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Differences among peritoneal and pleural mesothelioma: data from the Lombardy Region Mesothelioma Register (Italy)

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Key words
Asbestos; mesothelioma; peritoneum

Summary
Background: *The relationship between asbestos exposure and peritoneal mesothelioma (PEM) is under investigation. Some authors suggest that the association could be weaker than that observed for pleural mesothelioma (PLM).* **Objective:** *To compare individual, clinical and exposure characteristics of peritoneal and pleural mesothelioma cases that occurred in the Lombardy Region (Italy).* **Methods:** *Cases were drawn from the regional mesothelioma registry (base population >9 million). We selected all PEM cases diagnosed between 2000 and 2007 (N=110) and all PLM cases that occurred between 2000 and 2001 (N=515). Asbestos exposure data (occupational, environmental/familial, or both) were collected by a standardized and validated questionnaire administered to each case or case's relative. Based on available chest CT scans, we also investigated the concomitant presence of asbestosis and/or pleural plaques as markers of asbestos exposure.* **Results:** *PEM and PLM cases had similar proportions of occupational (around 60%) and environmental/familial (7%) asbestos exposure. The proportion of PEM subjects with co-existent occupational and environmental/familial exposures was, however, twice as high as PLM cases (6.1% vs 3.1%). Asbestosis and pleural plaques were more frequent in PEM than in PLM cases (7.7% and 20.9% vs 0.4% and 12.1%, respectively). No differences were detected for duration of exposure and latency among occupationally exposed cases.* **Conclusion:** *Our findings from a population-based Registry suggest that high cumulative asbestos exposures are the main risk factors not only for pleural but also for peritoneal mesothelioma.*

Riassunto
«Differenze fra i mesoteliomi pleurici e peritoneali: dati dal Registro Mesoteliomi Lombardia (Italia)». **Introduzione:** *Il ruolo dell'esposizione ad asbesto nella patogenesi del mesotelioma peritoneale è ancora controverso con alcuni studi che sembrano suggerire una relazione meno forte rispetto al mesotelioma pleurico.* **Obiettivo:** *Nel presente studio si indagano le caratteristiche individuali, cliniche e la storia espositiva dei casi di mesotelioma pleu-*

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rico e peritoneale raccolti dal Registro Mesoteliomi della Lombardia. **Metodi:** *Sono stati inclusi 110 casi di mesotelioma peritoneale occorsi dal 2000 al 2007 e 515 casi pleurici diagnosticati nel biennio 2000-01. Secondo la procedura del Registro Nazionale Mesoteliomi ed utilizzando un questionario standardizzato ciascun caso è stato classificato rispetto all'eventuale esposizione ad amianto. L'esposizione è poi stata categorizzata in professionale, extra-professionale (ambientale, familiare) o multipla (sia professionale che extra-professionale). Sono state visionate le TAC torace disponibili per il 93% dell'intera casistica, ricercando la presenza di placche pleuriche e/o di asbestosi come possibili indicatori di pregressa esposizione ad amianto.* **Risultati:** *La proporzione di soggetti con documentata esposizione professionale è risultata elevata e simile tra casi peritoneali e pleurici (superiore al 60%), mentre è stata osservata una proporzione doppia di casi peritoneali con esposizione multipla (6% vs 3%). Inoltre sia le placche pleuriche che l'asbestosi sono risultate più frequenti tra i casi peritoneali.* **Conclusioni:** *I risultati del presente studio confermano che l'esposizione ad amianto è la principale causa non solo del mesotelioma pleurico ma anche del peritoneale, e suggeriscono un possibile ruolo di esposizioni elevate nella genesi del mesotelioma peritoneale.*

Introduction

Malignant mesothelioma is a rare and fatal disease that can occur in the pleura, peritoneum, tunica vaginalis of testis and pericardium. The main risk factor is asbestos exposure. Other generally recognized causes of mesothelioma include exposure to erionite, a silicate fibre of the zeolites family which caused an endemic of pleural mesothelioma and lung cancer in Turkey, and to ionizing radiations mainly due to the use of Thorotrast as a radiographic contrast. The attributable risk of asbestos exposure was estimated as up to 80% for pleural malignant mesothelioma (PLM) (15) but was lower for peritoneal mesothelioma (PEM): 58% among men and 23% among women (1, 5). On the other hand, it has been suggested that PEM could occur primarily in workers with higher cumulative exposure and that the risk increases more steeply at high levels of exposure compared with PLM (4). A recent review on PEM suggested that the association with asbestos exposure could be weaker than that observed for PLM (1). Furthermore, Burdorf et al (3) in interpreting the absence of a temporal trend in the incidence rate of peritoneal mesothelioma in Sweden and the Netherlands advocated a less significant role of asbestos in the aetiology of peritoneal cases compared to pleural cases for which an increased incidence is already recognized.

A Regional registry of mesothelioma cases was established in the Lombardy Region (Northern Italy) to collect and investigate all incident cases arising from the resident population since 2000.

We compared exposure history and the main characteristics of PEM and PLM incident cases that occurred in Lombardy in the period 2000-2007.

Methods

All cases were selected from the Lombardy Mesothelioma Registry (LMR), a Regional registry which collects all incident cases of mesothelioma occurring in subjects residing in the region (base population >9.1 million). We selected all PEM cases diagnosed between 2000 and 2007 (No=110) and all PLM cases that occurred between 2000 and 2001 (No=515). We excluded later pleural cases because evaluation of PLM from 2002 may still be on-going and, moreover, we wanted to avoid a potential selection bias when comparing PLMs with PEMs (which were all thoroughly investigated), due to the fact that occupational cases are often reported first, in order to carry out medical-legal procedures.

For all selected cases we retrieved demographic information, gender, age at diagnosis, and histological type (epithelial, fibrous, biphasic or unspecified).

All cases were investigated by the LMR Expert Panel (comprising a pneumologist, an oncologist, a

pathologist, occupational physicians and an industrial hygienists) and classified according to the Guidelines (11) of the National Registry of Malignant Mesothelioma as *Certain*, *Probable* or *Possible* mesothelioma considering clinical records, radiological data and cyto-histological examinations. In particular a mesothelioma was defined as *"certain"* when histological and immuno-histochemical confirmation was available.

Information on asbestos exposure was collected through a standardized questionnaire administered by trained interviewers to the patient or, in fatal cases, to his/her next of kin. A detailed and complete occupational history including industrial sector, patient's job and specific tasks, job task of coworkers and description of workplace was collected to investigate asbestos exposure both in the workplace and in environmental settings. Moreover we obtained residential history, lifestyle habits, hobbies and occupational history of all cases' relatives. Each patient's exposure was classified as *Identified*, *Unknown*, *Unlikely*, and *Not Investigated*, according to potential occupational or environmental asbestos exposure. For cases with *"identified"* exposures we retrieved all sources of asbestos exposure (Occupational, Environmental/Familial, or both), duration of exposure (years) and latency (years since first exposure).

Based on re-examination of chest CT scans, which were available for 93% of the study population, we also investigated the concomitant presence of asbestosis and/or pleural plaques as markers of asbestos exposure.

Statistical analysis

Age-standardized incidence rates of PLM and PEM, stratified by gender, were calculated for the years 2000-2001 and 2000-2007, respectively, using the 14th General Census of the Italian Population (2001) as reference in direct standardization.

Potential differences in individual, clinical and exposure characteristics between PLM and PEM cases were investigated using Fisher's exact test.

All statistical analyses were performed with STATA statistical software version 10.0 (Stata Corp, Austin TX, USA).

Results

Average age-standardized incidence rates (per 1 million inhabitants) of PLM in the years 2000-2001 were 44 (95% CI 38-50) for males and 18 (95% CI 15-21) for females. Lower rates (years 2000-2007) were observed for peritoneal site: 2.3 (95% CI 1.8-2.9) for males and 1.5 (95% CI 1.2-1.9) for females. Incidence rates of PEM remained stable during the whole period with no clear temporal trend for either genders (ranging 1.8-2.9 for males; 1.2-1.9 for females) (figure 1).

Table 1 compares the main characteristics of PEM and PLM cases. PLM cases showed a higher proportion of males (63.9% vs. 51.8%) with a higher males/females ratio than PEM cases (1.8:1 vs. 1.1:1). Mean age at diagnosis of PEM and PLM cases was 66.9 (sd 11.0) and 67.9 (sd 10.8), respectively, with a similar distribution by age class between the two groups. As regards morphology, which was available for 104 (94.5%) PEMs and

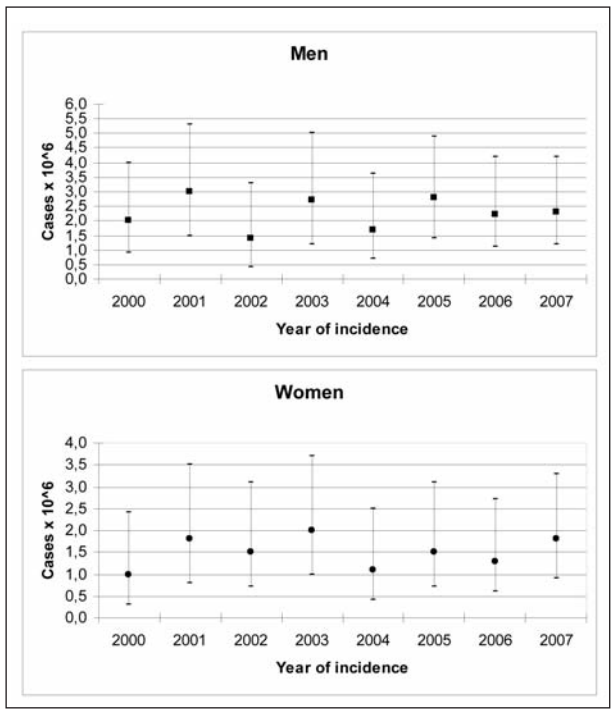

Figure 1 - Age-standardized incidence rates (x 1 million inhabitants) and 95% confidence intervals of peritoneal mesotheliomas in men and women, Lombardy, period 2000-2007

Table 1 - Comparison of the main characteristics (gender, age, morphology, level of diagnostic certainty, and modalities of interview) of peritoneal and pleural mesotheliomas

	Peritoneum (No=110)		Pleura (No=515)		P Value*
	No.	(%)	No.	(%)	
Gender:					
Males	57	51.8	329	63.9	0.018
Females	53	48.2	186	36.1	
Age at diagnosis:					
<45	3	2.7	14	2.7	0.927
45-64	39	35.5	169	32.8	
65-74	40	36.4	187	36.3	
75+	28	25.5	145	28.2	
Morphology:					
Epithelial	67	64.4	272	59.5	0.001
Fibrous	0	0.0	43	9.4	
Biphasic	12	11.5	76	16.7	
Unspecified	25	20.0	66	14.4	
Diagnosis:					
Certain	79	71.8	381	74.0	0.632
Probable	21	19.1	80	15.5	
Possible	10	9.1	54	10.5	
Interview					
Direct	48	43.6	280	54.4	0.115
Indirect	55	50.0	207	40.2	
No interview	7	6.4	28	5.4	

*Fisher's exact test

457 (88.7%) PLMs, the most represented histology was epithelial in both groups; no fibrous mesotheliomas were detected among the peritoneal cases. No differences were observed for level of diagnostic certainty (certain, probable, possible). Interviews were obtained for 103 (93.6%) PEMs and 487 (94.6%) PLMs.

Table 2 summarizes asbestos exposure details. We excluded from evaluation of exposure subjects not interviewed and cases with very poor information on exposure (i.e. *"unclassifiable"*: 4 PEMs and 29 PLMs). For the remaining subjects with good data on exposure (99 PEMs and 458 PLMs), the proportion of cases with recognized exposure to asbestos was 69.8% and 70.5% for PEM and PLM, respectively (p=0.508).

Exposure occurred in the workplace for almost 60% of cases, whereas extra-occupational exposure (environmental or familial) was retrieved for 7.1% of PEM and 7.4% of PLM cases. We also observed similar proportions (30.3% in PEM vs. 29.5% in PLM) of unidentified exposures. The proportion of subjects with both occupational and environmental/familial exposure was, however, twice as high among PEM cases (6.1% versus 3.1%). The observed difference was more evident among men: multiple exposure, both occupational and environmental, was recognised for 9.1% of male PEM vs. 2.7% of male PLM cases; whereas, in females, the prevalence of multiple exposure was similar among PEM and PLM cases. No differences were detected for duration of exposure and latency.

Table 2. Asbestos exposure details: comparison of peritoneal and pleural cases

	Peritoneum, No (%)			Pleura, No (%)			P Value*
	Men	Women	All	Men	Women	All	
Exposure:							
Occupational	38 (69.0)	18 (40.9)	56 (56.5)	213 (70.7)	62 (39.6)	275 (60.0)	0.508
Extra-occupational	3 (5.5)	4 (9.1)	7 (7.1)	14 (4.7)	20 (12.7)	34 (7.4)	
Both	5 (9.1)	1 (2.3)	6 (6.1)	8 (2.7)	6 (3.8)	14 (3.1)	
Unknown or Unlikely	9 (16.4)	21 (47.7)	30 (30.3)	66 (21.9)	69 (43.9)	135 (29.5)	
Duration of exposure (y)°:							
<10	9 (22.0)	4 (21.1)	13 (21.7)	37 (16.7)	18 (26.9)	55 (19.1)	0.241
10-19	8 (19.5)	10 (52.6)	18 (30.0)	32 (14.5)	25 (37.2)	57 (19.8)	
20-29	7 (17.0)	1 (5.3)	8 (13.3)	53 (24.0)	6 (9.0)	59 (20.5)	
>30	17 (41.5)	4 (21.0)	21 (35.0)	99 (44.8)	18 (26.9)	117 (40.6)	
Latency (y)§:							
<30	2 (4.7)	0 (0.0)	2 (3.2)	13 (5.9)	3 (4.5)	16 (5.5)	0.926
30-39	10 (23.3)	3 (15.8)	13 (21.0)	51 (23.0)	8 (11.9)	59 (20.4)	
40-49	15 (34.9)	7 (36.8)	22 (35.5)	77 (34.6)	17 (25.4)	94 (32.5)	
>50	16 (37.1)	9 (47.4)	25 (40.3)	81 (36.5)	39 (58.2)	120 (41.5)	
Asbestosis:							
yes	4 (8.2)	3 (7.1)	7 (7.7)	2 (0.7)	0 (0.0)	2 (0.4)	<0.001
no	45 (91.8)	39 (92.9)	84 (92.3)	305 (99.3)	172 (100)	477 (99.6)	
Pleural plaques:							
yes	14 (28.6)	5 (11.9)	19 (20.9)	36 (11.7)	22 (12.8)	58 (12.1)	0.023
no	35 (71.4)	37 (88.1)	72 (79.1)	271 (88.3)	150 (87.2)	421 (87.9)	

*Fisher's exact test calculated comparing all cases of PEM and PLM
°Available for 60 PEMs and 288 PLMs
§Available for 62 PEMs and 289 PLMs

Based on the re-examination of chest CT scans (available for 91 PEM and 479 PLM cases), the radiological presence of asbestosis or pleural plaques was significantly higher among PEM cases: 7.7% presented asbestosis and 20.9% showed pleural plaques (0.4% and 12.1% among PLM respectively, $p<0.001$). The higher prevalence of pleural plaques was concentrated among male cases only.

Table 3 reports the distribution of cases exposed to asbestos in different occupational sectors. The main difference we highlighted refers to subjects employed in asbestos-cement manufacture, where we found a higher proportion of PEMs (10% vs 1%). In addition, all 5 PLM cases who worked in this sector reported only occupational exposure, whereas 7 out of 11 PEM cases reported both occupational and environmental or familial exposure (they lived within 500 metres of the asbestos-cement plant where they or their cohabiting relatives were working). No detailed information on the type of asbestos used was available, even if a mixed exposure to chrysotile and amphibole can be presumed relying on historical data.

Discussion

In the present study we compared the characteristics of pleural and peritoneal mesothelioma in a large Italian population of subjects residing in the Lombardy Region.

Table 3. Distribution of cases with occupational exposure to asbestos by occupational sectors: comparison of peritoneal and pleural cases

Occupational sector	Peritoneum[§] No. (%)	Pleura[§] No. (%)	Total[§] No. (%)	P value *
Metal engineering industry	6 (5.5)	32 (6.2)	38 (6.1)	0.76
Steel industry	5 (4.6)	42 (8.2)	47 (7.5)	0.19
Oil extraction and refinery	2 (1.8)	4 (0.8)	6 (1.0)	0.31
Ore-mining	1 (0.9)	0 (0.0)	1 (0.2)	0.03
Textile industry	5 (4.6)	67 (13.0)	72 (11.5)	0.01
Synthetic textile industry	1 (0.9)	4 (0.8)	5 (0.8)	0.89
Refractorymaterials manufacture	1 (0.9)	1 (0.2)	2 (0.3)	0.23
Asbestos-cement manufacture	11 (10.0)	5 (1.0)	16 (2.6)	<0.001
Railways	2 (1.8)	6 (1.2)	8 (1.3)	0.58
Construction and maintenance of transport (excluding railways and shipbuilding)	2 (1.8)	17 (3.3)	19 (3.0)	0.41
Food and drink industry	3 (2.7)	7 (1.4)	10 (1.6)	0.30
Sugar refinery	1 (0.9)	1 (0.2)	2 (0.3)	0.29
Chemical and plastics industry	5 (4.6)	12 (2.3)	17 (2.7)	0.19
Rubber industry	1 (0.9)	11 (2.1)	12 (1.9)	0.39
Wood industry (not furniture)	1 (0.9)	3 (0.6)	4 (0.6)	0.70
Furniture manufacture	0 (0.0)	4 (0.8)	4 (0.6)	0.35
Tanning industry	2 (1.8)	0 (0.0)	2 (0.3)	0.03
Glass and ceramics industry	1 (0.9)	2 (0.4)	3 (0.5)	0.47
Paper industry	0 (0.0)	4 (0.8)	4 (0.6)	0.35
Other manufacturing industries	1 (0.9)	9 (1.8)	10 (1.6)	0.52
Jewellrymanufacture	0 (0.0)	4 (0.8)	4 (0.6)	0.35
Building/construction	11 (10.0)	78 (15.2)	89 (14.2)	0.16
Production of electricity and gas	0 (0.0)	6 (1.2)	6 (1.0)	0.25
Recycling	0 (0.0)	1 (0.9)	1 (0.2)	0.64
Agriculture and livestock	1 (0.9)	2 (0.4)	3 (0.5)	0.47
Hotels/restaurants/bars	0 (0.0)	1 (0.9)	1 (0.2)	0.64
Commerce	2 (1.8)	8 (1.6)	10 (1.6)	0.84
Transport	2 (1.8)	9 (1.8)	11 (1.8)	0.96
Public administration	0 (0.0)	2 (0.4)	2 (0.3)	0.51
Education	0 (0.0)	2 (0.4)	2 (0.3)	0.51
Military defence	2 (1.8)	5 (1.0)	7 (1.1)	0.44
Bank/post office/insurance	0 (0.0)	1 (0.9)	1 (0.2)	0.64
Healthcare	1 (0.9)	8 (1.6)	9 (1.4)	0.61
Other	6 (5.5)	5 (1.0)	11 (1.8)	<0.001

*Fisher's exact test

[§]Multiple exposures for each case are possible

Age-standardized incidence rates (per 1 million inhabitants) were similar to the National Italian rates for PEM (National rates: Males=2.1, Females=1.2) whereas they were slightly higher for PLM (National rates: Males=34.2, Females=10.9) (7,8), thus confirming the well-known widespread use of asbestos in the Lombardy Region. As reported in other studies, PEM rates were much lower than PLM rates and were stable over time (1, 3, 10).

PLM occurred more frequently among men, whereas the male/female ratio was close to unity for PEM, as observed in other populations (3, 7, 8). The observed differences in the male/female ra-

tio comparing PEM and PLM were attributed by some authors to the risk of misdiagnosis of PEM among women suffering from peritoneal carcinosis due to metastasis of ovarian cancer (13, 16). In our population, this potential misclassification bias was resolved by studying the complete case history and all available clinical data including radiological and histological reports. Furthermore the proportion of women with recognized asbestos exposure was similar in pleural and peritoneal cases.

Although recent studies suggested a weaker relationship between asbestos exposure and PEM cases (1), and Burdorf et al. speculated that the absence of an emerging increasing incidence of PEM cases could be due to "*a more limited role of occupational asbestos exposure in the aetiology of PEM*" (3), we observed a similar proportion of occupational and extra-occupational exposures to asbestos in PEM and PLM cases.

Our data seem to confirm an elevated asbestos exposure in PEM cases as demonstrated in other epidemiological studies (2, 4, 5, 12, 14, 15). Indeed, a higher proportion of PEM cases was characterized by both occupational and extra-occupational exposure and by radiological markers of such exposure (asbestosis and pleural plaques).

The distribution of subjects with occupational exposure to asbestos by industrial sectors was similar in PEM and PLM with the exception of asbestos-cement production. The proportion of PEM cases employed in this industry was almost ten times higher than PLM cases. A similar finding was recently described by the Italian Mesothelioma Registry (8).

The results we observed in the asbestos-cement plant under study, where both chrysotile and amphibole were used, were also concordant with the review conducted by Boffetta, who suggested a higher attributable fraction of mixed exposure for PEM rather than for PLM.

The exact mechanisms linking asbestos exposure to peritoneal mesothelioma is not completely understood. Researchers speculated on the possible role of retrograde lymphatic drainage that could move fibres from the pleural to the peritoneal cavity in the presence of asbestosis (2), or a penetration through the gastrointestinal tract that may occur in cases of heavy exposure (6), or again a direct diffusion of asbestos fibres into the blood stream and subsequently into the whole body (9).

In conclusion our findings suggest that asbestos exposure is the main risk factor not only for PLM but also for PEM. Any effort to identify unknown sources of exposure is therefore justified in terms of public health. The possible role of high levels or multiple sources of exposure in determining PEM cases, as suggested by our results, needs to be confirmed and requires further investigation.

No potential conflict of interest relevant to this article was reported

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