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Incidence of extrapleural malignant mesothelioma and asbestos exposure, from the Italian national register

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ABSTRACT

Objectives The epidemiology of extrapleural malignant mesothelioma is rarely discussed and the risk of misdiagnosis and the very low incidence complicate the picture. This study presents data on extrapleural malignant mesothelioma from the Italian National Mesothelioma Register (ReNaM).

Methods ReNaM works on a regional basis, searching for cases and interviewing subjects to investigate asbestos exposure. Classification and code criteria for certainty of diagnosis and exposure modalities are set by national guidelines. Between 1993 and 2004, 681 cases were collected. Incidence measures and exposure data refer to the ReNaM database. Age-standardised rates were estimated by the direct method using the Italian resident population in 2001. Correlations between the incidence of pleural and non-pleural malignant mesothelioma for the 103 Italian provinces were analysed.

Results Standardised incidence rates (Italy, 2004, per million inhabitants) were 2.1 and 1.2 cases for the peritoneal site (in men and women, respectively), 0.2 cases for the tunica vaginalis testis, and 0.1 in the pericardial site, varying widely in different parts of the country. Mean age at diagnosis for all extrapleural malignant mesothelioma cases was 64.4 years and the men/women ratio was 1.57:1. Median latency was over 40 years for all extrapleural sites combined. The correlation between pleural and peritoneal mesothelioma was 0.71 (Pearson's r coefficient, $p<0.001$). Modalities of exposure to asbestos fibres were investigated for 392 cases.

Conclusions The rarity of the disease, the low specificity of diagnosis and difficulties in identifying the modalities of asbestos exposure call for caution in discussing aetiological factors other than asbestos.

What this paper adds

- The epidemiology of non-pleural malignant mesothelioma, whose incidence is very low, is rarely discussed, and the diagnosis is still limited by poor sensitivity and specificity, with a particularly high risk of misdiagnosis in women.
- Recently it has been suggested that the association between asbestos exposure and peritoneal mesothelioma is weaker than for the pleural form, but the rarity of the disease, the low specificity of diagnosis and difficulties in identifying the modalities of asbestos exposure call for caution in discussing the role of aetiological factors other than asbestos.
- Between 1993 and 2004, 681 cases of non-pleural mesothelioma in Italy were collected through a national registration system, with individual recognition of asbestos exposure, applying standardised methods for diagnosis and exposure modalities.
- Exposure to asbestos was the most important risk factor, so the possibility of a weaker relationship needs to be carefully considered, depending on the misdiagnosis of other malignancies (especially in women) and on the difficulty of clearly identifying occupational exposure in non-industrial work settings, as well as non-occupational exposure, both of which are important for women.

INTRODUCTION

Malignant mesothelioma (MM) is a lethal tumour generally induced by exposure to asbestos. It arises from the serous membranes of the pleura and, less frequently, of the peritoneal and pericardial cavities and from the tunica vaginalis testis. The epidemiology of extrapleural malignant mesothelioma (EPMM) is rarely discussed. The European population-base cancer registries published figures for the incidence of peritoneal mesothelioma, which ranged between 0.1 and 0.25 cases (per 100 000 inhabitants) for men and 0.05 and 0.1 for women in 2001.[1] The United States SEER program reported incidence rates of 0.12 for men and 0.08 for women in 1973–2005 with no significant temporal trend in that period,[2] and predicted a ratio of 6.3 between pleural and peritoneal cases in the USA in the decades up to 2050.[3] Cases of pericardial and testicular mesothelioma are only sporadically reported and it is not easy to establish their extent and the aetiological characteristics from the epidemiological point of view.[4]

The differences between male and female incidence rates suggest that diagnosis of peritoneal MM still suffers poor sensitivity and specificity and the risk of misdiagnosis is particularly high for women with neoplasms from abdominal organs, above all primary peritoneal serous carcinoma and

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ovarian serous carcinoma.[5] The disease rarely presents as ovarian masses although ovarian mesotheliomas have been described.[6] Pleural/peritoneal incidence ratios vary widely in published studies, but generally the incidence of peritoneal mesothelioma is one order of magnitude lower than pleural forms.[7]

The relationship between MM and asbestos exposure has been definitely demonstrated, although some aspects of the biological causal mechanisms are still not clear. A lower attributable risk to asbestos for peritoneal than pleural MM, has been suggested, in the light of the lower men/women ratio in EPMM.[8] Taking account of fibre type, a dose–effect relationship with asbestos exposure has been shown for peritoneal MM, but with a distinct shape compared with pleural cases.[9] Moreover, the peritoneal MM risk rises with duration of exposure and latency, much more steeply than for the pleural form.[10]

Italy was one of the main raw asbestos-producing and asbestos-importing countries until the ban in 1992. A permanent MM epidemiological surveillance system has in fact been operative since 1993 (and was made mandatory in 2002), based on a national MM register (ReNaM) established at the National Institute for Occupational Safety and Health (ISPESL), which publishes figures for incidence, survival and asbestos exposure.[11–13] This paper presents the current data on EPMM from ReNaM.

METHODS

ReNaM has a regional structure: regional operating centres (COR) have been gradually established in 18 of the 19 Italian regions and one of the two autonomous provinces, covering almost the whole country (98.5% of the Italian population). The Italian mesothelioma register has been extensively described elsewhere.[11 14]

Occupational and residential history, and lifestyle habits, are obtained using a standardised questionnaire administered by a trained interviewer to the subject or next of kin. At present 6640 MM cases (out of 9166, 72.4%) and 437 EPMM cases (out of 681, 64.2%) have been interviewed. Occupational exposure is classified qualitatively, as definite, probable or possible. Definite occupational exposure refers to people whose work involved the use of asbestos or materials containing it. Probable exposure is attributed to those who have worked in a firm or sector where asbestos was certainly used, but whose exposure cannot be documented, and possible exposure to people who have worked in a firm or sector where asbestos might have been used.

At present the ReNaM has collected cases with a diagnosis of MM in the period 1993–2004. Italian regions, through each COR, did not all contribute equally during this period: Piedmont, Veneto, Tuscany and Apulia produced incidence regional case lists starting from 1993; Liguria, Emilia-Romagna and Marche from 1996; Sicily from 1998; Friuli Venezia-Giulia and Valle D'Aosta from 2000; and Campania from 2001. Lombardy has produced incidence figures for 2000 and 2001, but more recent data are still awaited. As yet, case lists from Lazio, Abruzzo, Basilicata, Calabria and Sardinia cannot be considered complete. Finally, Umbria, Molise and the two autonomous provinces of Trento and Bolzano did not collect any data at all.

Incidence measures refer to the space-territory coverage according to incidence data collection, as specified above. Age-standardised rates were estimated by the direct method using the Italian resident population in 2001. The men/women ratio for pleural and extrapleural case lists and the pleural/extrapleural ratio were calculated. The correlations between pleural and non-pleural MM incidence for each of the 103 Italian provinces were analysed, then stratified by sex. We estimated the person/years (PY) of observation, the number of pleural, peritoneal, pericardial and testicular MM cases and the crude rate for all provinces, with the Pearson's r correlation coefficient for all pairs of anatomical sites, and tested the statistical significance of these correlations. Finally, we calculated the crude rate of EPMM for the 8101 Italian municipalities. Exposure data refer to the whole ReNaM database. To provide an indication of the size of the industry, we estimated the cumulative population at risk for the branches of industry with a relevant number of EPMM cases. The initial size of the population was determined from the workforce at national census in 1961 and an annual change yearly was added (or detracted) depending on intercensual differences. All statistical analysis was carried out with SPSS software V.17.

RESULTS

We collected a case list of 9166 MM cases between 1993 and 2004. The pleural site was reported for 92.6% of the MM cases (8485), and peritoneal sites for 6.7% of all cases (614); pericardial and testicular sites accounted for, respectively, 0.4% and 0.3% (36 and 31 cases). The pleural/non-pleural ratio is 12.5/1 (13.8/1 for the peritoneal site) with no significant changes between 1993 and 2004. The men/women ratio is higher in the pleural group (2.75:1) than the extrapleural (1.57:1). Table 1 shows the distribution by sex, age, incidence period, diagnostic certainty, morphology and modalities of interview for 681 incident EPMM cases.

EPMM is a very rare disease, with standardised incidence rates for the peritoneal site of, respectively, 2.1 and 1.2 for men and women (cases per million inhabitants, Italy, 2004). It is more frequent in the tunica vaginalis testis (0.2 cases per million) than in the pericardium (0.1 per million in men and women). When restricted only to certain mesothelioma, the incidence rate for peritoneal MM is about 20% lower for both men and women.

The pooled national figures are determined by regional incidence which varies widely. Certain, probable and possible peritoneal incidence go from 0.9 per million inhabitants (Veneto and Apulia) to 6.1 (Piedmont) for men and from 0 (Valle d'Aosta, Friuli Venezia-Giulia, Liguria, Campania, Apulia, Sicily) to 3.9 (Piedmont) for women. Liguria and Friuli Venezia-Giulia have high rates for peritoneal mesothelioma in men (respectively, 5.5 and 4.9), but there were no female cases in 2004. The wide variability of EPMM cases among Italian municipalities is illustrated in figure 1.

Distribution by age differed significantly among anatomical sites. Cases <45 years accounted for only 1.9% in the pleural group, 3.1% in the peritoneal, 11.1% in the pericardial, and 3.2% in the group of testicular MM. In the 25–44-year age group, there were 31 recorded peritoneal cases (as opposed to 15 expected) assuming equal distribution (χ^2 test 264.7; $p<0.001$). Mean age at diagnosis for the overall EPMM cases was 64.4 years (range 18–95) for males and 65.4 years (range 19–94) for females, younger than for pleural MM (respectively, 68.3 years, range 22–97, and 69.5 years, range 30–103).

We interviewed 64.2% of EPMM cases (437/681) to identify their exposure modalities, and 73.1% of pleural MM (6203/8485) (table 2). Just over two-thirds of the peritoneal cases (69.7%, 276/396) had had occupational, environmental, household, or leisure-related exposure, compared with 81.3% of pleural MM with some form of exposure (5040/6203 cases). The proportion was much lower for women (53.1%), and for the combined male/female pericardial group (61.9%). In the latter far more men had a history of exposure (91.7%) than women (22.2%).

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Table 1 Non-pleural malignant mesothelioma (MM) cases collected in the Italian national mesothelioma register (ReNaM) by anatomical site, sex, age, period of diagnosis, level of diagnostic certainty, morphology and modalities of interview, Italy, 1993−2004

	Peritoneum	Pericardium	Tunica vaginalis testis	All non-pleural sites
Sex, n (%)				
M	362 (59)	23 (63.9)	31 (100)	416 (61.1)
F	252 (41)	13 (36.1)	−	265 (38.9)
Age, years, n (%)				
0−44	34 (5.5)	6 (16.7)	5 (16.1)	45 (6.6)
45−64	247 (40.2)	12 (33.3)	5 (16.1)	264 (38.8)
65−74	215 (35)	13 (36.1)	10 (32.3)	238 (34.9)
75+	118 (19.2)	5 (13.9)	11 (35.5)	134 (19.7)
Period of diagnosis, n (%)				
1993−1996	104 (16.9)	5 (13.9)	6 (19.4)	115 (16.9)
1997−2000	205 (33.4)	11 (30.6)	5 (16.1)	221 (32.4)
2001−2004	305 (49.7)	20 (55.6)	20 (64.5)	345 (50.7)
Diagnostic certainty, n (%)				
MM certain	491 (80)	28 (77.8)	31 (100)	550 (80.8)
MM probable or possible	123 (20)	8 (22.2)	−	131 (19.2)
Morphology, n (%)				
Epithelioid	328 (53.4)	10 (27.8)	15 (48.4)	353 (51.8)
Biphasic	53 (8.6)	7 (19.4)	5 (16.1)	65 (9.5)
Sarcomatous	17 (2.8)	2 (5.6)	2 (6.5)	21 (3.1)
MM NAS	167 (27.2)	10 (27.8)	9 (29.0)	186 (27.3)
Not available	49 (8.0)	7 (19.4)		56 (8.2)
Investigated by interview, n (%)				
Direct	152 (24.8)	6 (16.7)	10 (32.3)	168 (24.7)
Indirect	199 (32.4)	14 (38.9)	10 (32.3)	223 (32.7)
No interview	263 (42.8)	16 (44.4)	11 (35.5)	290 (42.6)
Total	614 (100.0)	36 (100.0)	31 (100.0)	681 (100.0)

NAS, not otherwise specified.

The economic sectors and the activities involving exposure to asbestos, their sizes in terms of PY and estimated risks by sector are reported in table 3.

Half the peritoneal MM cases had been exposed to asbestos in the asbestos-cement industry, shipbuilding and repair, heavy industry or construction sectors. The proportion of exposures in the asbestos-cement industry was higher for peritoneal (21.8% of total occupationally exposed subjects) than for pleural MM (4.0%). Figures were similar in the textile industry (9% for peritoneal and 6.3% for pleural) with a higher prevalence of females for peritoneal (75%) than pleural forms (58%).

Mean latency (defined as the time elapsing between the beginning of exposure to asbestos and diagnosis) was estimated for cases with sufficient information and was, respectively, 43.6 and 40.8 years for peritoneal MM in men and women. For the 10 men with pericardial MM it was 41.7, and 46.8 for the 13 cases with the testicular form.

There was a close correlation between pleural and peritoneal mesothelioma in the Italian provinces, with high statistical significance (Pearson's r coefficient 0.71; $p<0.0001$) even though some had high pleural rates but peritoneal rates lower than expected (figure 2). After analysis separately by sex, the correlations remained clearly significant (r 0.63 for men and 0.65 for women; $p<0.0001$ for both). The correlation was weaker between pleural and pericardial and testicular mesothelioma, and did not reach statistical significance (p=0.18 for both comparisons).

DISCUSSION

The ReNaM is one of the largest systems of epidemiological surveillance for malignant mesothelioma in the world. Case lists of peritoneal mesothelioma from a national registration system with identification of individual asbestos exposure modalities are not frequently published, and reports of pericardial or testicular cases are merely episodic. The Italian national programme of MM epidemiological surveillance covers a large part of the country (>340 million PY of observations) including some areas where there was substantial direct use of asbestos in shipbuilding, railway stock construction and maintenance, the asbestos-cement industry, and other industrial settings entailing ample exposure to asbestos in more recent years.

Some limitations regarding the ReNaM dataset need to be discussed. The registry has not been developed uniformly throughout the country. As stated in the Methods, some regions started collecting figures for the incidence even before the national register was set up in 1992; others started later and some are still not participating. Any attempt at assessing the pattern of MM incidence is therefore limited, particularly for EPMM, considering their small numbers. At present it is not possible even to estimate or compare the patterns of pleural and extrapleural mesothelioma incidence. Furthermore, the regions examine asbestos exposure at different levels, depending on their resources and knowledge. The national guidelines intended to standardise the collection of mesothelioma cases do help even out the imbalances, but many of the marked differences between regions persist. In addition, differences in diagnostic procedures make it harder to ensure complete detection for EPMM, and the acceptance of EPMM cases not backed by histological diagnosis implies a larger risk of false-positives than for pleural MM.

The substantial proportion of patients who were not interviewed (35.8% of EPMM cases) is another critical point of the surveillance system. When a long time elapses between diagnosis and the alert to the regional centre, proceeding with the interview becomes more difficult so closing this gap is important. Then too, considering the poor prognosis for this disease it is understandable that an appreciable number of patients will refuse interviews.

The epidemiology of EPMM is complicated by the low sensitivity and the poor specificity of the diagnosis. It is often hard to make a histological distinction between peritoneal epithelioid mesotheliomas and serous carcinomas diffusely involving the peritoneum, though immunohistochemistry and electron microscopy help clear up doubts; a clear distinction could be made between these two malignancies in all cases in which electron microscopy was carried out.[15]

The female component was particularly high for EPMM, with male/female ratios of 1.4:1 and 1.9:1 for peritoneal and pericardium, respectively, and there were 2.7 male pleural MM cases for each female in ReNaM, in agreement with other published case lists.[16]

Pericardial and peritoneal MM systematically have a worse prognosis (median survival 5−6.9 months) than pleural MM (median survival 7.9−10 months). A recent analysis found shorter survival for the most peritoneal MM cases, but at the same time a larger proportion of long-term survivors among these patients: longer survival was associated with female sex, age at diagnosis less than 75, and epithelioid morphology.[17] A

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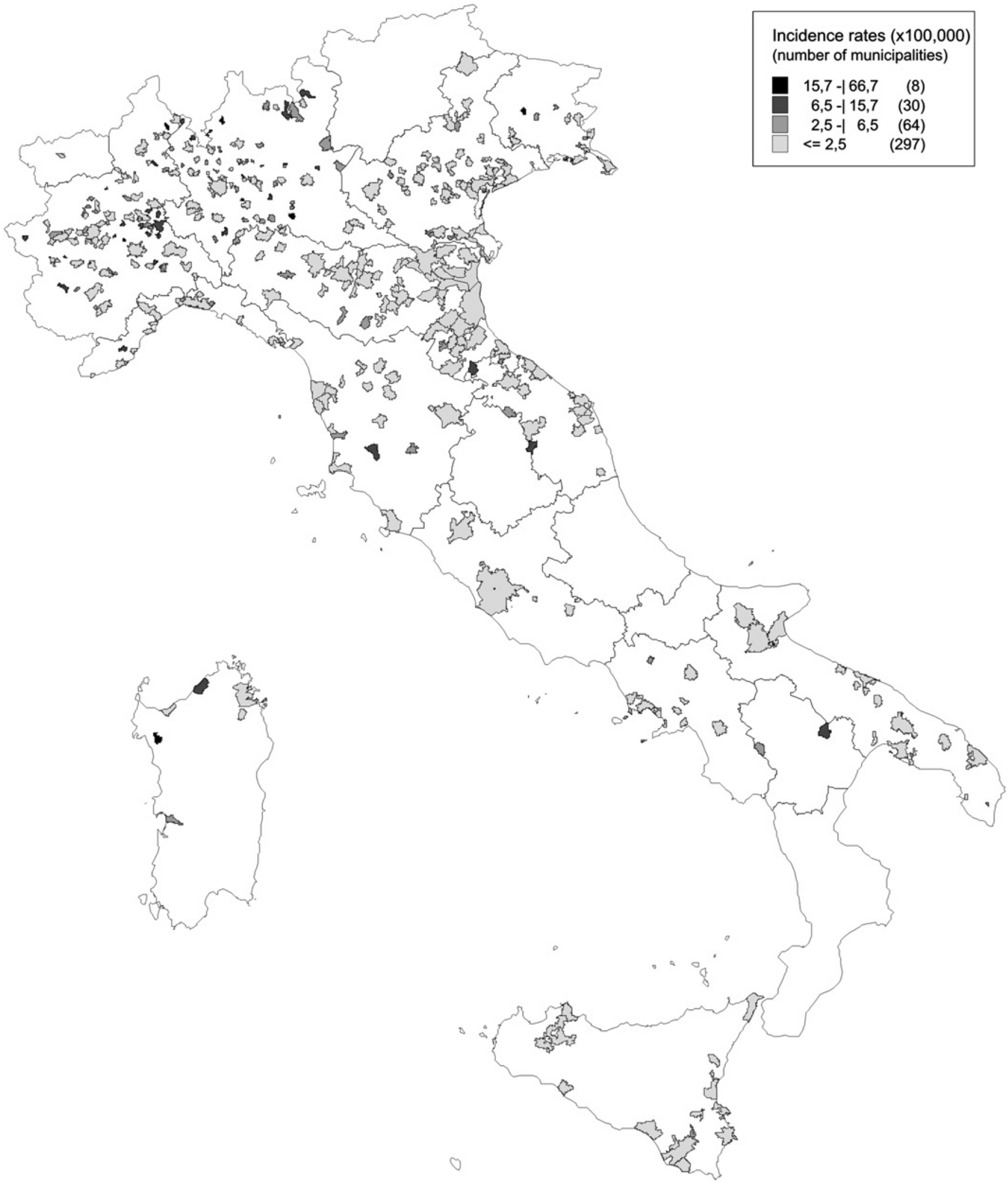

Figure 1 Crude incidence rates of non-pleural cases by Italian municipalities (n=8101). Italian national mesothelioma register (ReNaM). Italy, 1993−2004.

better prognosis for diffuse peritoneal MM has been reported for women, although the reasons are not clear.[18] The many reports of longer survival support the theory of misclassification with ovarian cancer.[12 19]

Epidemiological studies comparing the degree of asbestos exposure with occupation and ultimate site of mesothelioma indicate the peritoneal site as being associated with longer and more intense exposure.[20] Heavy exposures would promote the

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Table 2 Distribution of non-pleural malignant mesothelioma (MM) (number of cases and percentage) collected in the Italian national mesothelioma register (ReNaM) by asbestos exposure, Italy, 1993−2004

		Pleura, n (%)			Peritoneum, n (%)			Pericardium, n (%)			T.V. testis, n (%)
		Men	Women	All	Men	Women	All	Men	Women	All	Men
Asbestos exposure*	Occupational	3872 (82.3)	502 (33.6)	4374 (70.5)	188 (75.5)	50 (34)	238 (60.1)	11 (91.7)	1 (11.1)	12 (57.1)	13 (65)
	Household	48 (1.0)	238 (15.9)	286 (4.6)	2 (0.8)	13 (8.8)	15 (3.8)	—	—	—	—
	Environmental	133 (2.8)	161 (10.8)	294 (4.7)	4 (1.6)	13 (8.8)	17 (4.3)	—	1 (11.1)	1 (4.8)	—
	Leisure-related	41 (0.9)	45 (3.0)	86 (1.4)	4 (1.6)	2 (1.4)	6 (1.5)	—	—	—	1 (5)
	Unknown or improbable	613 (13.0)	550 (36.8)	1163 (18.7)	51 (20.5)	69 (46.9)	120 (30.3)	1 (8.3)	7 (77.8)	8 (38.1)	6 (30)
	Partial total	4707 (100)	1496 (100)	6203 (100)	249 (100)	147 (100)	396 (100)	12 (100)	9 (100)	21 (100)	20 (100)
	On-going	1517 (24.4)	765 (33.8)	2282 (26.9)	113 (31.2)	105 (41.7)	218 (35.5)	11 (47.8)	4 (30.8)	15 (41.7)	11 (35.5)
	Total	6224 (100.0)	2261 (100.0)	8485 (100.0)	362 (100.0)	252 (100.0)	614 (100.0)	23 (100.0)	13 (100.0)	36 (100.0)	31 (100.0)

For detailed classification criteria see: Nesti *et al*[11]; Marinaccio *et al*.[14]

migration of fibres to extrapulmonary sites, but it is still not clear how clearance affects this migration to pleural or peritoneal membranes. Bio-persistency of chrysotile fibres in the lung was shorter than for amphiboles.[21] Nevertheless chrysotile fibres have been observed in omentum and/or mesentery of MM cases, with no apparent breakdown, and some were long (≥5.0 μm), suggesting a role in the pathogenesis of peritoneal MM.[22]

The part played by asbestos exposure in the aetiology of peritoneal MM in women and men was investigated in an incident study in Sweden and the Netherlands. During the past 15 years no trend over time was observed in either country, so a role of occupational exposure to asbestos in peritoneal MM should be limited. In Sweden the higher annual incidence rates and the drop observed around 2000 suggested a previous possible misclassification with other peritoneal tumours in women.[8]

Among the few reports on the epidemiology of MM of the tunica vaginalis testis, between 34% and 41% of cases reported a history of asbestos exposure.[23] In the ReNaM case list we found the proportion of testicular MM with ascertained asbestos exposure (70%) was close to that for pleural MM.

The sectors involved in EPMM aetiology confirm the historical importance of asbestos cement industry and shipbuilding in Italy also considering the limited amounts of employed workers. A substantial sex difference in asbestos exposure was observed for pericardial cases (91.7% in men and 11.1% in women) suggesting a difficulty in investigating occupational, residential and familial history, especially for women. This must be taken into account when discussing any hypothetical difference in the attributable fraction for asbestos. The absence of exposures in the shipbuilding, railway and asbestos-cement industries (the sectors ‘traditionally’ involved in asbestos exposure for pleural MM) for all the 67 pericardial and testicular cases is noteworthy but not easy to interpret and these findings need to be confirmed in a larger sample.

Other risk factors are discussed in the aetiology of pleural mesothelioma such as exposure to different mineral fibres such as erionite or fluoroedenite, ionising radiation and positivity for papovavirus infection.[24−27] Our analysis covering all the Italian provinces provides evidence of a strong, significant correlation between pleural and peritoneal mesothelioma incidence in the general population. This could be due to the high level of territorial disaggregation. Nevertheless, some provinces have a lower peritoneal MM incidence rate than expected, considering the pleural MM incidence, suggesting differences in the capacity for detection of cases. The rarity of EPMM, the low specificity of diagnosis and the problems in identifying the modalities of asbestos exposure limit the possibility of verifying and quantifying the role of these factors. However, the findings of the Italian surveillance system for mesothelioma suggest caution in discussing the role of aetiological factors other than asbestos. The difficulty of clearly identifying occupational exposures in non-industrial work settings, as well as non-occupational

Table 3 Distribution of non-pleural malignant mesothelioma (MM) exposures (number* and percentage) collected in the Italian national mesothelioma register (ReNaM), by anatomical site and economic sector. Industries size as estimated person/years (PY) of observation, Italy, 1993−2004

Economic sector	Peritoneum, n (%)	Pericardium, n (%)	Tunica vaginalis testis, n (%)	Industry size (PY of observation (1000s)
Asbestos-cement industry	58 (21.8)	—	—	30
Building and construction	37 (13.9)	4 (28.6)	3 (18.8)	12540
Metal and steel mechanical industry	26 (9.8)	3 (21.4)	3 (18.8)	11840
Textile	24 (9.0)	1 (7.1)	1 (6.3)	2820
Transport and construction, transport maintenance and repair (no railways or shipbuilding)	17 (6.4)	1 (7.1)	2 (12.5)	5401
Shipbuilding	16 (6.0)	—	—	701
Railway stock	12 (4.5)	—	—	393
National defence	9 (3.4)	—	1 (6.3)	56
Other sectors (all with fewer than eight cases)	67 (25.2)	5 (35.7)	6 (37.5)	NA
All (numbers of exposures)	266 (100.0)	14 (100.0)	16 (100.0)	NA

*Some cases may have had more than one source of exposure.
NA, not available.

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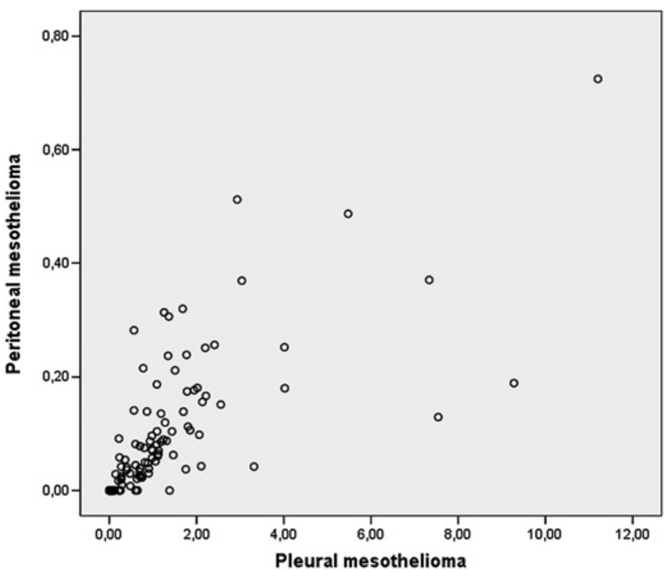

Figure 2 Correlation between pleural and peritoneal mesothelioma raw incidence rates (cases per 100 000 inhabitants) by Italian provinces (N=103). Italian national mesothelioma register (ReNaM). Italy, 1993–2004.

exposure, and the extent of misdiagnosis (which is not easy to quantify) must also be considered in relation to the likelihood of a less close relationship with asbestos for extrapleural MM.

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