



Peritoneal mesothelioma mortality in Italy: Spatial analysis and search for asbestos exposure sources



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ABSTRACT

Background: This study is part of a national plan of epidemiological surveillance of malignant mesothelioma (MM) mortality in Italy. The paper shows the results of malignant peritoneal mesothelioma (MPeM) mortality study in Italian Regions and municipalities.

Methods: National Bureau of Statistics data for MPeM municipal mortality (ICD-10, Code C45.1) were analyzed in the time-window 2003–2014: mortality standardized rates (reference Italian population, census 2011), temporal trends of the annual national rates, Standardized Mortality Ratios and a municipal clustering analysis were performed.

Results: 747 deaths for MPeM were recorded (0.10/100,000): 464 in men (0.14/100,000) and in 283 women (0.07/100,000). No significant MPeM mortality temporal trend was found.

Seventeen municipalities showed excesses of mortality for MPeM in at least one gender and/or overall population.

Four clusters in male population, and one in women were identified.

Conclusions: The study identifies some areas where remediation activities and/or health care actions may be warranted.

1. Introduction

Main risk factors for Malignant Mesothelioma (MM) are the occupational or non-occupational exposures to all types of asbestos fibres; erionite, talc or vermiculite contaminated with asbestos fibres also cause MM [1]. Non-occupational cases includes familial, environmental, leisure activities exposures. Environmental exposure to fluoro-edenite fibres occurred in Biancavilla, Italy, has been recently recognized to determine MM [2].

In an analysis of 50 European and USA populations, the incidence rates of Malignant Peritoneal Mesothelioma (MPeM) in men were one order of magnitude lower than those of Malignant Pleural Mesothelioma (MPM). Age-standardized incidence rates among men range from 0.5 to about 3 cases per million of inhabitants. In most populations, rates among women are in the range 0.2–2 per million and are lower than in men [3]. Different estimates of the proportion of MPeM cases with previous asbestos exposure can be found in the scientific literature. According to Cao et al, nearly 90% of MPeM is associated with asbestos exposure [4]; other Authors state that only

33–50% of patients diagnosed with MPeM report any known prior exposure to asbestos [3,5]. Attributable fractions for asbestos and MPeM of 58–75% among men and 23–33% among women were reported [6]. Marinaccio et al. on the basis of the Italian National Register of Malignant Mesothelioma (ReNaM) database, calculated that in 2014 Italian incidence rates of MPM in men and women were respectively 3.26 and 0.87 per 100,000 inhabitants, and 0.17 and 0.10 for MPeM [7]. The same Authors found that the percentages of female cases for MPM and MPeM were respectively 27.4 and 41.3. In ReNaM the proportion with definite asbestos exposure is 70% for MPeM vs 80% for MPM [8]. The evidence that asbestos exposure is related to the development of MPeM is stronger in men than in women [9] because of more chances of previous occupational asbestos exposure, but probably also for less potential misclassification in men than in women, for ovarian cancer, and other abdomen contiguous tumours, [10–12]. It has to be underlined that occupational exposure is more easily identified through structured questionnaires, while environmental exposure, and non-occupational exposure in general, may be unknown to the interviewed subject, thus leading to an increased number of cases with unknown/

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not probable exposure [13].

Occurrence of MPeM has been associated with high asbestos exposure, corresponding to the observation of high lung asbestos burden of MPeM cases [14]. Mensi et al. have recently hypothesized the same association observing in Lombardy, Italy, a higher proportions of asbestosis and of past employment in the asbestos-cement sector among MPeM cases [15]. After asbestos exposure, risk of MPeM shows a continuous increase, while MPM shows a flattening of the increase of risk after 40–50 years of latency [16].

In Italy, before the asbestos ban in 1992, about 3,748,550 tons of raw asbestos were mined, with a peak production of more than 160,000 tons/year (1976–1980); asbestos consumption began to decline in the late Eighties, some 10–20 years than in other European countries [17].

The present study is a part of national plan of epidemiological surveillance of MM mortality in Italy, on-going since 1992. The results for all mesotheliomas and for MPM are shown elsewhere [18]. This paper shows the results of MPeM mortality study in Italian Regions and municipalities, performed for the first time at national level, in 2003–

2. Materials and methods

Materials and methods have already been described in detail elsewhere [18]. Briefly, National Bureau of Statistics (ISTAT) data for MPeM municipal mortality (ICD-10, Code C45.1), were analyzed in the time-window 2003–2014, the period of available mortality data with a specific diagnostic code for malignant mesothelioma (ICD-10) in Italy at national level.

The country was divided into geographical macroareas, as defined by ISTAT: North-East (NE), North-West (NW), Centre (C), South (S), and two main islands, considered separately (Sicily, Si, and Sardinia, Sar). Mortality standardized rates (direct method, Italian population as reference, census 2011, <http://seriestoriche.istat.it/>), and their 95% Intervals of Confidence (95% CI), in overall population and by genders, were computed for macro-areas. The temporal trends of the annual national rates were calculated.

Standardized Mortality Ratios (SMRs), with the corresponding 95% Confidence Intervals (95% CIs), for each of the 8,047 Italian municipalities were elaborated, with respect to the regional figures. Regional reference rates were used in the calculation of expected figures, taking into account the geographic differences in population features and mortality experiences, for which the regional population is more similar than the national to that one of its municipalities. The 95% CIs were estimated based on Poisson's distribution.

A municipal clustering analysis identified the areas with major departures from expected figures. The analysis was performed according to the procedure Spatial Scan Statistics, using SatScan software (version 9.4.4), assuming a Poisson model for the distribution of the cases in each municipality. The clustering was performed in each geographical macro-areas (North-East, North-West, Centre, South, Sicily, Sardinia) separately.

Each municipality was identify by x, y coordinates of its townhall (centroid). The Relative Risk is the estimated risk within the cluster divided by that one outside of the cluster. We selected the clusters with the p-value < 0.10.

3. Results

In Italy, in 2003–2014 period, the deaths from MPeM were 747 (0.10/100,000): 464 in men (0.14/100,000) and 283 in women (0.07/100,000).

No significant MPeM mortality temporal trend was found, probably due to the low number of cases (Fig. 1).

17 municipalities showed excesses of mortality for MPeM in at least one gender and/or overall population, based on at least three cases (Table 1). Table 1 shows, for each of those, observed cases and SMR

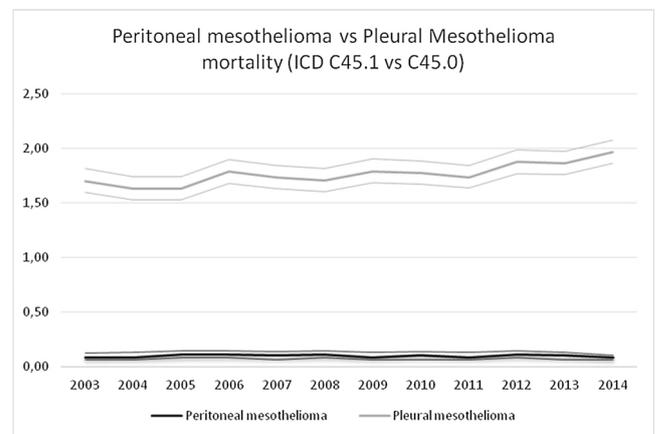


Fig. 1. Mortality for malignant pleural mesothelioma and malignant peritoneal mesothelioma in.

Italy: temporal trend of standardized rates (*100,000; 95% Confidence Interval), 2003–2014.

(95%CI) for MPeM, MPM and MM mortality.

Fig. 2 shows MPeM mortality significant clusters ($p < 0.10$): three in NW Regions (men in Casale Monferrato and Sestri Levante, women in Chiuro); one (men) in NE (Ronchi dei Legionari) and one (men) in Southern Regions (Castellammare di Stabia).

No significant clusters were found in Centre, Sicily and Sardinia.

Standardized rates were calculated for macro-areas, and compared to Italian overall rates (Standardized Relative Risks), showing higher values in NW (Table 2). Data show a north-south gradient.

4. Discussion

Our studies found that the MPeM deaths are 4.6% of the overall deaths for MM, corresponding to 4.0% in men and 6.1% in women [18]. The rates of mortality for MPeM are lower than those of incidence reported by Magnani et al for the year 2008 [19] and in the range reported by Boffetta in 50 European and USA populations [3]; gender ratio M/F for MPeM mortality (1.64) is higher than that reported by Conti et al. [10] for the years 1995–2010.

Considering the availability of the Italian ReNaM, some information may be considered in order to highlight the peculiarities of the MPeM mortality epidemiology, and to interpret the present results.

The Italian ReNaM, which covers almost completely the Italian country, provides accurate information on MM based on its permanent epidemiological surveillance system: incidence of malignant mesothelioma, recorded cases' asbestos exposures, impact of the disease at the population level and evaluation of any possible underestimated or unknown source of asbestos contamination. Surveillance systems comparable to ReNaM are scarce, being currently active in Australia, France and South Korea.

In a recent ReNaM publication, 21,398 collected cases (1993–2012) were analyzed studying gender differences and asbestos exposure modalities [20]. Gender ratio (M/F) was 2.63 for pleural cases, and 1.43 for peritoneal cases. MPeM were 1,392 (817 males, 575 females) out of 21,398 recorded cases (6.5%). Modalities of asbestos exposure were studied for 16,458 cases (76.9%). Referring to MPeM, asbestos exposure information were not available for, respectively, 222 and 184 cases. Out of the remaining 986 cases (595 males, 391 females), the exposures were as follows: occupational (576 cases: 444 males, 132 females), familial (47 cases: 4 males, 43 females), environmental (40 cases: 16 males, 24 females), due to leisure activities (15 cases: 7 males, 8 females). For 308 cases (124 males, 184 females) asbestos exposure was not identified (unknown/not attributable, following ReNaM definitions). MPeM gender ratios (M/F) for cases with ascertained exposure were as follows: 3.33 for occupational cases, 0.36 for non-occupational

Table 1
Mortality for malignant peritoneal mesothelioma, 2003–2014: significant SMRs, with at least 3 cases.

REGION	MUNICIPALITY	MALIGNANT PERITONEAL MESOTHELIOMA						MALIGNANT PLEURAL MESOTHELIOMA									
		MEN			WOMEN			OVERALL			MEN			WOMEN			
		OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI	
PIEMONTE	Grugliasco	< 3			3	826	281	2429	5	527	225	1233	12	115	66	200	10
PIEMONTE	Casale Monferrato	17	2948	1841	4722	799	2350	20	2059	1333	3181	185	1793	1552	2070	146	
LIGURIA	Sestri Levante	5	1212	518	2839			5	1022	436	2392	7	47	23	98	3	
LOMBARDIA	Sondrio	3	1395	474	4102			3	739	251	2172	< 3				4	
LOMBARDIA	Broni	3	2831	963	8323			4	2036	792	5237	40	1619	1189	2205	33	
LOMBARDIA	Lecco	3	614	209	1804			3	334	114	982	9	80	42	152	7	
FVG	Gorizia	3	343	117	1008			3	248	84	728	11	81	45	145	7	
FVG	Ronchi Legionari	4	1483	577	3813			5	1402	599	3281	22	530	350	802	3	
E. ROMAGNA	Fidenza	3	1534	522	4510			3	826	281	2428	3	65	22	192	4	
E. ROMAGNA	Bologna	3	100	34	294	254	525	10	173	94	318	89	125	102	154	28	
E. ROMAGNA	Forlì	3	328	112	965			3	180	61	528	20	94	61	145	10	
TOSCANA	Firenze	4	135	53	348	272	638	9	185	97	352	39	65	48	90	17	
TOSCANA	Livorno	6	460	211	1004			7	337	163	696	102	400	330	486	22	
CAMPANIA	C.mare Stabia	4	831	323	2136			4	589	229	1514	24	476	320	708	< 3	
CAMPANIA	Avellino	< 3						3	466	158	1370	< 3				< 3	
PUGLIA	Bari	7	491	238	1013			9	362	191	689	69	186	147	235	42	
SICILIA	Siracusa	< 3						3	366	124	1076	33	302	215	424	6	

REGION	MALIGNANT PLEURAL MESOTHELIOMA						MALIGNANT MESOTHELIOMA OVERALL											
	WOMEN			MEN			OVERALL			WOMEN			MEN			OVERALL		
	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS
PIEMONTE	191	104	352	22	141	93	214	113	67	190	17	276	172	442	31	168	119	239
PIEMONTE	2392	2034	2813	331	1971	1770	2196	1727	1509	1976	153	2134	1822	2500	364	1836	1657	2035
LIGURIA	87	30	255	10	55	30	101	16	59	156	5	126	54	296	21	102	67	156
LOMBARDIA	132	51	339	6	75	34	164	85	36	199	4	107	42	275	9	91	48	173
LOMBARDIA	2203	1569	3094	73	1822	1449	2291	1631	1237	2150	35	1897	1364	2638	85	1714	1386	2119
LOMBARDIA	104	50	214	16	88	54	143	114	70	186	8	96	49	190	24	107	72	159
FVG	261	126	538	18	106	67	168	94	57	155	8	246	125	486	23	115	77	173
FVG	399	136	1174	25	507	343	748	576	399	833	4	439	171	1130	32	551	390	778
E. ROMAGNA	235	91	604	7	110	53	227	145	74	286	4	184	72	473	12	155	88	270
E. ROMAGNA	98	68	142	117	114	95	137	105	101	149	40	110	81	150	145	116	98	136
E. ROMAGNA	131	71	241	30	104	73	148	105	72	153	12	123	70	215	39	110	81	151
TOSCANA	93	58	149	56	70	54	91	52	54	93	24	99	66	147	76	75	94	94
TOSCANA	302	199	457	124	374	313	445	369	308	442	26	269	183	394	142	341	290	402
CAMPANIA				24	345	232	513	506	366	701	3	120	41	352	39	402	294	549
CAMPANIA				4	60	23	153	89	41	194	5	203	87	475	11	117	66	210
PUGLIA				318	235	430	263	180	145	222	52	302	230	396	136	211	178	249
SICILIA				192	88	418	380	279	204	382	7	166	80	343	46	253	190	338



Fig. 2. Mortality for malignant peritoneal mesothelioma: statistically significant clusters among men and women. 2003–2014.

- Ticineto, Casale Monferrato.
- Sestri Levante.
- Chiuro, Piateda.
- Cormons, Villesse, Gorizia, Ronchi dei Legionari.
- Castellammare di Stabia, Gragnano, Vico Equense, Pompei.

cases, 0.09 for familial cases, 0.67 for environmental cases. The Authors underlined the outlier Italian situation within the international context for the higher percentage of female cases for MM than expected: about 28% of Italian MM cases occurs among women, and female percentage among recorded MPeM is 4.13%. The high number of female mesothelioma cases is due to the relevance of non-occupational exposures and to the historically high female workforce in chemical and plastic industries, and mainly in non-asbestos textile sector (40% of pleural and peritoneal MM female cases of occupational origin). Regarding the role of environmental exposure, they corroborate what other Authors are discussing for MM in general, and for MPeM in particular [21–26]. Our study on mesothelioma risk in Biancavilla, a Sicilian town located in area where amphibole fluoro-edenite fibres are present in the environment, found a standardized incidence ratio for MPeM, two cases, (SIR = 7.92, 95% CI: 0.96–20.00), higher than that for MPM (SIR = 5.76, 95% CI: 3.76–8.44) [27].

The higher percentage of MPeM in all MM cases in the female population with respect to the males could be due, in part, to the role of the misclassification of the ovarian tumours, as well as of other abdomen contiguous tumours [10–12]. Ovarian tumours are much more frequent than MPeM and were reported in 2008 as the second leading cause of gynaecological cancer death worldwide [28]: therefore a small percentage of cases of a more frequent cancer misclassified as cases of a

very rare cancer could decrease the ratio [10].

The higher rates in Northern macro-areas is in agreement with the industrial history of our country, with the main industrial settings located in these Regions.

Regarding the municipal analysis of mortality for MPeM, 17 municipalities showed significant SMRs in excess (with 3 or more cases), in at least one gender (or in overall population).

Ten municipalities out of 17 were located in NW and NE Regions. Apart from Casale Monferrato (asbestos-cement plant that constituted the majority of the workforce), no other municipalities showed excesses in both genders (Table 1).

In 3 municipalities (2 in NW and NE, one in C) the excess was detected in only women: in one of these (Bologna) railway carriages construction and repair activities are located), textile industry in Firenze and Grugliasco; in the latter, where the industry used asbestos-materials, also MM and MPM excesses were found only in women [18] widely employed in textile industry.

Excesses of MPeM mortality in male population only were detected in eleven municipalities. In 8 out of these, activities representing known sources of asbestos exposure were identified: asbestos-cement plants operating in the past in Broni and Bari, shipyards in Sestri Levante, where one of the oldest and biggest Italian shipyards has been operating since 1898, shipbuilding and repair in Ronchi de' Legionari, Gorizia, Livorno and Castellammare di Stabia; Fidenza is close to a municipality where an old oil refinery was located. In these industries the work-force was characterized by a high percentage of men. In 3 municipalities with excess of MPeM mortality in male population no asbestos exposure sources have been identified. An asbestos-cement plant was operating in the past in Syracuse, and a railway carriages asbestos removal facility in Avellino, where the excesses were observed in overall population. The excesses in areas characterized by the presence of shipyards and shipbuilding and repair are in agreement with the several articles that have documented the presence of asbestos-containing materials in vessels and the risk of mesothelioma in ship-workers, as reported in previous paper [18].

Cluster analysis, besides confirming some findings of SMR municipal analysis, i.e. the excesses in Casale Monferrato, Sestri Levante, Gorizia and Castellammare, provided evidence of excess risk in Chiuro, near a talc mine operating in the past. Three clusters (Casale Monferrato, Gorizia, Castellammare di Stabia) correspond to the areas that generated significant clusters of MPM mortality [18], even if including a lower number of municipalities.

The present first investigation of MPeM mortality, by municipality of residence at national level detected significant excesses in areas with higher frequency of MPM and, supposedly, with higher impact of asbestos, in agreement with the literature [14]. In a few cases, the excess of MPeM was not associated with a concurrent MPM excess. Our results concerning Northern Italy are consistent with the location of major industrial settings in this area of the country.

5. Conclusions

In general terms, most municipalities where excesses of MPeM were observed are also characterized by excesses of MPM. One hypothesis is that asbestos exposure levels might have been particularly elevated [29]. The present results confirm the need to include in the national epidemiological surveillance plan of MM mortality, MPM and MPeM, separately. Considering the peculiarities of MPeM epidemiology, it is warranted to develop a specific focus on MPeM mortality, using the information of concordance (or lack of concordance) with MPM mortality integrated with the incidence date of ReNaM, in order to advance in the understanding of determinants of mesothelioma sites in asbestos carcinogenicity.

Table 2

MPeM mortality age-standardized rates (*100,000) by macroareas and gender (2003–2014), and standardized relative risks. Reference Italian population, census 2011.

MacroArea	Gender	Obs	SR (95% CI)	SRR (95% CI)
NW	men	195	0.23 (0.2-0.27)	1.52 (1.28-1.8)
	women	118	0.11 (0.09-0.13)	1.48 (1.19-1.83)
	overall	313	0.16 (0.14-0.18)	1.5 (1.31-1.71)
NE	men	88	0.15 (0.12-0.19)	0.97 (0.77-1.22)
	women	61	0.08 (0.06-0.11)	1.09 (0.82-1.44)
	overall	149	0.11 (0.09-0.13)	1.01 (0.85-1.21)
Centre	men	82	0.13 (0.1-0.17)	0.86 (0.68-1.1)
	women	49	0.07 (0.05-0.09)	0.87 (0.64-1.19)
	overall	131	0.09 (0.08-0.11)	0.87 (0.72-1.05)
S	men	73	0.11 (0.09-0.14)	0.74 (0.57-0.95)
	women	41	0.05 (0.04-0.07)	0.68 (0.48-0.95)
	overall	114	0.08 (0.06-0.09)	0.71 (0.58-0.87)
Si	men	24	0.1 (0.06-0.16)	0.65 (0.42-1)
	women	10	0.03 (0.02-0.06)	0.45 (0.22-0.94)
	overall	34	0.06 (0.04-0.09)	0.57 (0.4-0.82)
Sa	men	2	0.02 (0-0.12)	0.15 (0-1267.28)
	women	4	0.04 (0.01-0.1)	0.51 (0.1-2.54)
	overall	6	0.03 (0.01-0.07)	0.29 (0.1-0.82)
ITALY	men	464	0.15 (0.14-0.17)	
	women	283	0.08 (0.07-0.08)	
	overall	747	0.11 (0.1-0.12)	

Legend Obs: Observed cases SR: Standardized Rates CI: Confidence Interval SRR: Standardized Relative Risk (each macro-area's rate vs Italy).

Conflict of interest

All authors declare that there are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Author statement

Amerigo Zona: Conception and design, interpretation of data, drafting and revising the article.

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All authors approve the final version to be published.

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