	DC	161	2	0	2.23	[25]
20	Mixed exposure	Mixed	United States	1941–1967	M	1074	DC	617	6	2	2.71	[26]
21	Crocidolite miners	Cr	Australia	1943–1966	PM	6916	DC	843	33	1	2.64	[27]
22	Cement workers	P Ch	Austria	1950–1981	NA	2816	DC	540	7	3	1.70	[28]
23	Insulation workers	Mixed	United States	1967	M	17800	BE	4951	173	285	3.75	[29]
24	Shipyard workers	P Ch	Sweden	1977–1979	M	3893	DC	NA	11	0	0.85	[30]
25	Miners	Am, Cr	South Africa	1945–1981	M	7317	BE	1225	22	6	1.72	[31]
26	Railroad construction work	Mixed	Italy	1970–1989	M	1534	DC	194	3	2	1.45	[32]
27	Textile product manufacture	Ch	United States	1940–1965	MF	3022	DC	1259	2	0	1.97	[33]
28	Miners	Antho	Finland	1953–1967	M	736	CR	NA	3	1	2.88	[34]
29	Cement workers	P Ch	Italy	1950–1980	M	2605	DC	1147	53	23	2.48	[35]
30	Asbestosis patients	Mixed	Italy	1979 ^a	F	631	DC	277	14	12	4.83	[36]
31	Cement workers	Mixed	Israel	1953–1992	M	3057	BE	NA	20	1	1.35	[37]
32	Various product manufacture	Ch	China	1972	M	515	MR	132	1	1	NA	[38]
33	Asbestosis patients	Mixed	Poland	1970–1997 ^a	M	907	DC	300	3	0	1.68	[39]
34	Cement workers	P Ch	Norway	1942–1976	M	541	CR	NA	18	0	3.10	[40]

^aPeriod of diagnosis.

Fiber type: Ch, pure chrysotile; P Ch, predominantly chrysotile; Cr, crocidolite (pure or predominant); Am, amosite (pure or predominant); Antho, anthophyllite; Tre-Act, tremolite-actinophyllite. Sex: M, males; F, females; MF, males and females; PM, predominantly males. Evidence: DC, death certificate; CR, cancer registry; BE, best evidence (*ad hoc* investigation); MR, routine medical records. TD, total deaths; PIMD, pleural mesothelioma deaths; PeMD, peritoneal mesothelioma deaths; LC SMR, standardized mortality ratio of lung cancer; NA, not available.

exception of cohorts of cement workers from Canada [12], insulators from United States [29] and asbestosis patients from Italy [36] in which $\geq 4\%$ of total deaths were from peritoneal mesothelioma. There was a strong correlation between the percentage of peritoneal mesothelioma deaths and both the percentage of pleural mesothelioma deaths (Figure 5) and the standardized mortality ratio of lung cancer (not shown in detail, correlation coefficient 0.85, $P < 0.0001$). The latter result replicates the finding of a previous analysis of a smaller number of cohort studies [41].

A higher proportion of studies of cohorts of workers exposed to chrysotile (either as unique or as predominant fiber type) reported no peritoneal mesothelioma deaths (nine of 15) as compared with studies of cohorts of workers to amphiboles or mixed fibers (four of 17; Table 2, column 3; chi-square test, P value 0.04). The proportion of mesothelioma deaths over total

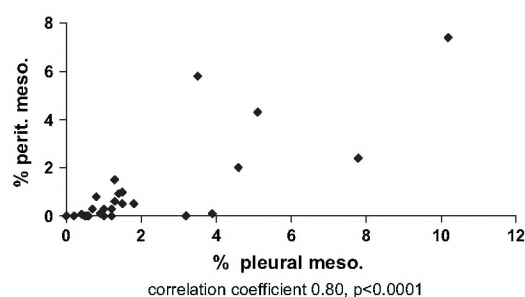


Figure 5. Correlation of percentage of pleural and peritoneal mesothelioma deaths in cohorts of asbestos-exposed workers.

deaths was higher in cohorts exposed to amphiboles or mixed fibers than in cohorts exposed to chrysotile (Table 2), but the difference was not statistically significant (P value after

Table 2. Percentage of peritoneal mesothelioma deaths (PMDs) over total deaths (TDs), by type of asbestos fiber

Asbestos type	Cohort number (see Table 1)	<i>n</i> cohorts with no PMD	PMD/TD (%) ^a	
			Median	Range
Overall		13 of 32	0.2	0.05–7.4
Pure chrysotile	2, 7, 17, 22, 32	4 of 5	0.8	NA
Predominant chrysotile	4, 5, 10, 11, 14, 18, 22, 24, 29, 34	5 of 10	0.3	0.05–2.0
Amphiboles	1, 3, 8, 16, 21, 25	0 of 6	0.7	0.1–2.4
Mixed	6, 9, 12, 13, 15, 20, 23, 26, 30, 31, 33	4 of 11	2.7	0.3–7.4

^aInformation on proportion of PMD available for 30 cohorts (see Table 1 for details), excluding cohorts with no PMD.

Two cohorts (number 19 and 28) excluded from the analysis.

NA, not applicable.

adjustment for geographic region, 0.09). It was not possible to assess the effect of different types of amphibole fibers. Similar conclusions were noticed in a previous analysis of a smaller number of cohorts [41]. No effect of geographic region on the proportion of mesothelioma deaths over total deaths was detected [*P* value, on the basis of four regions (United States, UK, Western Europe, other countries) and adjusted for asbestos type, 0.9]. Only four studies were available of women (Table 1), pre-empting detailed analyses. No difference was found in the proportion of peritoneal mesothelioma deaths over total deaths according to diagnostic accuracy (death certificate versus best evidence, results not shown in detail). An effect of period of employment was apparent, with the cohorts of workers first employed before 1950 having a lower proportion of peritoneal mesothelioma deaths over total deaths than cohorts of workers employed later (*P* value after adjustment for geographic region, 0.005). This finding might reflect improved diagnostic accuracy during recent decades.

The dose–response relationship between occupational asbestos exposure and peritoneal mesothelioma risk has been investigated on the basis of the studies providing information on quantitative asbestos exposure [41]. The risk of peritoneal mesothelioma for workers exposed to amphiboles was proportional to the square of cumulative exposure, while a similar estimate could not be obtained for chrysotile-exposed workers [41, 42].

The important role of occupational exposure to asbestos in causing peritoneal mesothelioma has been confirmed in two community-based studies. A study from 24 of the United States [43] included 657 death certificates with peritoneal cancer (not specified as to histological type) as underlying cause recorded during 1984–1992. The occupation listed on the death certificate of these decedents (typically, the last occupation) was more frequently a job-entailing exposure to asbestos than the occupation of controls (deaths from other causes, matched 10 : 1 to cases). In particular, the odds ratio (OR) of peritoneal cancer was 180 [95% confidence interval (CI) 23, 1375] for insulation workers and 7.6 (95% CI 2.3, 25) for manufacturers of nonmetallic mineral products, including asbestos. When the authors applied a matrix for asbestos exposure on the basis of the jobs listed on the death certificate, they found a strong relationship with probability and intensity of exposure.

In a case–control study from Los Angeles and New York, USA, 20 cases of (or deaths from) peritoneal mesothelioma among men were compared with death certificate controls [44].

Interviews were conducted with next of kin. Exposure to asbestos, either self-reported or derived from occupational history, was present for 17 of the cases (OR 3.1, 95% CI 0.8, 15). The fraction of peritoneal mesothelioma attributable to asbestos exposure in this population was 58% (95% CI 20, 89).

Two studies provided evidence of an increased risk of peritoneal mesothelioma following nonoccupational exposure to asbestos. In a study from England, two cases of peritoneal mesothelioma were reported in women with household exposure [45]. No cases were reported among individuals with neighborhood exposure, while for seven cases, including three in men, there was no evidence of occupational or environmental exposure to asbestos. In a study from United States, eight cases of peritoneal mesothelioma were reported among women without occupational exposure; household exposure was reported for seven of them and residential exposure for three, including the case without household exposure [46]. In the case–control study from Los Angeles and New York mentioned above, no cases of peritoneal mesothelioma had residential exposure to asbestos [44].

exposure to other mineral fibers

Erionite is a silicate fiber belonging to the family of zeolites [47]. An increased risk of pleural mesothelioma and lung cancer has been reported among residents in a contaminated area from Cappadocia, Turkey, in which no sources of asbestos exposure were identified [48–50]. In particular, in a survey of 141 deaths in four villages, during 1979–1983, 29 deaths from pleural mesothelioma (20.5%) and four deaths from peritoneal mesothelioma (3.5%) were identified [50]. In a study of 162 Cappadocian migrants to Sweden, one case of peritoneal mesothelioma was identified [51].

There is no evidence of an increased risk of peritoneal mesothelioma among workers exposed to man-made vitreous fibers [52], although the available studies do not have a sufficient statistical power to detect a small increase in risk.

ionizing radiation

Three cohorts of patients receiving Thorotrast for radiological examinations reported results on peritoneal mesothelioma risk (Table 3). Although a formal estimate of the risk is complicated by uncertainties in the calculation of expected deaths, these

Table 3. Peritoneal mesothelioma in patients exposed to Thorotrast

Country, circumstance of exposure	Follow-up period; method	<i>n</i> patients	<i>n</i> perit. meso	<i>n</i> pl. meso	Comments	Reference
Denmark, cerebral arteriography	1935–1992; CR	999	6	2	Pathological verification. p53 mutation in peritoneal meso: 0 of 6	[53]
Germany, limb or cerebral arteriography	NR; AS	2326	4	5		[54]
Japan, arteriography	1945–1992; AS	370	1	0	Three additional retroperitoneal neoplasms	[55]

perit., peritoneal; meso, mesothelioma; pl., pleural; CR, cancer registry; AS, active surveillance; NR, not reported.

patients experienced a cumulative incidence of peritoneal mesothelioma between 0.2% and 0.6%, higher than that of many cohorts of asbestos-exposed workers listed in Table 1. The incidence of peritoneal mesothelioma among Thorotrast patients was comparable with, or even greater than, that of pleural mesothelioma. The deposition of α -particles in abdominal organs adjacent to the peritoneum, such as the liver, spleen and lymph nodes is a plausible explanation of these findings. The time of appearance of peritoneal mesotheliomas in the Danish cohort of Thorotrast patients was longer than that of other cancers whose risk was also increased, such as liver and lung cancer [53]. An additional three cohorts of Thorotrast patients have been studied [56–58], but results for peritoneal mesothelioma have not been reported. The evidence on the risk of peritoneal mesothelioma following exposure to other sources of ionizing radiation is limited to a few case reports, e.g. of cancer patients who underwent radiotherapy [59].

other risk factors

A large number of studies detected sequences of the papovavirus, simian virus 40 (SV40) in samples of pleural mesothelioma [60]; however, the causal nature of this association has been questioned [61], and laboratory contamination may explain some of the findings [62]. In one of these studies, 11 German cases of peritoneal mesothelioma were also included, seven of which were positive for SV40 Tag sequences [63].

A possible role of chronic pancreatitis in peritoneal mesothelioma has been indicated, but not formally evaluated [64]. Genetic factors have been indicated to play a role in pleural mesothelioma [65]. Very limited information is available on the peritoneal form of the disease. In the case-control study from Los Angeles and New York mentioned above, the mother of an asbestos-exposed case of peritoneal mesothelioma was reported to have suffered from the same neoplasm [66]. No studies are available on other potential risk factors (e.g. nutrition).

conclusions

The rarity of the peritoneal mesothelioma and its diagnostic uncertainties limit our understanding of its epidemiological features. Asbestos is the main known cause of the disease, but other risk factors are likely to be involved in its etiology and pathogenesis. Although the evidence is not conclusive, this review of cohort and case-control studies indicates that the association between asbestos exposure and peritoneal

mesothelioma is less strong than in the case of pleural mesothelioma. This might explain the relatively low correlation between the incidence of the two diseases. The other known risk factors explain only a very small proportion of cases of peritoneal mesothelioma. Despite these limitations, control of exposure to asbestos, in particular at the workplace, remains the main approach for the prevention of peritoneal mesothelioma.

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