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Geographical patterns of mesothelioma incidence and asbestos exposure in Lombardy, Italy

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Mesothelioma incidence; cancer registry; asbestos; geographical pattern

Parole chiave
Incidenza di mesotelioma; registro tumori; amianto; distribuzione geografica

Summary
Background: *Measuring malignant mesothelioma (MM) occurrence is a useful means to monitor the impact of past asbestos exposure and possibly identify new sources of asbestos exposure.* **Objectives:** *Aim of this study is to describe the results of the MM registry of the Lombardy Region, North-West Italy, the most populated (currently, 10 million inhabitants) and industrialised Italian region.* **Methods:** *We extracted from the Lombardy Region Mesothelioma Registry (Registro Mesoteliomi Lombardia, RML) database all incident cases of MM (pleura, peritoneum, pericardium, and tunica vaginalis testis) with first diagnosis in 2000 through 2012. For each Province, we calculated crude and standardised incidence rates using Italy 2001, European, and world (Segi's) standard populations. To examine spatial patterns of MM occurrence across municipalities we drew maps of crude rates smoothed according to the Besag, York and Mollié (BYM) method.* **Results:** *We recorded 4442 MM cases (2850 in men and 1592 in women), representing about one fourth of MM cases occurring in Italy. Occupational exposure was more frequent in men (73.6%) than in women (38.2%). The crude regional rates were 4.7 per 100,000 person-years in men and 2.5 per 100,000 person-years in women. The highest rates were observed in the Pavia Province (crude rates: 8.7 per 100,000 in men and 5.3 and per 100,000 person-years in women).* **Conclusions:** *This study documented high MM occurrence in both genders, attributable to extensive asbestos exposure in the past.*

Riassunto
«Distribuzione geografica dell'incidenza di mesotelioma e dell'esposizione ad amianto in Lombardia». **Introduzione:** *La misurazione della frequenza di mesotelioma maligno (MM) è un mezzo adeguato per monitorare l'impatto della pregressa esposizione ad amianto e possibilmente identificare nuove fonti di esposizione ad amianto.* **Obiettivi:** *Scopo dello studio è quello di descrivere i risultati del registro mesoteliomi della Regione Lombardia, la*

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più popolata (attualmente, 10 milioni di abitanti) ed industrializzata regione italiana. **Metodi:** *Dall'archivio del Registro Mesoteliomi Lombardia (RML) sono stati estratti tutti i casi incidenti di MM (pleura, peritoneo, pericardio e tunica vaginale del testicolo) con prima diagnosi tra il 2000 e il 2012. Per ogni Provincia sono stati calcolati i tassi di incidenza grezzi e standardizzati utilizzando le popolazioni standard italiana 2001, europea e mondiale (Segi). Per esaminare la distribuzione spaziale della frequenza di MM per comune sono state create mappe di tassi grezzi lisciati secondo il metodo di Besag, York and Mollié (BYM).* **Risultati:** *Sono stati registrati 4442 casi (2850 negli uomini e 1592 nelle donne), corrispondenti a circa un quarto di tutti i casi in Italia. L'esposizione occupazionale era più frequente negli uomini (73,6%) rispetto alle donne (38,2%). I tassi grezzi regionali erano 4,7 per 100.000 anni-persona negli uomini e 2,5 per 100.000 anni-persona nelle donne. I tassi più elevati sono stati osservati in Provincia di Pavia (tassi grezzi: 8,7 per 100.000 anni-persona negli uomini e 5,3 per 100.000 anni-persona nelle donne).* **Conclusioni:** *Il presente studio ha documentato una elevata incidenza di MM sia tra gli uomini che tra le donne, attribuibile alla grande pregressa esposizione ad amianto.*

Introduction

Asbestos is a recognised cause of malignant mesothelioma (MM), lung, laryngeal, and ovarian cancer, while evidence regarding the association with other cancer sites (pharynx, stomach, colon, and rectum) is considered limited (21). All forms of asbestos possess carcinogenic properties, although with different potencies (with regard to MM, amphiboles are more potent than chrysotile) (10, 23, 25). In addition, asbestos causes non-neoplastic diseases, including asbestosis, pleural effusions, and diffuse pleural thickening (49). It has been estimated that worldwide every year more than 100,000 people die from MM, lung cancer, or asbestosis (44).

The great majority of MM cases are caused by asbestos (or other asbestiform fibers, like erionite and fluoro-edenite). In absence of asbestos, a background incidence rate of 1-2 per million person-years has been estimated (10, 30). Over 90% of MM originate from pleura, <10% from peritoneum, and very rarely from pericardium and tunica vaginalis testis (26). Prognosis after pleural MM diagnosis is very poor, with median survival time ranging from 5.0 to 13.2 months in population-based studies (37).

Several countries established MM registries to monitor MM incidence over time, identify sources of asbestos exposure, provide medico-legal assistance to patients and their families, evaluate survival, and forecast future trends of MM incidence (20, 28, 39, 50). Italy has been using large quantities of chrysotile and amphiboles (>3.5 million tons produced or imported from 1945 to the 1992 ban) and is currently among the countries with the highest MM frequency worldwide (27, 41, 48). In 2002, a national MM registry (*Registro Nazionale Mesoteliomi, ReNaM*) has been set up, organised as a network of regional registries (*Centri Operativi Regionali*, COR), some of which had started activities earlier (26, 28, 38).

The Lombardy region, North-West Italy is the most populated (currently, 10 million inhabitants, one-sixth of the Italian population) and industrialised of the 20 Italian regions. It is the fourth largest Italian region, covering an area of 23,844 km^2, with 12 Provinces and 1546 municipalities (figure 1). The territory can be divided in four zones, from North to South: the Alps (mostly in the Province of Sondrio) with a low population density, the Pre-Alps (covering the Northern parts of the Provinces of Varese, Como, Lecco, Bergamo, and Brescia), the Po Valley, and a small hilly area (Apennines mountains) South-West (Province of Pavia). The Po Valley includes a Northern highly industrialised area (Provinces of Varese, Como, Milan, Monza and Brianza, Bergamo, and Brescia) and a Southern mainly rural area (Provinces of Pavia, Lodi, Cremona, and Mantua).

In Lombardy a regional MM registry (*Regi-stro Mesoteliomi Lombardia,* RML was established in 2000. Using RML data for the period 2000-2012 we recently described temporal patterns and made projections of MM incidence in the future decades (31). Our aim in the present paper is to describe for

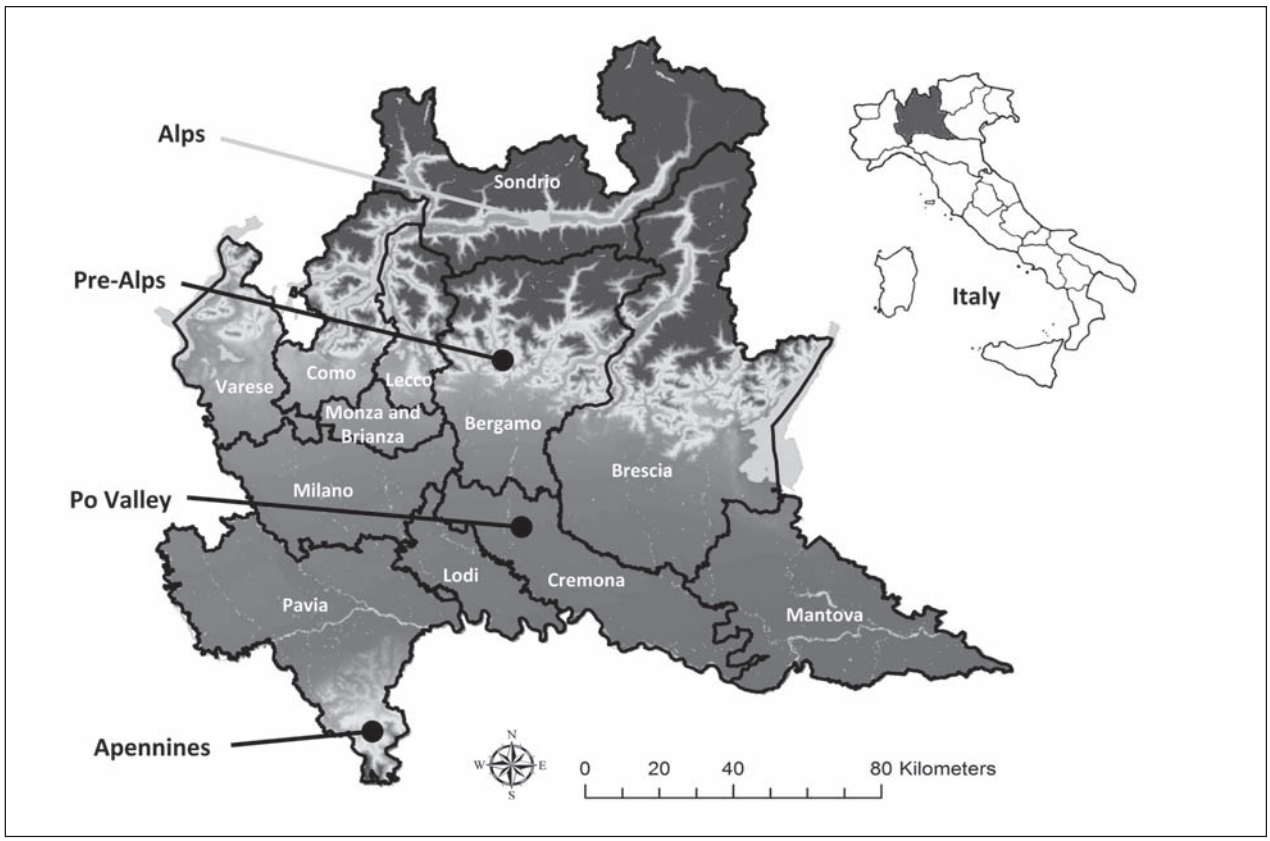

Figure 1 - Map of Lombardy Region, North-West Italy

the same period the geographical patterns of MM incidence and asbestos exposure, including their distribution across Provinces and municipalities.

Methods

Ascertainment of mesothelioma cases

The RML collects all MM cases of the pleura, peritoneum, pericardium, and tunica vaginalis testis reported among Lombardy residents at the time of diagnosis (36). In Italy, reporting of MM cases is compulsory (laws 277/1991 and 81/2008): the pathology, pneumology, surgery, and oncology departments of more than 100 hospitals in the region report suspected MM cases to the RML. Completeness of reporting is periodically verified using several sources, including pathology, hospital admission (within and outside Lombardy), mortality, cancer registry, and the Italian Workers' Compensation Authority (*Istituto per l'Assicurazione contro gli Infortuni sul Lavoro*, INAIL) databases. During weekly meetings, a panel of experts evaluates individual information on medical diagnosis, including histology and immunochemistry, cytology, imaging, and the presence of pleural plaques, a recognised marker of asbestos exposure (12, 49). MM diagnosis is established on a case-by-case basis considering all available clinical information. Cases are finally classified as "definite MM" (histological diagnosis of MM, possibly with immuno-histochemical confirmation and imaging), "probable MM" (usually, cytology suggesting MM plus imaging), "possible MM" (positive imaging), or "non-MM" (26). Morphology is defined and coded according to the WHO histological classification and the International Classification of Diseases for Oncology (ICD-O), Third Edition (47).

Assessment of asbestos exposure

MM patients (or their next-of-kin) are interviewed (mostly face-to-face) by trained personnel using a standardised questionnaire (38) to collect detailed information on lifetime occupational history (industry, occupation, work environment characteristics). In addition, the patient is asked to provide the following information on each cohabitant (father, mother, spouse, other): what was his/her longest occupation (industry, job), how many years did the patient live with the cohabitant, whether the cohabitant used to bring dirty work clothes at home and whether the patient used to brush or wash them. Domestic and home-related activities involving potential asbestos exposure are investigated, including: ironing on asbestos-coated ironing-boards; small repair works (as mason, plumber, motor mechanic, or electrician), thermal insulation; use of asbestos gloves; and use of any asbestos-containing objects. The questionnaire also contains a section on lifetime residential history, including questions on town and complete address, house type, presence of asbestos cement tiles or water-tanks, and presence of industries in the vicinity (e.g. asbestos cement, petro-chemical, railroad, or shipbuilding industries). Based on this information, the lifetime asbestos exposure is classified as "occupational" (definite, probable, or possible), "para-occupational" (i.e., related to the cohabitants), "home-related" (i.e., related to activities performed within the house), or "environmental" (residence in vicinity of asbestos industries) (38). Subjects without any identified asbestos exposure are classified as "unknown". Finally, subjects not interviewed or with insufficient information at interview are categorised as "no information/not classified".

Subjects may have been exposed to asbestos from more than one source. Patients ever exposed to asbestos at the workplace (where asbestos airborne levels were usually order of magnitudes higher than in other settings), are classified as occupationally exposed irrespective of other exposure sources (para-occupational, environmental, or home-related). For patients never occupationally exposed to asbestos, we usually follow this exposure hierarchy: para-occupational > home-related > environmental. However, the final decision is taken on a case-by-case basis, considering also information on time since first exposure and length of exposure to each source.

Statistical analysis

We selected from the RML database all MM cases (definite, probable, or possible) where the date of first diagnosis (histology, cytology or imaging) was between 1 January 2000 and 31 December 2012, the period in which activities of case ascertainment, evaluation, and interview have been completed. Separately for men and women we tabulated demographics, clinical characteristics, sources of asbestos exposure, and, for each Province and for the city of Milan, main industrial sectors in which subjects had been ever exposed to asbestos.

Standardised rates

We calculated crude and standardised rates for each Province and for the city of Milan using the Italian 2001, European, and world (Segi's) standard populations. Confidence intervals (CI) of rates were calculated using the formula proposed by Tiwari, Clegg, and Zou (15, 46). We calculated 90% instead of 95% CIs in order to avoid a reductive interpretation of confidence intervals as statistical significance tests at the conventional two-tailed 5% level (45). Population data by municipality, year, sex, and age were provided by the Italian Network of Cancer Registries (*Associazione Italiana dei Registri Tumori*, AIRTum) (http://www.registri-tumori.it/cms/) or downloaded from the Italian National Institute of Statistics (*Istituto Nazionale di Statistica*, ISTAT) (http://demo.istat.it/). Data management and statistical analyses were performed with Stata 13 (43).

Maps of smoothed crude incidence rates

For each of the 1546 municipalities we calculated the crude average incidence rates. In addition, to account for overdispersion we produced smoothed rates using the Bayesian Besag, York, and Mollié (BYM) model, now very popular in the analysis of data available at small area level (11). In detail, let's assume that the observed number of incident cases

in the i-th municipality (i = 1, …, 1546) follows a Poisson distribution with parameter $\theta_i * D_i$, where θ_i is the incidence rate and D_i the population size in the i-th municipality. A random effect log-linear model is then specified for the incidence rate:

$$\log(\theta_i) = u_i + v_i.$$

The *heterogeneity* random term u_i captures the variability in the rates which is not spatially structured and is assumed to follow *a priori* a Normal distribution with 0 mean and precision λ_u. The *clustering* random terms v_i capture the spatially structured overdispersion and follow a priori an intrinsic conditional autoregressive model (ICAR). That is, defining S_i the set of the municipalities adjacent to the i-th one with cardinality n_i, the conditional distribution of $v_i|v_{j\Sigma Si}$ is assumed normally distributed with mean $\overline{v}_i$ (mean of the terms of areas adjacent to the i-th one) and precision $\lambda_v * n_i$. Through these two random terms, the BYM model shrinks each rate estimate toward both the local and the general (in this case, regional) mean, thus producing maps that permit to better investigate the geographical distribution of disease occurrence. All computations were made by Markov Chain Monte Carlo (MCMC) using the WinBUGS software (22). We drew maps of simple crude and BYM smoothed rates produced by WinBUGS using the Stata command *spmap*.

Results

Characteristics of mesothelioma patients

We recorded 4442 subjects with MM, 2850 men (64.2%) and 1592 women (35.8%), with a male/female ratio of 1.79 (table 1). Median age at diagnosis was 70.4 in men and 73.8 in women. Pleura was the site of MM origin in over 90% of cases. The number of pleural MM was much higher in men than in women, while the number of peritoneal MM was similar. MM diagnosis was evaluated as definite in 75-80%. Morphology was available for more than 80% of patients. The most represented morphology was the epithelioid. Pleural plaques were detected in 13.8% of men and 8.0% of women. Interview was obtained for more than 90% of affected subjects, either from the patients themselves or from one of their relatives.

Exposure to asbestos

Overall, 2201 men (77.2%) had ever been exposed to asbestos (any source) in their life (table 2). Occupational asbestos exposure was identified for 2099 (73.6%) subjects, with the Provinces of Lodi and the City of Milan showing the lowest percentages. Environmental exposure was found for 31 MM cases (10.8%) in Pavia. No asbestos exposure could be identified at interview for 493 (17.3%) men, with the highest percentages in Lodi and in the City of Milan. The latter also showed the highest proportion of MM cases with no or insufficient information.

Asbestos exposure (any source) was found for 824 women (51.8%) (table 3). Occupational exposure was identified in 608 (38.2%) MM cases, with percentages ranging from 19.5% (Lodi) to 61.4% (Bergamo). Para-occupational exposure regarded 63 women (4.0%), 26 (13.9%) in Pavia, which also showed 47 MM cases (25.1%) with environmental asbestos exposure. In 624 (39.2%) women, no asbestos exposure could be found at interview, with percentages ranging from 26.5% (Bergamo) to 68.6% (Mantua). Lack of useful information on asbestos exposure concerned 144 (9.0%) women.

In men, 731/2099 (34.8%) of MM cases had been exposed to asbestos in metal mechanic and metallurgy industries, 705 (33.6%) in building construction, and the remaining in various sectors (<10% each) (table 4). Exposure in metal mechanic and metallurgy industries was frequent (about 30% or more) in most Provinces except Como, Cremona, Pavia, and Sondrio. In the Milan and Mantua Provinces there were many men exposed to asbestos in large industries that have been producing various components of industrial plants (eg, chemical, thermoelectric, and petrochemical) while in the Brescia Province asbestos exposure mainly occurred in workers employed in iron and steel foundries. The percentage of men exposed to asbestos in building construction ranged from 21.9 (city of Milan) to 63.3% (Sondrio). The highest percentage of men

Table 1 - Characteristics of subjects with malignant mesothelioma (MM) by gender, Lombardy Region Mesothelioma Registry, 2000-2012

	Men		Women	
	N	%	N	%
Total	2850	100	1592	100
Age at diagnosis				
20-49	113	4.0	49	3.1
50-54	118	4.1	45	2.8
55-59	212	7.4	91	5.7
60-64	396	13.9	150	9.4
65-69	523	18.4	238	15.0
70-74	608	21.3	295	18.5
75-79	461	16.2	311	19.5
80-84	257	9.0	247	15.5
85+	162	5.7	166	10.4
Site				
Pleura	2693	94.5	1462	91.8
Peritoneum	134	4.7	125	7.9
Pericardium	6	0.2	5	0.3
Tunica vaginalis testis	17	0.6	-	-
Diagnosis				
Definite	2340	82.1	1203	75.6
Probable	245	8.6	157	9.9
Possible	265	9.3	232	14.6
Morphology (ICD-O code)				
MM not otherwise specified (90503)	169	5.9	107	6.7
Fibrous/sarcomatoid/desmoplastic MM (90513)	241	8.5	76	4.8
Epithelioid MM (90523)	1707	59.9	967	60.7
Biphasic MM (90533)	391	13.7	152	9.6
Unknown	342	12.0	290	18.2
Presence of pleural plaques	394	13.8	127	8.0
Interview				
Patient	1658	58.2	706	44.4
Relative	1061	37.2	771	48.4
Not performed	131	4.6	115	7.2

Abbreviations: ICD-O, International Classification of Diseases for Oncology, Third Edition

exposed in non-asbestos textile and clothing production was in Como (29.8%). The relatively high number of men exposed to asbestos in the motor vehicle production and repair sector is explained by the presence in the past of two large automotive industries in the Milan Province. Men in the food and beverage sector were mainly exposed to asbestos in sugar producing plants. We recorded a high number of men exposed to asbestos during the military service (Navy). In the Province of Pavia we recorded the highest proportion (20.1%) of men exposed in a large asbestos-cement industry, while smaller asbes-

Table 2 - Number of cases (%) of malignant mesothelioma in men by Province of residence at diagnosis and exposure to asbestos, Lombardy Region Mesothelioma Registry, 2000-2012

Province	Occupational	Para-occupational	Home-related	Environmental	Unknown*	No information/ not classified**	Total
Lombardy region	2099 (73.6)	16 (0.6)	24 (0.8)	62 (2.2)	493 (17.3)	156 (5.5)	2850 (100)
Bergamo (BG)	270 (84.1)	2 (0.6)	2 (0.6)	1 (0.3)	38 (11.98)	8 (2.5)	321 (100)
Brescia (BS)	193 (81.8)	2 (0.8)	0 (0.0)	1 (0.4)	37 (15.7)	3 (1.3)	236 (100)
Como (CO)	104 (74.8)	2 (1.4)	1 (0.7)	3 (2.2)	21 (15.1)	8 (5.8)	139 (100)
Cremona (CR)	70 (76.1)	0 (0.0)	0 (0.0)	4 (4.3)	16 (16.3)	3 (3.3)	93 (100)
Lecco (LC)	77 (72.6)	0 (0.0)	2 (1.9)	3 (2.8)	23 (21.7)	1 (0.9)	106 (100)
Lodi (LO)	41 (62.1)	0 (0.0)	0 (0.0)	0 (0.0)	21 (31.8)	4 (6.1)	66 (100)
Monza and Brianza (MB)	171 (73.1)	1 (0.4)	1 (0.4)	1 (0.4)	44 (18.8)	16 (6.8)	234 (100)
City of Milan (MIC)	210 (56.8)	2 (0.5)	4 (1.1)	9 (2.4)	103 (27.8)	42 (11.4)	370 (100)
Milan (MIP)***	435 (77.3)	1 (0.2)	4 (0.7)	5 (0.9)	82 (14.6)	36 (6.4)	563 (100)
Mantua (MN)	78 (83.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (16.0)	1 (1.1)	94 (100)
Pavia (PV)	194 (67.8)	5 (1.7)	6 (2.1)	31 (10.8)	38 (13.3)	12 (4.2)	286 (100)
Sondrio (SO)	30 (69.8)	0 (0.0)	0 (0.0)	0 (0.0)	9 (20.9)	4 (9.3)	43 (100)
Varese (VA)	225 (75.2)	1 (0.3)	4 (1.3)	4 (1.3)	46 (15.4)	19 (6.4)	299 (100)

*Subjects without any identified asbestos exposure
**Not interviewed or with insufficient information at interview
***Excluding the city of Milan

tos-cement plants have been operating in Bergamo and Lecco Provinces.

The majority of women (398/608, 65.5%) had been exposed to asbestos in the non-asbestos textile (cotton, wool, and silk manufacture) and clothing production sectors (table 5) in various Provinces. The other industrial sectors accounted for less than 10% of exposure. The Province of Pavia had the highest percentage (18.4%) of women ever exposed in the asbestos cement-industry.

Mesothelioma incidence

In both men and women, the Province of Pavia showed distinctly high crude and age-standardised incidence rates of MM (table 6 and figure 2). Rates

Table 3 - Number of cases (%) of malignant mesothelioma in women by Province of residence at diagnosis and exposure to asbestos, Lombardy Region Mesothelioma Registry, 2000-2012

Province	Occupational	Para-occupational	Home-related	Environmental	Unknown*	No information/ not classified**	Total
Lombardy region	608 (38.2)	63 (4.0)	75 (4.7)	78 (4.9)	624 (39.2)	144 (9.0)	1592 (100)
Bergamo (BG)	102 (61.4)	7 (4.2)	3 (1.8)	0 (0.0)	44 (26.5)	10 (6.0)	166 (100)
Brescia (BS)	51 (38.9)	2 (1.5)	3 (2.3)	1 (0.8)	67 (51.1)	7 (5.3)	131 (100)
Como (CO)	51 (54.3)	4 (4.3)	0 (0.0)	0 (0.0)	31 (33.0)	8 (8.5)	94 (100)
Cremona (CR)	21 (4.4)	4 (7.7)	0 (0.0)	2 (3.9)	21 (40.4)	4 (7.7)	52 (100)
Lecco (LC)	20 (40.0)	3 (6.0)	6 (12.0)	1 (2.0)	15 (30.0)	5 (10.0)	50 (100)
Lodi (LO)	8 (19.5)	0 (0.0)	1 (2.4)	1 (2.4)	21 (51.2)	10 (24.4)	41 (100)
Monza and Brianza (MB)	72 (48.3)	2 (1.3)	11 (7.4)	2 (1.2)	46 (30.9)	16 (10.7)	149 (100)
City of Milan (MIC)	53 (20.8)	5 (2.0)	22 (8.6)	15 (5.9)	126 (49.4)	34 (13.3)	255 (100)
Milan (MIP)***	105 (41.0)	5 (2.0)	16 (6.3)	3 (1.2)	101 (39.5)	26 (10.1)	256 (100)
Mantua (MN)	7 (20.0)	0 (0.0)	0 (0.0)	1 (2.9)	24 (68.6)	3 (8.6)	35 (100)
Pavia (PV)	38 (20.3)	26 (13.9)	8 (4.3)	47 (25.1)	59 (31.5)	9 (4.8)	187 (100)
Sondrio (SO)	9 (24.3)	0 (0.0)	2 (5.4)	0 (0.0)	24 (64.9)	2 (5.4)	37 (100)
Varese (VA)	71 (51.1)	5 (3.6)	3 (2.2)	5 (3.6)	45 (32.4)	10 (7.2)	139 (100)

*Subjects without any identified asbestos exposure
**Not interviewed or with insufficient information at interview
***Excluding the city of Milan

were higher than the regional average in the Provinces of Bergamo, Lecco, Milan (excluding the city of Milan) and Varese (men), and in the Provinces of Bergamo, Lodi, Monza and Brianza, Sondrio (women).

Crude MM rates for each municipality are shown in figure 3. The spatial pattern is more evident when using smoothed BYM rates (lower panels), rather than simple rates (upper panels). At least seven darker areas, corresponding to higher rates, are visible in men (labelled as M1-M7) and five in women (F1-F5). The most affected M1/F1, located in the Province of Pavia, is an area where a large asbestos-cement plant had been operating in the

Table 4 - Number of cases (%) of malignant mesothelioma among 2099 men with occupational asbestos exposure by Province of residence at diagnosis and exposure to asbestos in the main industries*, Lombardy Region Mesothelioma Registry, 2000-2012

Province	MMM	BC	TC	MVPR	CP	FB	M	T	R	AC	RPM	EP	HSS
Lombardy region	731 (34.8)	705 (33.6)	188 (9.0)	136 (6.5)	122 (3.5)	98 (4.7)	87 (4.2)	76 (3.6)	71 (3.4)	65 (3.1)	51 (2.4)	51 (2.4)	39 (1.9)
Bergamo (BG)	116 (43.0)	93 (34.4)	30 (11.1)	23 (8.5)	15 (5.6)	10 (3.7)	8 (3.0)	5 (1.8)	11 (4.1)	8 (3.0)	2 (0.7)	3 (1.1)	5 (1.9)
Brescia (BS)	77 (39.9)	76 (39.4)	15 (7.8)	15 (7.8)	5 (2.6)	10 (5.2)	4 (2.1)	5 (2.6)	2 (1.0)	3 (1.5)	1 (0.5)	5 (2.6)	4 (2.1)
Como (CO)	18 (17.3)	34 (32.7)	31 (29.8)	4 (3.9)	1 (1.0)	4 (3.9)	7 (6.8)	4 (3.9)	7 (6.8)	1 (1.0)	2 (1.9)	2 (1.9)	4 (3.9)
Cremona (CR)	19 (27.1)	33 (47.1)	4 (5.7)	1 (1.4)	2 (2.9)	6 (8.6)	6 (8.6)	3 (4.3)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lecco (LC)	29 (37.7)	18 (23.4)	5 (6.5)	2 (2.6)	3 (3.9)	3 (3.9)	3 (3.9)	5 (6.5)	1 (1.3)	4 (5.2)	5 (6.5)	3 (3.9)	2 (2.6)
Lodi (LO)	16 (39.0)	13 (31.7)	2 (4.9)	1 (2.4)	8 (19.5)	1 (2.4)	7 (7.3)	2 (4.9)	1 (2.4)	0 (0.0)	1 (2.4)	3 (7.3)	0 (0.0)
Monza and Brianza (MB)	60 (35.1)	70 (40.9)	18 (10.5)	9 (5.3)	7 (4.1)	5 (2.9)	3 (1.8)	3 (1.8)	12 (7.0)	1 (0.6)	3 (1.8)	3 (1.8)	1 (0.6)
City of Milan (MIC)	67 (31.9)	46 (21.9)	4 (1.9)	15 (7.1)	15 (7.1)	6 (2.9)	12 (5.7)	4 (1.9)	11 (5.2)	3 (1.4)	11 (5.2)	3 (1.4)	8 (3.8)
Milan (MIP)**	202 (46.4)	129 (29.7)	27 (6.2)	35 (8.0)	30 (6.9)	18 (4.1)	24 (5.5)	18 (4.1)	18 (4.1)	4 (0.9)	13 (3.0)	10 (2.3)	4 (0.9)
Mantua (MN)	28 (35.4)	30 (38.0)	0 (0.0)	4 (5.1)	4 (5.1)	10 (12.7)	1 (1.3)	3 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.6)	2 (2.6)
Pavia (PV)	31 (16.0)	73 (37.6)	5 (2.6)	11 (5.7)	3 (1.6)	13 (6.7)	9 (4.6)	16 (8.3)	5 (2.6)	39 (20.1)	9 (4.6)	4 (2.1)	4 (2.1)
Sondrio (SO)	1 (3.3)	19 (63.3)	6 (20.0)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.0)	1 (3.3)
Varese (VA)	67 (29.8)	71 (31.6)	41 (18.2)	16 (7.1)	29 (12.9)	11 (4.9)	7 (3.1)	6 (2.7)	1 (0.4)	2 (0.9)	4 (1.8)	10 (4.4)	4 (1.8)

Abbreviations: AC, asbestos-cement; BC, building construction, CP, chemical and plastics; EP, energy production; FB, food and beverage; HSS, health and social services; M, military; MMM, metal mechanic and metallurgy; MVPR. motor vehicle production and repair; R, rubber; RPM, railroad production and maintenance; T, transport; TC, textile and clothing production.

*Only industries with at least 30 cases are listed in decreasing order; a subject may have been exposed to asbestos in more than one industrial sector in his/her occupational history

***Excluding the city of Milan

town of Broni in the period 1932-1993. M2/F2 in the Province of Varese, M3/F3 in the Provinces of Monza-Brianza, Lecco and Bergamo, and M4/F4 in the Province of Bergamo and Brescia, are largely industrialised areas with factories of various sectors, including metal mechanic and metallurgy, building construction, non-asbestos textile and clothing production, chemical and plastics, motor vehi-

Table 5 –Number of cases (%) of malignant mesothelioma among 608 women with occupational asbestos exposure by Province of residence at diagnosis and exposure to asbestos in the main industries*, Lombardy Region Mesothelioma Registry, 2000-2012

Province	TC	MMM	HSS	R	FB	CP	AC
Lombardy region	398 (65.5)	51 (8.4)	38 (6.3)	23 (3.8)	21 (3.5)	18 (3.0)	12 (2.0)
Bergamo (BG)	81 (79.4)	6 (5.9)	1 (1.0)	2 (2.0)	1 (1.0)	2 (2.0)	4 (4.0)
Brescia (BS)	38 (74.5)	3 (5.9)	2 (3.9)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
Como (CO)	41 (80.4)	5 (9.8)	3 (5.9)	0 (0.0)	1 (2.0)	1 (2.0)	0 (0.0)
Cremona (CR)	7 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)
Lecco (LC)	13 (65.0)	5 (25.0)	1 (5.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lodi (LO)	5 (62.5)	1 (12.5)	1 (12.5)	1 (12.5)	2 (25.0)	0 (0.0)	0 (0.0)
Monza and Brianza (MB)	54 (75.0)	1 (1.4)	2 (2.8)	6 (8.3)	2 (2.8)	2 (2.8)	0 (0.0)
City of Milan (MIC)	15 (28.3)	8 (15.1)	8 (15.1)	3 (5.7)	4 (7.5)	4 (7.5)	1 (1.9)
Milan (MIP)**	64 (61.0)	15 (14.3)	8 (7.6)	6 (5.7)	3 (2.9)	4 (3.8)	0 (0.0)
Mantua (MN)	3 (42.9)	0 (0.0)	2 (28.6)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)
Pavia (PV)	14 (36.8)	1 (2.6)	3 (7.9)	4 (10.5)	5 (13.2)	0 (0.0)	7 (18.4)
Sondrio (SO)	7 (77.8)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Varese (VA)	56 (78.9)	5 (7.0)	6 (8.4)	0 (0.0)	0 (0.0)	5 (7.0)	0 (0.0)

Abbreviations: AC, asbestos-cement; CP, chemical and plastics; FB, food and beverage; HSS, health and social services; MMM, metal mechanic and metallurgy; R, rubber; TC, textile and clothing production.
*Only industries with at least 10 cases are listed in decreasing order; a subject may have been exposed to asbestos in more than one industrial sector in his/her occupational history
***Excluding the city of Milan

cle production and repair, and rubber. M5/F5 is a non-industrialised, mountain area in the Province of Sondrio with a low population density, in which rates are elevated but based on a few cases employed in various sectors. The high rates in M6 (Province of Mantua) are attributable to asbestos exposure in a large industry producing components of industrial plants and in sugar refineries. M7 is an area in the Province of Cremona where high rates are associated to asbestos exposure in various industrial sectors, including metal mechanic and metallurgic and building construction, either in the Province of Cremona itself or in adjacent Provinces (Mantua and Brescia).

Table 6 - Number of cases, person-years, and crude and age-standardised incidence rates (×100,000 person-years, age 0-99 years) of malignant mesothelioma by gender and province of residence at diagnosis, Lombardy Region Mesothelioma Registry, 2000-2012

Province	Men						Women					
			Rate*						Rate*			
	MM cases	Person-years	Crude	Italy	Europe	World	MM cases	Person-years	Crude	Italy	Europe	World
Lombardy region	2850	60,584,108	4.7	5.2	3.5	2.3	1592	63,505,520	2.5	2.1	1.4	0.9
Bergamo (BG)	321	6,737,484	4.8	5.9	4.0	2.7	166	6,845,176	2.4	2.3	1.5	1.0
Brescia (BS)	236	7,690,254	3.1	3.6	2.5	1.7	131	7,854,847	1.7	1.5	1.1	0.7
Como (CO)	139	3,636,139	3.8	4.4	2.7	1.8	94	3,804,489	2.5	2.2	1.4	0.9
Cremona (CR)	93	2,226,276	4.2	4.6	2.9	2.0	52	2,328,508	2.2	1.9	1.3	0.9
Lecco (LC)	106	2,089,074	5.1	6.0	3.8	2.5	50	2,168,556	2.3	2.0	1.3	0.8
Lodi (LO)	66	1,376,193	4.8	5.4	3.7	2.5	41	1,423,825	2.9	2.5	1.5	1.0
Monza and Brianza (MB)	234	5,178,147	4.5	5.3	3.4	2.3	149	5,388,656	2.8	2.5	1.6	1.1
City of Milan (MIC)	370	8,015,345	4.6	4.5	2.9	1.9	255	8,929,336	2.9	2.0	1.3	0.8
Milan (MIP)**	563	11,277,357	5.0	5.8	3.8	2.5	256	11,709,412	2.2	2.0	1.3	0.8
Mantua (MN)	94	2,521,610	3.7	3.8	2.7	1.9	35	2,646,319	1.3	1.1	0.8	0.6
Pavia (PV)	286	3,279,133	8.7	8.5	5.9	4.0	187	3,497,715	5.3	4.0	2.7	1.8
Sondrio (SO)	43	1,148,810	3.7	4.1	2.7	1.8	37	1,196,767	3.1	2.6	1.7	1.1
Varese (VA)	299	5,408,286	5.5	6.1	3.9	2.6	139	5,711,914	2.4	2.0	1.3	0.9

*Rates standardised to the Italian population, 2001 (Italy), the European population (Europe), and the world (Segi's) population (World)
**Excluding the city of Milan

Discussion

In this study we documented a large impact of past asbestos use in the Lombardy Region, with over 4400 MM cases in a 13-year period, representing about one fourth of all MM occurring in Italy (26). Occupational exposure was predominant in males (about 75% vs <40% in women). The study was made possible by the high-quality population registry of MM patients (RML), which has been recording all MM cases among Lombardy inhabitants since 2000 (31, 36). Identification of sources of asbestos exposure was made possible in a large percentage of cases thanks to the high interview rate (95%) of MM cases or their next-of-kin.

The high number of affected men was largely expected, because Lombardy is highly populated and has been the region with the largest number of men employed in industrial sectors in which asbestos has been widely used, including the mechanic (motor vehicle construction and repair), metallurgy (iron and steel foundries), chemical, and rubber. The impact was remarkable also in women (male-female ratio about 2). In most Provinces there were large numbers and percentages of women ever employed and exposed in the non-asbestos textile and clothing production industry. Several studies documented the presence of asbestos in this sector (5, 7, 13, 14, 32) and asbestos fibres have been found in necropsy lung samples of textile workers with MM (9).

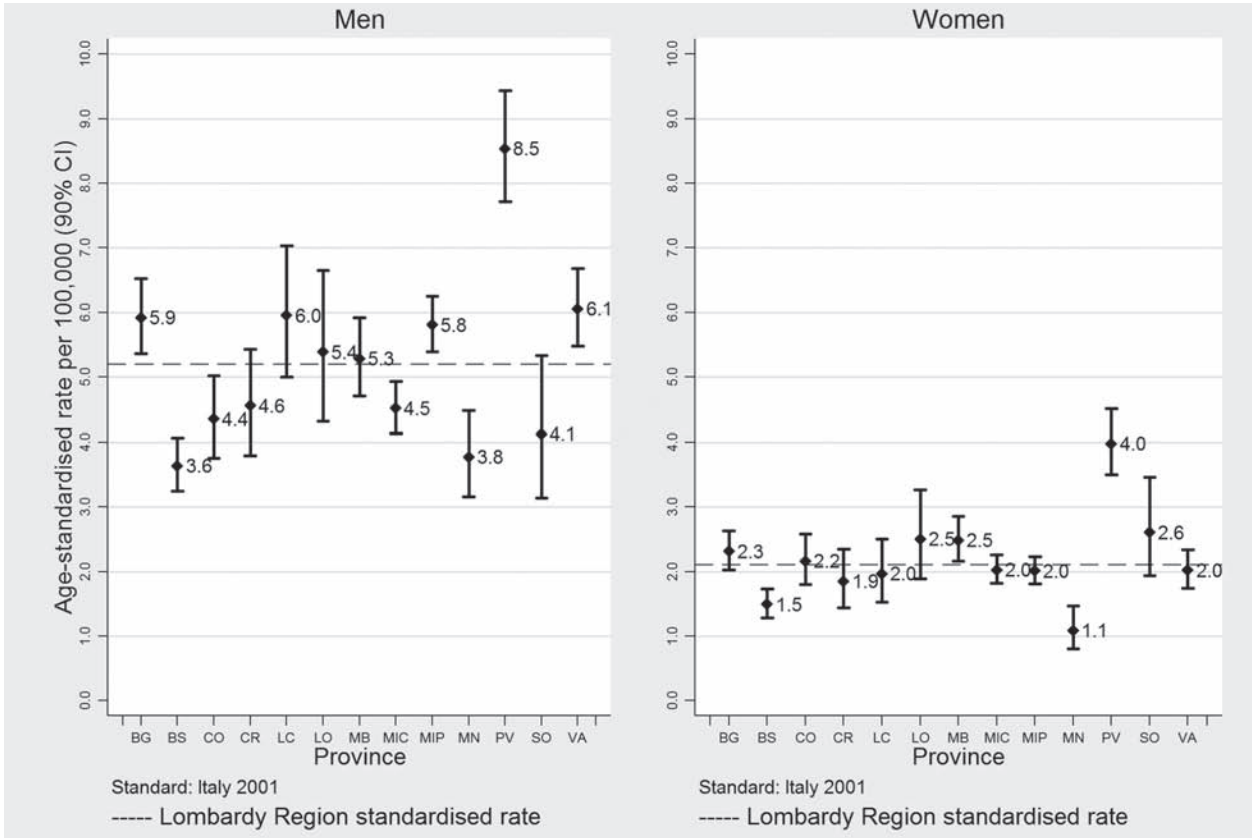

Figure 2 - Age-standardised rates (×100,000 person-years, age 0-99 years; standard: 2001 Italian population) of malignant mesothelioma by gender and Province of residence at diagnosis, Lombardy Region Mesothelioma Registry, 2000-2012

Our findings (high proportion of affected women) are in line with results regarding Italy as a whole: in the period 1993-2012 among 21,463 MM cases, the National MM registry ReNaM recorded 38.4% women (male/female ratio 2.5) (26). Also other countries (e.g., Denmark, France, and Spain) recorded a relatively high number of affected women, while others (e.g., UK and USA) show a higher male/female ratio, reflecting different male-female patterns of past asbestos exposure.

For a large proportion (39.2%) of women we were not able to identify any source of asbestos exposure at interview. Failure to identify occupational asbestos exposure doesn't necessarily imply that occupation did not play a role. Rather, it may indicate that interview is an incomplete tool to uncover asbestos exposure (for example, many subjects might not be aware of asbestos presence at the workplace) or that some exposures are currently still unrecognised (34). Another possible explanation for the high number of cases in women is the widespread low-level past environmental exposure to asbestos from industries using asbestos and from asbestos containing materials, most importantly asbestos-cement roofs in buildings.

The highest MM rates in both genders in the Province of Pavia and the larger proportion of women with para-occupational and environmental exposure can be explained by the presence of the second largest Italian asbestos-cement factory, located in Broni. A cohort study of workers (1254 men, 42 women) in that factory showed an increased mortality from pleural (26 cases in men, 2 in women) and peritoneal (7 men) cancer (40). Several studies had shown a high MM incidence/mortality among residents in Broni and nearby towns (2, 17-19, 24).

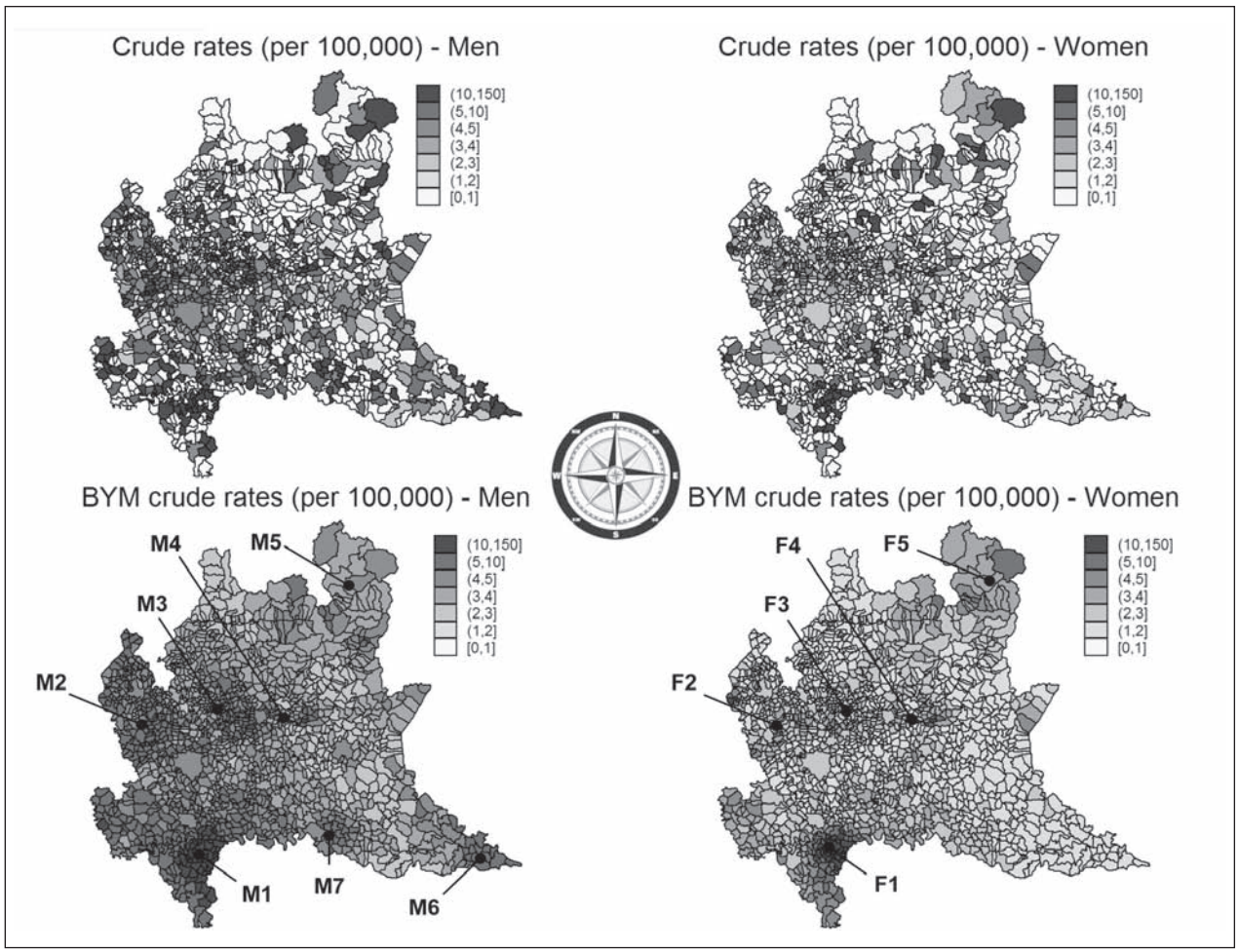

Figure 3 - Crude incidence rates of malignant mesothelioma by gender and municipality, Lombardy Region Mesothelioma Registry, 2000-2012. Upper panels: simple crude rates. Lower panels; smoothed Bayesian crude rates calculated with the Besag, York, and Mollié (BYM) model

More recently, using RML data 2000-2011, we documented a high impact (especially in women) also in families (37 cases) of the asbestos-cement factory workers and among residents in Broni (48 cases, about 10,000 residents) and in the surrounding municipalities, notably the nearby town of Stradella (16 cases, about 11,000 residents) (35). Indeed, in the present analysis we found that the town of Broni and Stradella ranked first in terms of either risk (MM incidence) or impact (number of cases). In Broni the incidence rate was 100.0 per 100,000 person-years (57 cases) in men and 68.4 per 100,000 person-years (44 cases) in women. Among residents in Stradella the incidence rate was 33.6 per 100,000 person-years (23 cases) in men and 43.5 per 100,000 person-years in women (33 cases). Also the nearby towns showed elevated rates, although based on smaller number of cases due to the small population size.

Several studies have been performed in various Provinces in the Region to investigate the association between MM and asbestos exposure, either through case reports or by measuring asbestos fibre burden in lung, including the above-mentioned in the non-asbestos textile industry (5, 7, 9, 13, 14, 32), agriculture (recycling of jute bags contaminated by asbestos) (8), steel industry (6), rotogravure (33), thermostat manufacturing (1), and oilseed production (42).

Before the implementation of the RML, a Provincial MM registry maintained by the Local Health Unit of Brescia was active. In the period 1993-1999, 190 cases were recorded among residents in Brescia Province, most of whom occupationally exposed to asbestos in various industrial sectors, including construction and iron and steel and metal working (3). The same Local Health Unit performed a study in Sarnico (Province of Bergamo, near the Lake Iseo, Province of Bergamo and Brescia), where two adjacent factories, one producing asbestos ropes and gaskets and the other manufacturing non-asbestos textile products, had been operating. A high number of MM cases among workers living in the area and exposed to asbestos in those two factories was reported in 1977-1996 (9 men, 12 women) (4). In the present analysis, among residents in Sarnico we found quite high MM incidence rates also in 2000-2012: men: 26.8 per 100,000 person-years (10 cases); women, 36.4 per 100,000 person-years (15 cases).

Several chemical plants were present in Angera (Varese Province), including one producing a specific asbestos containing insulation material, called "angerite", widely used in the Italian chemical sector (16). In the present analysis, we found a high impact of asbestos exposure on MM incidence among residents in Angera: men: 11.6 per 100,000 person-years (4 cases); women, 26.2 per 100,000 person-years (10 cases).

Other clusters of MM cases in Lombardy have been reported in the areas of Legnano (Milan Province: non-asbestos textile and metal engineering industries) and Dalmine (Bergamo Provinces: metal production manufacturing, metal engineering, construction, non-asbestos textile, and asbestos-cement industries) (16).

In this work BYM models proved a useful tool for visualising geographical MM distribution: they clearly showed areas of high MM incidence much better than maps of observed crude incidence rate. BYM models were also used in the Piedmont Region to map standardised mortality ratios (SMRs) (i.e., areas with incidence greater than the regional average (29). Since almost all cases are due to asbestos exposure (10, 30), in the present study we preferred to model directly MM incidence rates, because any mesothelioma case can be considered an excess.

Conclusions

MM registries are instrumental for continuous documentation of the impact of asbestos use on MM incidence. Thanks to the existence of the Lombardy Mesothelioma Registry, in this study we were able to document a high mesothelioma burden in the region, reflecting extensive occupational (mainly in men) and non-occupational (mainly in women) asbestos exposure in the past. More than 4000 cases were recorded in the first 13 years of activity of the registry (2000-2012). Contrary to other countries, in which the number of men diagnosed with MM was largely predominant, in Lombardy (as in Italy as a whole), the number of affected women is quite large.

No potential conflict of interest relevant to this article was reported

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