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Impact of an asbestos cement factory on mesothelioma incidence: Global assessment of effects of occupational, familial, and environmental exposure

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ABSTRACT

Few studies have examined the incidence of malignant mesothelioma (MM) associated with distinct sources of asbestos exposure (occupational, familial, or environmental). We assessed the impact of asbestos exposure—global and by source—on the incidence of MM in Broni, an Italian town in which an asbestos cement factory once operated (1932–1993). Based on data collected by the Lombardy Mesothelioma Registry, we calculated the number of observed and expected MM cases among workers, their cohabitants, and people living in the area in 2000–2011. We identified 147 MM cases (17.45 expected), 138 pleural and nine peritoneal, attributable to exposure to asbestos from the factory. Thirty-eight cases had past occupational exposure at the factory (2.33 expected), numbering 32 men (26 pleural, six peritoneal) and six women (four pleural, two peritoneal). In the families of the workers, there were 37 MM cases (4.23 expected), numbering five men (all pleural) and 32 women (31 pleural, one peritoneal). Among residents in Broni or in the adjacent/surrounding towns, there were 72 cases of pleural MM (10.89 expected), numbering 23 men and 49 women. The largest MM excess was found in the towns of Broni (48 observed, 3.68 expected) and Stradella (16 observed, 1.85 expected). This study documents the large impact of the asbestos cement factory, with about 130 excess MM cases in a 12-year period. The largest MM burden was among women, from non-occupational exposure. Almost half of the MM cases were attributable to environmental exposure.

1. Introduction

There is a "pandemic" of asbestos-related diseases worldwide. It has been estimated that 107,000 people die from malignant mesothelioma (MM), lung cancer, or asbestosis every year (Stayner et al., 2013). The largest burden of MM incidence and mortality is in countries that began using asbestos many decades ago (those in Western Europe, North America, and Oceania). Although many of them have banned asbestos production, import, and use, peak MM frequency has not been reported yet because of the long time lapse ("latency") between exposure and MM occurrence. Conversely, in newly industrialising countries that are increasingly using asbestos (those in Asia, Eastern Europe, and South America), MM incidence is relatively low (although underreporting of mortality and lack of incidence data have been noted in many countries) and is bound to increase in the coming years (Delgermaa et al., 2011; Park et al., 2011; Sim, 2013; Stayner et al., 2013). The International Agency for Research on Cancer (IARC) recently confirmed Group 1 inclusion ("carcinogenic to humans") for all forms of asbestos, including serpentine (chrysotile) and amphibole (crocidolite, amosite, tremolite asbestos, actinolite asbestos, anthophyllite asbestos), although their different potencies have been acknowledged (IARC, 2012). In addition to MM and lung cancer, sufficient evidence of a causal link has been evaluated between asbestos exposure and cancer of the larynx and ovary, while evidence regarding the association with other cancer sites (pharynx, stomach, colon, and rectum) is considered still limited (IARC, 2012). For these reasons, several researchers and scientific organisations, including the World Health Organization (WHO), the International Commission on Occupational Health (ICOH), the International Labour Office, and the Joint Policy Committee of the Societies of Epidemiology, have called for a global ban on asbestos mining, use, and export (ICOH, 2014; Sim, 2013; Terracini, 2006).

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Although many studies have investigated the effects of occupational exposure to asbestos among cohorts of workers, there have been few studies on the impact of asbestos exposure on their families (familial, household, or domestic exposure) or among people who live near asbestos mines or factories (environmental exposure), and very few studies have examined those sources of exposure comprehensively (Barbieri et al., 2012; Boffetta and Stayner, 2006; Bourdes et al., 2000; Ferrante et al., 2007; IARC, 2012; Joubert et al., 1991; Magnani et al., 1993, 2001, 2013; Musti et al., 2009; Rake et al., 2009; Vianna and Polan, 1978).

Broni is a small town (<10,000 inhabitants) in the Province of Pavia in Lombardy, north-west Italy, where an asbestos cement factory (Fibronit) has been operating, employing about 2741 men and 714 women overall (Oddone et al., 2014). It was the second oldest and largest asbestos cement factory in Italy (Mirabelli et al., 2010), covering an area of 135,000 m^2 about 600 m west from the historical centre of the town. It produced cement in 1919–1931 and asbestos cement products in 1932–1993: Portland cement 325 was mixed with chrysotile and crocidolite, and small quantities of amosite were added to produce asbestos cement pipes and sheets. The percentage in weight of crocidolite was 10–15% in sheets and could be 30% or more in pipes. On average, 110 kg of asbestos fibres and 772 kg of Portland cement were used in the department producing corrugated sheets. In the early years about 8000 t/year of asbestos cement products (plain or corrugated sheets, pipes, others) was produced. In the 1960s production increased up to 100,000 t/year. As of 1970s, several tasks were performed manually and there were no ventilation systems. Workers used no personal protection devices and in general there were poor work hygiene practices (e.g. no change of clothes and showering at the end of shift) (Oddone et al., 2014). Only between the end of the 1970s and the 1980s measures were taken to reduce airborne fibre concentrations (installation of air filtering units and introduction of automated processes) (Oddone et al., 2014). Asbestos use was stopped following the approval of Law 257/1992 on asbestos ban, although residual use has been documented in 1993 (Ferrari et al., 1994). The factory continued cement production until 1997; however, no remediation works were done. It was definitely closed in 2000. In the following years remediation works were done in the factory area and in other parts of the town of Broni. In 2002 the town of Broni was included by law 388/2000 in a government list of environmentally contaminated sites (*Siti di Interesse Nazionale*, SIN) in Italy (Pirastu et al., 2011). The occupational impact among 1296 workers (1254 men, 42 women) who were still working in the factory in 1970 or who were hired subsequently was recently investigated. The standardised mortality ratio (SMR) for pleural cancer was 17.99 in males (26 deaths against 1.45 expected) and 68.90 in women (2 observed, 0.03 expected). In men, seven deaths from cancer of peritoneum and retroperitoneum (0.69 expected) yielded an SMR of 10.10, while no deaths were observed among women (0.03 expected). Three deaths of asbestosis were observed in males (0.02 expected) with an SMR of 130.69 (Oddone et al., 2014).

Several geographical studies have shown marked excesses of mortality from pleural cancer among people living in the Broni area (Fig. 1) (Amendola et al., 2003; Di Paola et al., 2000; Fazzo et al., 2012a,b; Magnani et al., 1994; Pirastu et al., 2011).

Those studies were important for estimating the impact of asbestos use at the factory, and their findings contributed to the inclusion of

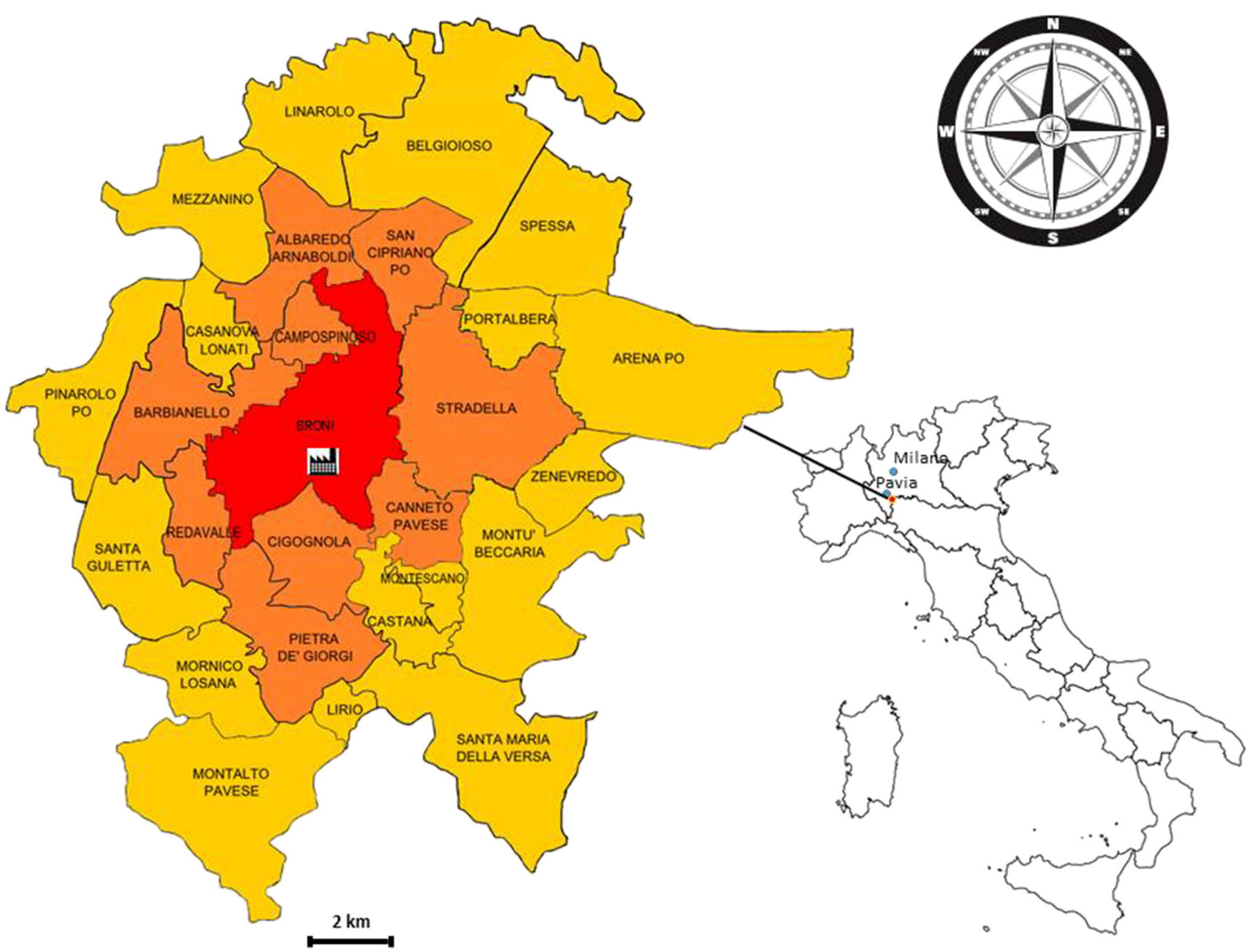


Fig. 1. Map of the area of Broni, Lombardy, northern Italy, showing the asbestos cement factory, the town of Broni, nine adjacent municipalities, and 17 surrounding municipalities.

the town of Broni among contaminated sites in Italy (Pirastu et al., 2011). However, they had several limitations. First, except one study that attempted to evaluate incident MM cases using pathology information (Magnani et al., 1994), they only analysed mortality. Second, they only studied pleural cancers. Third, they used as reference the mortality rates of the whole population, which includes people exposed to asbestos: this approach leads to underestimation of the effect (Boffetta and Stayner, 2006). Fourth, as they relied on subjects' residence at death, they could not distinguish the different sources of asbestos exposure (occupational, familial, or environmental).

We aimed to quantify the global impact of asbestos on MM incidence among: a) workers employed at the Broni factory (occupational exposure); b) their cohabitants (familial exposure arising from fibres on the workers' clothes or hair); and c) people living in Broni or in surrounding towns (environmental exposure arising from outdoor pollution related to the factory). We used information on MM cases collected by the Lombardy Mesothelioma Registry (*Registro Mesoteliomi Lombardia*, RML) in 2000–2011 (http://www.ispesl.it/renam/Cor.asp#lombardia). The documentation of the effects of asbestos exposure outside the occupational setting as well is important for the local communities, as non-occupationally exposed MM cases are increasingly entitled to compensation (e.g. in France, Korea, and Japan). Quantifying the global impact of asbestos on health may have positive repercussions for countries that still use it and in which perception of the magnitude of health effects attributable to asbestos is still poor.

2. Materials and methods

2.1. Lombardy Mesothelioma Registry

The RML is part of a national network (*Registro Nazionale Mesoteliomi*, ReNaM) (Nesti et al., 2003). It collects all MM cases of the pleura, peritoneum, pericardium, and tunica vaginalis of testis diagnosed in people living in Lombardy (currently almost 10 million inhabitants) at diagnosis, even if admitted to hospitals outside Lombardy (Mensi et al., 2007). The departments of pathology, pneumology, surgery, and oncology of more than 100 hospitals notify the RML of suspected MM cases. The completeness of reporting is periodically verified using several sources, including pathology, hospital admission, mortality, cancer registry, and the Italian Workers' Compensation Authority (*Istituto per l'Assicurazione contro gli Infortuni sul Lavoro*, INAIL) databases. A panel of experts evaluates the information on clinical diagnosis and asbestos exposure. The presence of pleural plaques, a recognised marker of asbestos exposure (Anonymous, 1997; Boffetta and Stayner, 2006), is also recorded. Verified MM cases are finally classified as certain, probable, or possible.

Patients (or their next-of-kin) are then interviewed (mostly face-to-face) by trained personnel using a standardised questionnaire (Nesti et al., 2003) to collect detailed information on lifetime occupational history (industry, occupation, work environment characteristics) and lifestyle habits. Information on people with whom the patients have been living is also recorded. In particular, 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. Moreover, domestic and leisure-time 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. Regarding environmental exposures, 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, a panel of experts classifies lifetime asbestos exposure as occupational (certain, probable, possible), familial (i.e., related to the cohabitant), domestic or leisure-time (i.e., related to activities performed within the house), or environmental (Nesti et al., 2003). Subjects with no evidence of asbestos exposure at interview are classified as non-exposed. The information stored in the RML database allows the tracking of clusters of MM cases attributable to the same workplace.

2.2. Classification of asbestos exposure associated with the Broni factory

In this study, we selected from the RML database all cases where the date of first diagnosis was between 1 January 2000 and 31 December 2011, the period in which all activities (case ascertainment and interview) were completed. We did not consider asbestos exposure from domestic and leisure-time activities (e.g. ironing or small repair works) because it is not associated with the Broni factory. We classified MM cases in mutually exclusive groups as follows: 1) "Occupational exposure", if the patient had ever worked at the Broni factory; 2) "Familial exposure", if the patient had been living with a worker employed at the factory; 3) "Certain environmental exposure", if the patient had ever lived in Broni (4411 males and 4949 females on 1 January 2007); and 4) "Potential environmental exposure", if the patient did not report any asbestos exposure at interview, further divided into patients living in nine towns adjacent to Broni or in 17 surrounding towns (Fig. 1). Patients who had ever lived in Broni were flagged and thus could be tracked in the RML database irrespective of residence at diagnosis; for patients living in other towns, only the last residence was available in the RML database.

If there were multiple exposures, we followed this hierarchy of intensity according to national guidelines: occupational > familial > certain environmental > potential environmental (Nesti et al., 2003). More precisely, MM cases classified as having potential environmental exposure had never been living in Broni, had never lived with workers exposed to asbestos, had never used asbestos at home, and had never been occupationally exposed to asbestos (neither in the Fibronit factory nor in other workplaces); the patients classified as having certain environmental exposure had never lived with a worker exposed to asbestos, had never used asbestos at home, and had never been occupationally exposed to asbestos; finally, patients classified as having familial exposure had never used asbestos at home and had never been occupationally exposed to asbestos. Fibronit workers were classified as occupationally exposed in the plant irrespective of possible additional exposures in other jobs or industries.

2.3. Statistical analysis

The RML is a population-based registry and covers a "dynamic" population, in which subjects continuously enter (birth, immigration) and exit (death, emigration) Lombardy (Pearce, 2012; Vandenbroucke and Pearce, 2012). Therefore, there are no defined cohorts within the registry for which we could formally calculate person-years at risk. To calculate the expected number of MM cases, we used the following approximation. For the Broni factory, we considered 3455 asbestos cement workers employed since 1932, 2741 men and 714 women (Oddone et al., 2014), assuming all workers were alive during our study period (2000–2011). In north-west Italy, the average number of members per family went from 3.0 in the 1971 national census to 2.3 in the 2011 census (http://www.istat.it/en/files/2013/12/Nota-diffusione_popolazione_e_famiglie20122013.pdf). Since the relevant exposure occurred several decades ago, for familial exposure we therefore assumed that each worker in the Broni factory had two family members ($3455 \times 2 = 6910$, equal number of men and women).

For environmental exposure, we used the sex- and age-specific population in every town (on 1 January 2007) available through the Italian Network of Cancer Registries (*Associazione Italiana Registri Tumori*, AIRTum) (http://www.registri-tumori.it/cms/). For environmental exposure in Broni, we tracked and counted also MM cases occurring among people who moved away from the town; therefore, the population at risk is larger than that of Broni residents. For this reason, we assumed a 10% yearly turnover of the population to take into account the changing (increasing) study base (Nelson et al., 2005).

We then applied to the above populations (considered over a 12-year period, i.e. 2000–2011) the average regional MM incidence rates for people never exposed to asbestos, which were 1.2 and 1.1 × 100,000 person-years in men and women, respectively. These rates were calculated using as numerator the number of non-exposed cases, who are known from RML. The population not exposed to asbestos in Lombardy (denominator) is not known. However, in a recent (2002–2005) large case–control study we performed in Lombardy, using a job-exposure matrix we found that among the 2120 controls (randomly sampled from the general population), 67.8% of male and 90.0% of female had never been exposed to asbestos (De Matteis et al., 2012). To estimate the unexposed population at risk we therefore multiplied the population figures by 0.678 (men) and 0.900 (women).

For environmental exposure in Broni and surrounding towns, we used sex- and age-specific (5-year classes) non-exposed reference rates. As we did not know the relevant age distributions, we used a different approach to analyse occupational and familial exposure. In contrast with a dynamic population, a cohort of workers and their cohabitants ages with time. We therefore applied the average 2000–2011 non-exposed regional incidence rates calculated among subjects aged ≥70 years, which were 6.0 and 4.2 × 100,000 person-years. A similar approach was used in a study of MM incidence near an asbestos mine in Balangero, Piedmont, north-west Italy (Mirabelli et al., 2008).

For every exposure category, we calculated the standardised incidence ratio (SIR) as the ratio of observed and expected MM cases (Checkoway et al., 2004). Confidence intervals (CI) were calculated using the Poisson exact formula (Breslow and Day, 1987). Data management and statistical analyses were performed with Stata 13 (StataCorp, 2013).

3. Results

In 2000–2011, there were 147 MM cases (17.45 expected), attributable to occupational, familial, or environmental exposure to asbestos

Table 1
Populations and number of observed and expected cases of malignant mesothelioma in the Broni area, Lombardy, northern Italy, by exposure type, 2000–2011.

Exposure	Population at risk		Men			Women			Total		
	Male	Female	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
All			60 54 pleural 6 peritoneal	9.88	6.1 (4.6–7.8)	87 84 pleural 3 peritoneal	7.57	11.5 (9.2–14.2)	147 138 pleural 9 peritoneal	17.45	8.4 (7.1–9.9)
Occupational	2741[a]	714[a]	32 26 pleural 6 peritoneal	1.97	16.2 (11.1–22.9)	6 4 pleural 2 peritoneal	0.36	16.7 (6.1–36.3)	38 30 pleural 8 peritoneal	2.33	16.3 (11.5–22.4)
Familial	3455[b]	3455[b]	5 All pleural	2.49	2.0 (0.7–4.7)	32 31 pleural 1 peritoneal	1.74	18.4 (12.6–26.0)	37 36 pleural 1 peritoneal	4.23	8.7 (6.2–12.1)
Environmental	25,327	27,126	23 All pleural	5.42	4.2 (2.7–6.4)	49 All pleural	5.47	9.0 (6.6–11.8)	72 All pleural	10.89	6.6 (5.2–8.3)
Town of Broni	9704[c]	10,888[c]	20	1.79	11.2 (6.8–17.3)	28	1.89	14.8 (9.8–21.4)	48	3.68	13.0 (9.6–17.3)
Adjacent towns	8773[d]	9398[d]	2	1.57	1.3 (0.2–4.6)	17	1.57	10.8 (6.3–17.3)	19	3.14	6.1 (3.6–9.4)
Albaredo Arnaboldi	108	95	–	0.02		–	0.02		–	0.04	
Barbianello	411	435	–	0.08		–	0.08		–	0.15	
Campospinoso	409	438	–	0.07		–	0.09		–	0.17	
Canneto Pavese	699	712	–	0.14		2	0.12		2	0.26	
Cigognola	677	720	–	0.14		1	0.13		1	0.27	
Pietra De' Giorgi	444	420	–	0.09		–	0.07		–	0.16	
Redavalle	503	535	–	0.10		–	0.10		–	0.19	
San Cipriano Po	241	226	–	0.03		–	0.03		–	0.07	
Stradella	5281	5817	2	0.91		14	0.94		16	1.85	
Surrounding towns	12,143[d]	12,779[d]	1	2.06	0.5 (0.01–2.7)	4	2.01	2.0 (0.5–5.1)	5	4.07	1.2 (0.4–2.9)
Arena Po	802	816	–	0.13		1	0.14		1	0.28	
Belgioioso	2937	3097	1	0.44		1	0.45		2	0.90	
Casanova Lonati	246	235	–	0.04		–	0.03		–	0.07	
Castana	363	378	–	0.08		–	0.07		–	0.14	
Linarolo	1117	1180	–	0.15		–	0.15		–	0.31	
Lirio	80	67	–	0.02		–	0.01		–	0.03	
Mezzanino	726	735	–	0.12		–	0.12		–	0.24	
Montalto Pavese	451	480	–	0.10		–	0.09		–	0.20	
Montescano	185	201	–	0.03		–	0.03		–	0.06	
Montù Beccaria	869	904	–	0.16		–	0.16		–	0.32	
Mornico Losana	368	358	–	0.08		–	0.07		–	0.14	
Pinarolo Po	776	835	–	0.15		–	0.12		–	0.27	
Portalbera	713	766	–	0.11		1	0.10		1	0.21	
Santa Giuletta	785	858	–	0.15		1	0.15		1	0.30	
Santa Maria della Versa	1209	1330	–	0.22		–	0.23		–	0.45	
Spessa	276	299	–	0.04		–	0.04		–	0.08	
Zenevredo	240	240	–	0.04		–	0.03		–	0.07	

Abbreviations: CI, confidence interval; Exp, expected; Obs, observed; SIR, standardised incidence ratio.
[a] For occupational exposure, the population was estimated using data of the cohort of workers of the Broni factory, which comprised 2741 men and 714 women (Oddone et al., 2014).
[b] For familial exposure, the population was estimated assuming two family members (equal number of men and women) for each worker at the Broni factory (3455 subjects).
[c] For environmental exposure in Broni, we calculated the population at risk assuming a yearly 10% turnover of the population (4411 males and 4949 females on 1 January 2007).
[d] For environmental exposure in adjacent and surrounding towns, the population in each town on 1 January 2007 was used (source: AIRTum).

from the Broni factory (Table 1). The absolute MM excess was greater in women (87 cases, 7.57 expected) than in men (60 cases, 9.88 expected). There were 138 pleural and nine peritoneal MM cases. There were no cases of MM of the pericardium or tunica vaginalis of the testis.

3.1. Occupational exposure in the asbestos cement factory

Of 38 patients with occupational exposure at the Broni factory (2.33 expected), 32 were men (26 pleural and six peritoneal MM) and six were women (four pleural and two peritoneal MM). Although in relative terms the men and the women had similar SIRs (Table 1), the absolute excess was greater in men. At diagnosis, 28 patients (73.7%) were still living in Broni, nine (23.7%) in the adjacent/surrounding towns, and one (2.6%) outside the area. The average length of employment at the Broni factory was 19.2 years, and the 25th, 50th, and 75th percentiles were 11, 19.5, and 25 years, respectively. One worker had been employed for one year at the factory; the others had been employed for 4–35 years. Time since first employment in the factory in Broni (latency) ranged from 21 to 61 years (median: 47 years). There were 18 patients out of 38 (47.4%) with pleural plaques, 14 (43.8%) among the 32 males MM patients and four (66.7%) among the six affected women.

Among the 32 men, 18 had been occupationally exposed to asbestos only within the Fibronit, while 14 had been exposed also in other industrial sectors (10 in construction, two in mechanic, one in refractory material production, and one in both construction and mechanic industries). Except for two men (one employed for one year and the other employed seven years in Fibronit), the length of employment in the asbestos cement factory was longer than the length of asbestos exposure experienced in other industries. All the six affected women had been occupationally exposed to asbestos exclusively in the Broni factory.

3.2. Familial exposure

We identified 37 patients (4.23 expected) with familial exposure: five men (all pleural MM) and 32 women (31 pleural and one peritoneal MM) (Table 1). The greatest excess, in relative and absolute terms, was in women. At diagnosis, 20 patients (54.1%) were still living in Broni, 10 (27.0%) in the area, and seven (18.9%) had moved to other towns in Lombardy. On average, they had lived with a worker for 18.4 years, the 25th, 50th, and 75th percentiles were 12, 18, and 26 years, respectively, and the minimum and maximum durations were two and 39 years, respectively. Latency ranged from 12 to 76 years (median: 54 years). We recorded 13 MM patients out of 37 (35.1%) with pleural plaques, one (20.0%) among the five male MM patients and 12 (37.5%) among the 32 affected women.

3.3. Environmental exposure

All 72 patients (10.89 expected) with environmental exposure residing in Broni or the nearby towns had pleural MM (Table 1). The relative and absolute excesses were higher in women than in men. Among those who had ever lived in Broni, there were 48 patients (20 men, 28 women) against 3.68 expected (Table 1). At diagnosis, 26 patients (54.2%) were still living in Broni, seven (14.6%) in the area, and 15 (31.2%) elsewhere. The average length of residence in Broni was 35.1 years, the 25th, 50th, and 75th percentiles were 18, 39, and 52 years, respectively, and the minimum and maximum durations were two and 70 years. Time since first residence in Broni ranged from 15 to 85 years (median: 50 years). Subjects with pleural plaques were five out of 48 (10.4%), four (20.0%) among the 20 affected men and one (3.6%) among the 28 women.

In the nine towns adjacent to Broni (about 18,000 inhabitants), there were 19 pleural MM cases (3.14 expected); the SIRs were 1.3 (men) and 10.8 (women) (Table 1). In the town of Stradella, there were two cases in men (0.91 expected) and 14 in women (0.94 expected). None of the two male patients living in Stradella had pleural plaques. The women living in Canneto Pavese and Cigognola had no pleural plaques, while there were four (28.6%) among the 14 women living in Stradella.

In the 17 surrounding towns (Table 1) (about 25,000 inhabitants), there were a total five pleural MM cases (4.07 expected): one in men (2.06 expected) and four in women (2.01 expected); the SIRs for the men and women were 0.5 and 2.0, respectively, with wide CIs. Two out of five MM patients (40.0%) had pleural plaques, the male patient and one (25.0%) among the four women.

4. Discussion

In this study we found 147 MM cases (138 pleural, nine peritoneal) between 2000 and 2011 attributable to occupational, familial, or environmental asbestos exposure from the asbestos cement factory in Broni, with an overall excess of about 130 cases above the regional average for non-exposed people. The absolute impact from occupational exposure was greatest in men, but the overall MM burden (excess cases) was higher in women.

Considering occupational and familial exposure together, men and women suffered a similar burden of MM cases (37 and 38, respectively). This result was expected because the workforce in the Broni factory was predominantly male (2741 workers, 79.3%).

In men we estimated a SIR of 2.0 for familial exposure ad a SIR of 4.2 for environmental exposure. The confidence intervals around these SIRs are largely overlapping and they can be considered statistically similar.

Men and women with environmental exposure in Broni had comparable relative risks (SIR 11.2 and 14.8, respectively), but in absolute terms there were more MM cases among women (28 against 20 in men). In the adjacent towns, women had higher relative risks (SIR 10.8) than men (SIR 1.3) and also a higher absolute MM burden (17 cases versus two in men). The largest contribution came from the town of Stradella (14 cases in women against two in men). There are at least two explanations for these gender differences. First, Stradella and Broni are by far the most populated towns. Second, men were in general much more frequently employed in industry/occupations involving asbestos exposure. For instance, in the RML dataset 2000–2011, 1871 (77.0%) out of 2430 interviewed men had been occupationally exposed to asbestos (in any industrial sector or occupation), versus 551/1354 (40.7%) in women.

The study was made possible by the high-quality population registry of MM patients (RML), which has recorded all MM cases among Lombardy inhabitants since 2000 (Mensi et al., 2007). The completeness of the RML was recently evaluated via comparison of its data with that of cancer registries covering four Lombardy provinces (Brescia, Mantova, Milan, Sondrio) in 2000–2004 (Nicita et al., 2014): no MM case was missed by the RML. In the RML, complete collection of clinical information and evaluation of MM cases is performed weekly. The interview rate is high: 94% of MM cases were interviewed in the region (54% patient, 40% next-of-kin); the Province of Pavia, nearest to the factory, had a similar rate (98% interviewed: 53% patient, 45% next-of-kin).

This study has some intrinsic limitations. First, patients who lived outside Lombardy at the time of diagnosis were not included. Second, in the case of environmental exposure, the RML cannot track patients with past residence in the adjacent/surrounding towns who were living outside the area at the time of diagnosis. This results in some underestimation of MM cases and therefore of SIRs. Nonetheless, considering that most subjects (100 out of 123, 81.3%) with occupational, familial, or environmental exposure in Broni (who can be tracked in the RML even if they were to have moved) were still living there at the time of diagnosis, underestimation was probably modest (i.e. we expect we missed about 20% of MM cases in the adjacent/surrounding towns). Third, we were only able to roughly estimate the population at risk and hence the expected MM cases of the workers, their family members, and residents in Broni. In particular, we chose a conservative approach (overestimation of population at risk and therefore of expected numbers). Finally, when analysing environmental exposure, we could not subtract from the resident population the 3455 factory workers, most of whom were also living in the area. Although these intrinsic limitations and approximations led to underestimation of the SIRs, they had little influence when calculating the absolute number of excess MM cases.

4.1. Asbestos levels within the Broni factory

In the period 1981–1990 seven non-systematic campaigns of airborne asbestos monitoring were performed within the Broni factory (Oddone et al., 2014). In 1981 and 1983, levels were below 2 fibres/cc (ff/cc), the recommended threshold at that time. In 1984, levels were below the thresholds for total fibres (5 ff/cc), amosite (0.5 ff/cc), chrysotile (2 ff/cc), and crocidolite (0.2 ff/cc). In 1988, after a breakdown of a machine, high levels of chrysotile and amosite were measured (10 and 2 ff/cc, respectively). The accident also caused the emission of large quantities of asbestos fibres in the environment. In 10 samples collected in March 1990, levels were 1.4 (one sample), 0.8–1.0 (two samples), 0.4–0.6 (one sample), and 0.2–0.4 ff/cc (two samples). In 34 air samples collected in May 1990, levels of asbestos fibres were over 0.4 ff/cc in three samples and between 0.2 and 0.4 ff/cc in two samples.

Unfortunately, no previous measurements (when production was highest, tasks were performed manually, and measures to reduce fibre dispersion were absent) are available. The elevated SMR for asbestosis in the cohort of workers (Oddone et al., 2014) and the presence in this study of pleural plaques in 47.4% of MM cases are indirect signs of high asbestos exposures in the past.

4.2. Environmental asbestos levels in workers' families

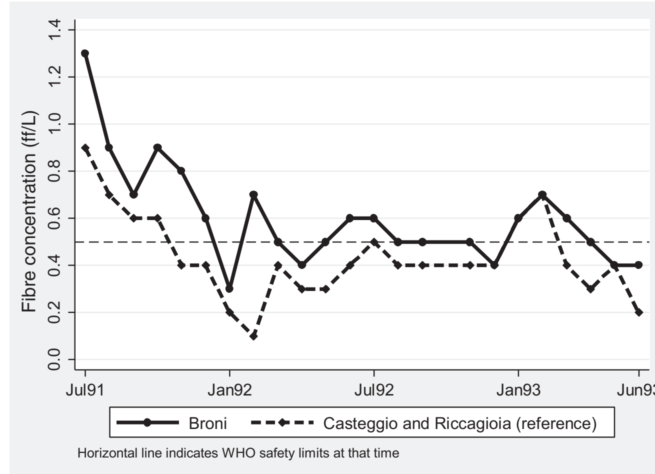
There are no data on asbestos exposure regarding cohabitants of employees in the asbestos cement factory. In this study, the presence of pleural plaques in 35.1% of MM patients indicates that significant asbestos exposure had occurred in the past.

4.3. Environmental asbestos levels in Broni residents

Measurements of airborne environmental levels of asbestos were made in 1991–1993, when the asbestos cement production was declining. Three monitoring stations were established in the town of Broni near the factory, located respectively south/south-east, east/north-east, and north/north-east. One station, taken as reference, was mounted in two sites 15 km south-west, in the town of Casteggio (from July 1991 to June 1992), and Riccagioia, a nearby rural zone (from July 1992 to June 1993) (Ferrari et al., 1994).

Asbestos fibre concentrations were counted using a phase contrast optical microscope (PCM). Average monthly means, reported in the Proceedings of the 13th National Congress of the Italian Association of Industrial Hygienists (AIDII) (Ferrari et al., 1994) are reproduced in Fig. 2. The overall mean/median in Broni (0.60/0.60 ff/L) was higher (p-value = 0.004 from t-test on log-fibre concentration) in comparison with those measured in the reference locations (0.44/0.40 ff/L) and also compared with WHO safety limits in force in those years (0.5 ff/L). Concentrations declined over time in both sampling locations (p = 0.03). In interpreting these results, one should take into account that measures to reduce fibre dispersion in the factory had been implemented in the factory in the 1970s–1980s and that production was declining from tens of thousands per year to 7527 in 1987, 7308 in 1988, 8359 in 1989, 6114 in 1990, 5287 in 1991, 2093 in 1992, and 504 in 1993 (Ferrari et al., 1994).

In 2000 a systematic monitoring project (*Lombardy Region Asbestos Plan*, PRAL) was started. The project was initially focused on the town of Broni. Later, monitoring activities were extended to the main 11 cities in Lombardy to measure background environmental asbestos levels. Analyses are performed by the Lombardy Environmental Protection Agency (ARPA) using a scanning electron microscope equipped with an energy dispersion microanalysis system (SEM-EDS) and a PCM (Agenzia Regionale per la Protezione dell'Ambiente (ARPA) Lombardia, 2011; Somigliana et al., 2009). Several air samples had been taken monthly in seven Broni sites (two near the former Fibronit factory and five within 1 km from it). The annual averages (in ff/L) measured with SEM-EDS were as follows: 0.11 (2000), 0.31 (2001), 0.22 (2002), 0.09 (2003), 0.02 (2005), 0.02 (2005), 0.04 (2006), 0.03 (2007), and 0.012 (2008). The elevated values in 2001–2002 were found in air samples taken while remediation works were being performed in the square in front of the factory. Conversely, the levels measured in 2000 and 2003–2008 were very close to background levels measured in the 11 cities in 2007–2008 (Agenzia Regionale per la Protezione dell'Ambiente (ARPA) Lombardia, 2011; Somigliana et al., 2009). In Broni, the average annual levels (ff/L) measured with PCM were as follows: 1.26 (2004), 1.31 (2005), 0.75 (2006), 0.3 (2007), and 0.4 (2008). It should be noted that PCM counts all type of fibres, while SEM–EDS can discriminate asbestos fibres. In Broni, airborne ultrafine asbestos fibres were measured in 2008–2009: concentrations were quite similar to those found in Milan in the same years (Agenzia Regionale per la Protezione dell'Ambiente (ARPA) Lombardia, 2011; Somigliana et al., 2009).



Source: Ferrari et al. (1994)

Fig. 2. Environmental asbestos concentrations (monthly means, ff/L) in the town of Broni and in two reference sites, the town of Casteggio (July 1991–June 1992) and a nearby rural area (July 1992–June 2003). Source: Ferrari et al. (1994).

No data are available on environmental asbestos levels in Broni at the time the factory was fully active. In our study, the presence of pleural plaques in 10.4% of MM cases witnesses the occurrence of asbestos exposure in the past.

To our knowledge, there are no data on the lung content of asbestos fibres among people living in the Broni area. It might nonetheless be relevant a study that measured asbestos fibre burden in people living in the city of Bari, Apulia, south Italy, where an asbestos cement plant owned by the same company (Fibronit) employed about 417 workers from 1934 to 1989 (Coviello et al., 2002; Mirabelli et al., 2010). Chrysotile (80%), crocidolite (15%), and amosite (5%) were used in the plant. In three non-occupationally exposed MM patients who had been living in Bari <2 km from the plant, there were 110,000 and 1,700,000 ff/g of dry lung in two men and 2,300,000 ff/g in a woman, compared to a mean of 166,000 ff/g in a reference group (13 subjects dead from heart diseases in Brescia, Lombardy region) (Barbieri et al., 2012).

4.4. Oher sources of asbestos exposure in the Broni area

The area of Broni is predominantly rural and one of the major productions is wine. There was a very small asbestos cement factory in Arena Po (Fig. 1), which has been operating using chrysotile since 1963, employing a maximum of 75 workers (Mirabelli et al., 2010). An even smaller (maximum <50 workers) asbestos cement plant was present in Portalbera (Fig. 1). Other industries involving asbestos exposure include, among the others, a shop of rail-road equipment maintenance and factories producing machinery and filters for wine production.

Beyond the 147 MM cases directly or indirectly associated with asbestos exposure from the Fibronit factory, in 2000–2011 the RML recorded 57 MM cases (47 males and 10 females) in the local population. Among men, exposure to asbestos occurred in the following sectors (subjects may have been exposed in more than one sector, therefore the numbers shown exceed the number of MM cases): construction (18 subjects), mechanic (12), transports (six), public administration (five), food and beverage (four), wood and furniture (three), rail-road equipment maintenance (two), energy production (two), and agriculture (one). Among women, asbestos exposure occurred in the sectors: food and beverages (three subjects), textile (two), public administration (two), rail-road equipment maintenance (one), agriculture (one), rubber (one), and refractory material production (one). There were no MM cases employed in the two small asbestos cement plants.

4.5. Comparison with other studies

Previous studies have documented increased mortality from pleural cancer in the Broni area (Table 2) (Amendola et al., 2003; Di Paola et al., 2000; Fazzo et al., 2012a,b; Magnani et al., 1994; Pirastu et al., 2011) and increased mortality from pleural and peritoneal cancers among the factory workers (Oddone et al., 2014). In Broni, 46 deaths from pleural cancer were recorded in 1980–1997 (Amendola et al., 2003), 35 in 1995–2002, and 24 in 2003–2009 (Fazzo et al., 2012b; Pirastu et al., 2011). Therefore, taking into account a partial temporal overlap across studies (1996–97) and the fact that mortality data were not available in 2004–2005, there were 105 deaths against the approximate 10 expected in a 30-year period. There also was excess mortality in nearby towns, most notably Stradella (19 cases in 1995–2002) (Fig. 1) (Fazzo et al., 2012a). Only one study was able to partially assess the incidence of MM using pathology information from a large hospital in Pavia. The authors identified 20 cases (13 men, seven women) of histologically confirmed pleural MM in 1980–1989 in Broni (16 cases), Redavalle (three cases), and Stradella (one case) (Magnani et al., 1994). Differently from our study, these geographical studies showed similar relative risks of pleural cancer mortality in men and in women; only one study found higher risks in women in the period 2003–2009 (Table 2). However, those studies were only based on residence at death and they could not discriminate occupational from other sources of exposure to asbestos, either within the Fibronit or in other industries.

Among 1296 workers in the Broni factory (1254 men, 42 women) still employed there in 1970 or hired subsequently, there were 26 deaths from pleural cancer among men (1.45 expected) and two among women (0.03 expected) in the follow-up period 1970–2004. Seven deaths from cancer of the peritoneum or retroperitoneum were also recorded in men (0.69 expected) (Oddone et al., 2014).

Our study provides additional and updated evidence of the large impact of the Broni factory on MM incidence in the local community. Using detailed clinical and exposure information, we were able to quantify MM incidence and distinguish the impact of different sources of asbestos exposure. Based on the referent non-exposed rates, we estimated a greater excess of MM cases in a shorter interval than previous studies.

Given the large quantities of different types of asbestos used over the years, the excess of MM cases among the factory workers found in this study (38 cases, 2.33 expected) was largely anticipated. Compared to the recent mortality cohort study (Table 2) (Oddone et al., 2014), we estimated a similar relative risk among men (SIR = 16.2 in our study, SMR = 17.99 for pleural cancer and 10.10 for cancer of peritoneum and retroperitoneum in their study). For women, they found an SMR of 68.90 for pleural cancer mortality, much higher than our SIR of 16.7, but based on two deaths only and with a wide confidence interval. The numbers of cases included in our study differ from that analysed

Table 2
Synthesis of mortality studies from pleural or peritoneal cancer in the Broni area, Lombardy, northern Italy.

Reference	Period	Cause of death	R	Men			Women			Total			Towns involved/notes
				O	E	SMR	O	E	SMR	O	E	SMR	
Geographical studies													
Magnani et al. (1994)	1980–87	PC	L	6	0.79	7.59	6	0.55	10.91	12	1.34	8.96	Broni
	1980–87	PC	L	11	1.93	5.70	7	1.31	5.34	18	3.24	5.56	Broni, Cigognola, Redavalle, Stradella Also reports 20 MM histologically verified MMP cases (13 M, 7 F; four in 1980–84, 16 in 1985–89) in Broni (16 cases), Redavalle (3), Stradella (1)
Di Paola et al. (2000)	1988–94	PC	I	–	–	–	–	–	–	21	1.48	14.20	Broni
Amendola et al. (2003)	1980–97	PC	P	27	2.80	9.64	19	1.90	10.00	46	5.6	8.25	Broni
	1980–97	PC	P	55	41.40	1.33	68	44.1	1.54	123	85.0	1.45	Broni (46 cases), Bastida Pancarana (3), Canneto Pavese (2), Casteggio (4), Cigognola (3), Montù Beccaria (2), Pietra De' Giorgi (3), Redavalle (4), Stradella (12), Voghera (22), Others (22)
Fazzo et al. (2012b)	1995–2002	PC	I	22	1.54	14.33	13	0.97	13.40	35	2.51	13.94	Broni. Same results reported in Pirastu et al. (2011)
	2003, 2006–09	MMP	I	11	0.96	11.45	13	0.59	21.85	24	1.55	15.48	Broni
	2003, 2006–09	MMP	I	29	6.05	4.68	28	1.69	17.11	57	7.74	7.36	Males: Broni, Barbianello, Bosnasco, Campospinoso, Canneto Pavese, Corvino San Quirico, Montalto Pavese, Portalbera, Rovescala, Santa Giulietta, Santa Maria della Versa, Stradella, Zenevredo Females: Broni, Arena Po, Bosnasco, San Cipriano Po, Stradella
Fazzo et al. (2012a)	1995–2002	PC	I	39	5.62	7.03	24	2.61	9.34	63	8.33	7.56	Males: Broni (22 cases), Stradella (9), Campospinoso (3), Cigognola (2), Barbianello (2), Casanova Lonati (1) Females: Broni (13 cases), Stradella (10), Castana (1)
Occupational cohort study													
Oddone et al. (2014)	1970–2004	PC	L	26	1.45	17.99	2	0.03	68.90	28	1.48	18.92	Workers (1254 M, 42 F) at the asbestos cement factory in Broni.
		PRC	L	7	0.69	10.10	0	0.03	–	7	0.72	9.72	Males, asbestosis: 3 observed, 0.02 expected SMR 130.69

Abbreviations: E, expected number of deaths; F, female; I, Italy; L, Lombardy region; M, male; MMP, malignant mesothelioma of the pleura; O, number of observed deaths; P, Province of Pavia; PC, pleural cancer: PRC, cancer of the peritoneum and retroperitoneum; R, reference mortality rates used to calculate expected deaths; SMR, standardised mortality ratio.

in the mortality study for a number of reasons. First, we included the whole workforce (3455 subjects). Second, the two studies cover different periods, (2000–2011, 1970–2004). Third, we analysed MM incidence and not mortality which can be affected by disease misclassification (Checkoway et al., 2004).

In our study, the marked MM excess among family members (37 cases, 4.23 expected; mostly women) is likely due to the contamination of the home environment with fibres from work clothes or hair, similarly to what observed among wives of asbestos workers in Italy and other countries (Bourdes et al., 2000; Ferrante et al., 2007; Magnani et al., 1993, 2001; Rake et al., 2009; Reid et al., 2008). Our estimate of MM risk in women (SIR = 18.4) is very similar to that found in the cohort of 1780 wives of workers of the oldest and larger Italian asbestos cement factory (Eternit) located in Casale Monferrato, in the nearby Piedmont region, north-west Italy. The authors found an SMR of 18.00 (based on 21 death from pleural cancer) and an SIR of 25.19 (based on 11 incident pleural MM) (Ferrante et al., 2007; Magnani et al., 1993).

The elevated MM incidence among Broni inhabitants was expected given the closeness of the factory to the centre of the town. It is in agreement with studies performed in asbestos-contaminated areas in Italy and other countries (Barbieri et al., 2012; Boffetta and Stayner, 2006; Magnani et al., 2013; Maule et al., 2007; Reid et al., 2008). A case–control study in Casale Monferrato found particularly elevated odds ratios (ORs) of pleural MM within 5 km from the asbestos cement factory. In particular, taking as reference a distance of >15 km (five cases, 68 controls), the ORs (adjusted for age, sex, asbestos cement occupation, domestic exposure, and relatives' asbestos cement occupation), were 6.8 within 3 km (26 cases, 45 controls) and 12.5 between 3 and 5 km (13 cases, 13 controls) (Maule et al., 2007). The ORs decreased with increasing distance from the plant as follows: 5–7 km, OR = 3.9 (10 cases, 31 controls); 7–9 km, OR = 4.2 (five cases, 16 controls); 9–11 km, OR = 5.6 (six cases, 15 controls); 11–13 km, OR = 1.6 (four cases, 36 controls); 13–15 km, OR = 1.0 (one case, 13 controls). In Broni, where most people lived <3 km from the plant, we found SIRs of 11.2 among men and 14.8 among women, which are in substantial agreement with findings in Casale Monferrato.

In a previous case–control study in Casale Monferrato an odds ratio of 8.2 (12 pleural MM cases, 42 controls) had been found for people living in the surrounding towns, which is similar to the SIR of 6.1 found in our study for the adjacent towns (Magnani et al., 2001). The result for Stradella (14 cases in women, 0.94 expected; 2 cases in men, 0.91 expected) is possibly explained by a combination of facts, including the closeness to Broni (4–5 km, both towns located in the Po River valley, north of the hilly region), the large population involved (over 11,000 inhabitants) (Table 2), and the prevailing winds in the area, with 46% of wind hours >2 m/s directed east (Ferrari et al., 1994). Two adjacent towns (Canneto Pavese, two MM cases, 0.26 expected; Cigognola, one case, 0.27 expected) also showed elevated relative risks (Table 1), while there were no cases in the remaining towns, in which, however, population size is very small (Table 1). Beyond exposure to wind-born asbestos fibres, different sources of exposure can be postulated for people living in adjacent towns, for example residence near streets on which trucks transported asbestos to the factory (Maule et al., 2007). In the surrounding towns (most with very small populations and some partly protected by hills), we found few or no MM cases and a modest overall MM excess.

In Italy, a study using a similar approach evaluated the effect of occupational and non-occupational exposure related to an asbestos mine in Balangero (closed in 1985) among mine workers (including clerical workers and employees of sub-contractors) and their family members, residents in proximity to the mine, and in other occupational groups that used or reused material from the mine (Mirabelli et al., 2008). Using data from the Piedmont mesothelioma registry, the authors found a much higher number of pleural MM cases (14 among mine workers and 13 among other people) in 1990–2001 than previously reported in a cohort study of miners (two cases as of 1987). Similarly, a recent study used the Lazio mesothelioma registry data to identify familial clusters of MM in the Lazio region, central Italy (Ascoli et al., 2014). Studies of this nature are feasible throughout Italy and in other countries in which there are mesothelioma registries. They would contribute to a more thorough evaluation of the magnitude of MM burden attributable to asbestos exposure among workers, their families, and the whole community.

5. Conclusions

This study documents the large impact of an asbestos cement factory in Broni, Italy on MM incidence in the area, where there were about 130 excess cases in 2000–2011. In absolute terms, women suffered a greater MM burden than men, mainly because of diffuse familial and environmental exposure. This study underlines the importance of assessing the impact of asbestos exposure not only among workers, but also among their family members and in the community at large. In fact, approximately half of the MM cases were attributable to environmental exposure, a quarter to occupational exposure, and a quarter to familial exposure. Continuous documentation of the effects of asbestos exposure beyond the occupational setting is important not only for local communities, but also to increase awareness of health effects of asbestos in countries that still use it and in which the perception of the magnitude of health effects attributable to asbestos is still poor.

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