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Title: 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 (1932-1997). Based on data collected by the Regional 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 146 MM cases (12.57 expected), 138 pleural and eight peritoneal, attributable to exposure to asbestos from the factory. Thirty-six cases had past occupational exposure at the factory (0.64 expected), numbering 30 men (25 pleural, five peritoneal) and six women (four pleural, two peritoneal). In the families of the workers, there were 37 MM cases (3.03 expected), numbering five men (all pleural) and 32 women (31 pleural, one peritoneal). Among residents in Broni or the surrounding towns, there were 73 cases of pleural MM (8.90 expected), numbering 24 men and 49 women. The largest MM excess was found in the towns of Broni (47 observed, 3.02 expected) and Stradella (16 observed, 1.51 expected). This study documents the large impact of the asbestos cement factory, with about 133 excess MM cases. The largest MM burden was among women, from non-occupational exposure. Almost half of the MM cases were attributable to environmental exposure.

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Dear Editor of Environment International,

we are submitting a manuscript on the impact of asbestos exposure, related to an asbestos-cement factory, on mesothelioma incidence in a community in northern Italy. Differently from previous works, we were able (thanks to a mesothelioma registry operating in the region), to evaluate the global impact on workers, their family members, and the rest of the population. We found a large overall impact of asbestos exposure, with over 130 excess cases in 12 years. Moreover, the largest burden was in women, and environmental exposure accounted for half of the cases.

Continuous documentation of the effects of asbestos exposure also outside the occupational context is important not only for local communities, but also to increase awareness of the health effects of asbestos in countries that still use it and in which the perception of the real entity of health effects attributable to asbestos is still poor.

We assure that the manuscript is an original work, has not been previously published whole or in part, and is not under consideration for publication elsewhere.

None of the authors have any actual or potential competing financial interests regarding the submitted article.

All authors have read the manuscript, agree the work is ready for submission to a journal, and accept responsibility for the manuscript's contents.

Thank you for your attention and best regards,

Dario Consonni

Milan, July 29, 2014

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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 (1932–1997). Based on data collected by the Regional 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 146 MM cases (12.57 expected), 138 pleural and eight peritoneal, attributable to exposure to asbestos from the factory. Thirty-six cases had past occupational exposure at the factory (0.64 expected), numbering 30 men (25 pleural, five peritoneal) and six women (four pleural, two peritoneal). In the families of the workers, there were 37 MM cases (3.03 expected), numbering five men (all pleural) and 32 women (31 pleural, one peritoneal). Among residents in Broni or the surrounding towns, there were 73 cases of pleural MM (8.90 expected), numbering 24 men and 49 women. The largest MM excess was found in the towns of Broni (47 observed, 3.02 expected) and Stradella (16 observed, 1.51 expected). This study documents the large impact of the asbestos cement factory, with about 133 excess MM cases. The largest MM burden was among women, from non-occupational exposure. Almost half of the MM cases were attributable to environmental exposure.

**Key words:** Asbestos, Mesothelioma, Cancer incidence, Occupational exposure, Familial exposure, 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, actinolite, anthophyllite), although their different potencies have been acknowledged (IARC, 2012). In addition to MM and lung cancer, a causal link has been established between asbestos exposure and cancer of the larynx and ovary, while evidence regarding the association with other cancer sites (pharynx, stomach, colorectal) is still limited (IARC, 2012). For these reasons, several researchers and scientific organisations, including the World Health Organization, International Commission on Occupational Health (ICOH), 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).

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., 2001; Magnani et al., 2013; Magnani et al., 1993; 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, northern Italy, in which an asbestos cement factory (Fibronit) operated between 1919 and 1992, employing about 3,500 workers overall (80% men) (Oddone et al., 2014). In 1932–1992, the factory produced asbestos cement products: Portland cement 325 was mixed with chrysotile and crocidolite, and small quantities of amosite were added to produce asbestos cement tubes and sheets. The

occupational impact among 1,296 workers (1,254 men, 42 women) who were still working there in 1970 or who were hired subsequently was recently investigated (Oddone et al., 2014).

Several geographical studies have shown marked excesses of mortality from pleural cancer among people living in the Broni area (Figure 1) (Amendola et al., 2003; Di Paola et al., 2000; Fazzo et al., 2012a; Fazzo et al., 2012b; 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 the Broni area in a government list of environmentally contaminated sites in Italy. 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 included 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 dust 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 and/or from erosion of asbestos roofs and other asbestos-containing products). We used information on MM cases collected by the Lombardy Mesothelioma Registry (*Registro Mesoteliomi Lombardia*, RML) in 2000–2011. 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*) (Nesti et al., 2003). It collects all MM cases of the pleura, peritoneum, pericardium, and tunica vaginalis of the 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. 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. 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. The industry and occupational history of the people with whom the patients have been living are also recorded. Lifetime asbestos exposure is classified as occupational (certain, probable, possible), familial, 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 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 (4,411 males and 4,949 females on 1 January 2007); 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 (Figure 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 classified cases in mutually exclusive categories according to the following hierarchy: occupational > familial > certain environmental > potential environmental (Nesti et al., 2003).

## *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; Vandembroucke 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 the recently studied cohort size of 1,254 men and 42 women (Oddone et al., 2014), assuming all workers were alive during our study period (2000–2011). For familial exposure, we assumed that each worker in the Broni factory had five family members ( $1,296 \times 5 = 6,480$ , equal number of men and women). For Broni residents, we assumed a 10% yearly turnover of the population to take into account the changing study base (Nelson et al., 2005). Lastly, 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 dei Registri Tumori*, AIRTum) (<http://www.registri-tumori.it/cms/>).

To calculate the expected number of MM cases, we applied to the above populations (considered over a 12-year period, i.e. 2000–2011) the average regional MM incidence rates based on non-exposed cases. For environmental exposure in the surrounding towns, we used sex- and age-specific (5-year classes) reference rates. As we did not know the relevant age distributions, we used a different approach to analyse occupational, familial, or environmental exposure in Broni. In contrast with a dynamic population, a cohort of workers and their cohabitants age with time. We therefore applied the average 2000–2011 regional incidence rates calculated among subjects aged  $\geq 70$  years, which were 4.1 and 3.7 ( $\times 100,000$  person–years). A similar approach was used in a study of MM incidence near an asbestos mine in Balangero, Piedmont, northern Italy (Mirabelli et al., 2008). For the population with environmental exposure while living in Broni, we used as reference the overall non-exposed rates (1.0 and  $0.8 \times 100,000$  person–years in men and women, respectively).

For every exposure category, we calculated the standardised mortality ratio (SMR) 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 146 MM cases (12.57 expected), attributable to occupational, familial, or environmental exposure to asbestos from the Broni factory (Table 1). The absolute MM excess was greater in the women (87 cases, 6.48 expected) than in the men (59 cases, 6.09 expected). There were 138 pleural and eight peritoneal MM cases. There were no cases of MM of the pericardium or tunica vaginalis of the testis.

#### *3.1 Occupational exposure*

Of 36 patients with occupational exposure at the Broni factory (0.64 expected), 30 were men (25 pleural and five peritoneal MM) and six were women (four pleural and two peritoneal MM). Although in relative terms the women had higher SMR (Table 1), the absolute excess was greater in the men. At diagnosis, 27 patients (75.0%) were still living in Broni, eight in the adjacent/surrounding towns, and one outside the area. The average length of employment at the Broni factory was 19.3 years, and the 25th, 50th, and 75th percentiles were 12.5, 19.5, and 25.5 years, respectively. One worker had been employed for one year at the factory; the others had been employed for 4–35 years.

### *3.2 Familial exposure*

We identified 37 patients (3.03 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 the women. At diagnosis, 20 patients (54.1%) were still living in Broni, 10 in the area, and seven had moved to other towns in Lombardy. On average, they had lived with a worker for 19.8 years, the 25th, 50th, and 75th percentiles were 12.0, 18.0, and 26.0 years, respectively, and the minimum and maximum durations were two and 44 years, respectively.

### *3.3 Environmental exposure*

All 73 patients (8.90 expected) with environmental exposure residing in Broni or the nearby towns had pleural MM (Table 1). Among those who had ever lived in Broni, there were 47 patients (19 men, 28 women) against 3.02 expected (Table 1). The relative and absolute excesses were higher in the women than in the men. At diagnosis, 25 patients (53.2%) were still living in Broni, seven (14.9%) in the area, and 15 (31.9%) elsewhere. The average length of residence in Broni was 39.0 years, the 25th, 50th, and 75th percentiles were 18.0, 39.0, and 52.0 years, respectively, and the minimum and maximum durations were two and 70 years.

In the nine towns adjacent to Broni (about 18,000 inhabitants), there were 20 pleural MM cases (2.56 expected); the SMRs were 2.7 (men) and 11.8 (women) (Table 1). In the town of Stradella, there were two cases in men (0.65 expected) and 14 in women (0.86 expected). In the 17 surrounding towns (Table 1) (about 25,000 inhabitants), there were a total six pleural MM cases (3.32 expected): two in men (1.48 expected) and four in women (1.84 expected); the SMRs for the men and women were 1.4 and 2.2, respectively, with wide CIs.

## **4. Discussion**

In this study we found 146 MM cases (138 pleural, eight 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 133 cases. Although the impact from occupational exposure was greatest in men, the MM burden (excess cases) was higher in women because of familial and environmental exposure.

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, the RML cannot track patients living in the surrounding towns who were living outside the area at the time of diagnosis. Nonetheless, considering that most subjects (97 out of 120, 80.8%) 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. 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 1,296 factory workers, most of whom were also living in the area. Although these intrinsic limitations and approximations led to underestimation of the SMRs, they had little influence when calculating the absolute number of excess MM cases over the expected number of cases.

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; Fazzo et al., 2012b; 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 the 30-year period. Moreover, there was

excess mortality in nearby towns, most notably Stradella (19 cases in 1995–2002) (Figure 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). Among 1,296 workers in the Broni factory (1,254 men, 42 women) still employed there in 1970 or hired subsequently, there were 26 deaths from pleural cancer among the men (1.45 expected) and two among the women (0.03 expected) in the follow-up period of 1970–2004. Moreover, seven deaths from cancer of the peritoneum or retroperitoneum were recorded in the 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 (36 cases, 0.64 expected) was largely expected. Compared to the recent cohort study (Oddone et al., 2014), we estimated higher SMRs for both sexes. There are several possible reasons for this difference. First, we analysed MM incidence, not mortality, which can be affected by disease misclassification (Checkoway et al., 2004). Second, the population at risk in our study was only estimated in an approximate manner; in particular, the age of the subjects was not available and we used reference rates for ages  $\geq 70$  years. Third, we used referent rates calculated among subjects unexposed to asbestos. Fourth, the period considered in this study was shorter and more recent, hence the relevant population was older. Although more refined calculations for expected MM cases would have produced a more accurate estimation of the relative MM excess (SMR), we would have obtained very similar results in terms of absolute MM excess (difference between observed and expected cases), considering that the numbers of expected cases would have to be about 1.5 in men and 0.1 in women (against the respective 0.62 and 0.02 estimated in our study) to obtain the same SMRs of the recent formal cohort study (Oddone et al., 2014).

In our study, the marked MM excess among family members (mostly women; 37 cases, 0.72 expected) is likely due to contamination of the domestic environment with fibres from work clothes or hair. Similar findings have been observed among wives of asbestos workers in Casale Monferrato, Piedmont, northern Italy (Ferrante et al., 2007; Magnani et al., 2001), and in other countries (Rake et al., 2009; Reid et al., 2008).

The elevated MM incidence among Broni inhabitants 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)

The result for Stradella (16 cases, 1.51 expected) is probably due to the location of the Fibronit factory in the Broni territory, which is very close to the western border of Stradella. In all other nearby towns, we found few or no MM cases and a modest overall MM excess. Different sources of exposure can be postulated, for example residence near streets on which trucks transported asbestos to the factory (Maule et al., 2007).

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 documented the large impact of the asbestos cement factory in Broni on MM incidence in the area, where there were about 133 excess cases in 2000–2011. In absolute terms, women had a greater MM burden than men, mainly because of 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, half of the MM cases were attributable to environmental exposure, a quarter to occupational exposure, and a quarter to familial exposure. Given the availability of a national MM registration network, studies of this type can be performed in other areas in Italy. Continuous documentation of the effects of asbestos exposure outside the occupational context is also important not only for local communities, but also for increasing awareness of the 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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- Amendola P, Belli S, Binazzi A, Cavalleri A, Comba P, Mastrantonio M, et al. Mortality from malignant pleural neoplasms in Broni (Pavia), 1980-1997 (Italian). *Epidemiol Prev* 2003;27:86-90.
- Ascoli V, Romeo E, Carnovale Scalzo C, Cozzi I, Ancona L, Cavariani F, et al. Familial malignant mesothelioma: a population-based study in central Italy (1980-2012). *Cancer Epidemiol* 2014;38:273-8.
- Barbieri PG, Mirabelli D, Somigliana A, Cavone D, Merler E. Asbestos fibre burden in the lungs of patients with mesothelioma who lived near asbestos-cement factories. *Ann Occup Hyg* 2012;56:660-70.
- Boffetta P, Stayner LT. Pleural and Peritoneal Neoplasms. in: Schottenfeld D, Fraumeni JFJ, eds. *Cancer Epidemiology and Prevention Third Edition*. New York: Oxford University Press. 2006.
- Bourdes V, Boffetta P, Pisani P. Environmental exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis. *Eur J Epidemiol* 2000;16:411-7.
- Breslow NE, Day NE. *Statistical Methods in Cancer Research. Volume II - The Design and Analysis of Cohort Studies*. IARC Sci Publ 1987:1-406.
- Checkoway H, Pearce N, Kriebel D. *Research Methods in Occupational Epidemiology*. New York: Oxford University Press. 2004.
- Delgermaa V, Takahashi K, Park EK, Le GV, Hara T, Sorahan T. Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008. *Bull World Health Organ* 2011;89:716-24, 24A-24C.
- Di Paola P, Mastrantonio M, Carboni M, Belli S, De Santis M, Grignoli M, et al. Esposizione ad amianto e mortalità per tumore maligno della Pleura in Italia (Italian). *Rapporti ISTISAN* 2000;1:1-34.
- Fazzo L, De Santis M, Minelli G, Bruno C, Zona A, Marinaccio A, et al. Pleural mesothelioma mortality and asbestos exposure mapping in Italy. *Am J Ind Med* 2012a;55:11-24.
- Fazzo L, Minelli G, De Santis M, Bruno C, Zona A, Marinaccio A, et al. Mesothelioma mortality surveillance and asbestos exposure tracking in Italy. *Ann Ist Super Sanita* 2012b;48:300-10.
- Ferrante D, Bertolotti M, Todesco A, Mirabelli D, Terracini B, Magnani C. Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. *Environ Health Perspect* 2007;115:1401-5.

- IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 100C: Arsenic, Metals, Fibres, and Dusts. Lyon, France: International Agency for Research on Cancer. 2012.
- ICOH. ICOH Statement: Global asbestos ban and the elimination of asbestos-related diseases (October 2013). *ICOH Newsletter* 2014;12:5-6.
- Joubert L, Seidman H, Selikoff IJ. Mortality experience of family contacts of asbestos factory workers. *Ann N Y Acad Sci* 1991;643:416-8.
- Magnani C, Comba P, Di Paola M. Pleural mesotheliomas in the Po River valley near Pavia; mortality, incidence and the correlations with an asbestos cement plant (Italian). *Med Lav* 1994;85:157-60.
- Magnani C, Dalmaso P, Biggeri A, Ivaldi C, Mirabelli D, Terracini B. Increased risk of malignant mesothelioma of the pleura after residential or domestic exposure to asbestos: a case-control study in Casale Monferrato, Italy. *Environ Health Perspect* 2001;109:915-9.
- Magnani C, Fubini B, Mirabelli D, Bertazzi PA, Bianchi C, Chellini E, et al. Pleural mesothelioma: epidemiological and public health issues. Report from the Second Italian Consensus Conference on Pleural Mesothelioma. *Med Lav* 2013;104:191-202.
- Magnani C, Terracini B, Ivaldi C, Botta M, Budel P, Mancini A, et al. A cohort study on mortality among wives of workers in the asbestos cement industry in Casale Monferrato, Italy. *Br J Ind Med* 1993;50:779-84.
- Maule MM, Magnani C, Dalmaso P, Mirabelli D, Merletti F, Biggeri A. Modeling mesothelioma risk associated with environmental asbestos exposure. *Environ Health Perspect* 2007;115:1066-71.
- Mensi C, Termine L, Canti Z, Rivolta G, Riboldi L, Pesatori AC, et al. The Lombardy Mesothelioma Register, Regional Operating Centre (ROC) of National Mesothelioma Register: organizational aspects (Italian). *Epidemiol Prev* 2007;31:283-9.
- Mirabelli D, Calisti R, Barone-Adesi F, Fornero E, Merletti F, Magnani C. Excess of mesotheliomas after exposure to chrysotile in Balangero, Italy. *Occup Environ Med* 2008;65:815-9.
- Musti M, Pollice A, Cavone D, Dragonieri S, Bilancia M. The relationship between malignant mesothelioma and an asbestos cement plant environmental risk: a spatial case-control study in the city of Bari (Italy). *Int Arch Occup Environ Health* 2009;82:489-97.
- Nelson DI, Concha-Barrientos M, Driscoll T, Steenland K, Fingerhut M, Punnett L, et al. The global burden of selected occupational diseases and injury risks: Methodology and summary. *Am J Ind Med* 2005;48:400-18.
- Nesti M, Adamoli S, Ammirabile F, Ascoli V, Barbieri PG, Cacciarini V, et al. Linee guida per la rilevazione e la definizione dei casi di mesotelioma maligno e la trasmissione delle informazioni all'ISPEL da parte dei Centri Operativi Regionali. Seconda edizione (Italian). Roma: ISPEL. 2003.
- Nicita C, Buzzoni C, Chellini E, Ferretti S, Marinaccio A, Mensi C, et al. A comparative analysis between regional mesothelioma registries and cancer registries: results of the ReNaM-AIRTUM project (Italian). *Epidemiol Prev* 2014;(in press)
- Oddone E, Ferrante D, Cena T, Tunesi S, Amendola P, Magnani C. Asbestos cement factory in Broni (Pavia, Italy): a mortality study (Italian). *Med Lav* 2014;105:15-29.
- Park EK, Takahashi K, Hoshuyama T, Cheng TJ, Delgermaa V, Le GV, et al. Global magnitude of reported and unreported mesothelioma. *Environ Health Perspect* 2011;119:514-8.
- Pearce N. Classification of epidemiological study designs. *Int J Epidemiol* 2012;41:393-7.
- Pirastu R, Zona A, Ancona C, Bruno C, Fano V, Fazzo L, et al. Mortality results in SENTIERI Project (Italian). *Epidemiol Prev* 2011;35:29-152.
- Rake C, Gilham C, Hatch J, Darnton A, Hodgson J, Peto J. Occupational, domestic and environmental mesothelioma risks in the British population: a case-control study. *Br J Cancer* 2009;100:1175-83.
- Reid A, Heyworth J, de Klerk N, Musk AW. The mortality of women exposed environmentally and domestically to blue asbestos at Wittenoom, Western Australia. *Occup Environ Med* 2008;65:743-9.
- Sim MR. A worldwide ban on asbestos production and use: some recent progress, but more still to be done. *Occup Environ Med* 2013;70:1-2.
- StataCorp. Stata: Release 13. Statistical Software. College Station, TX: StataCorp LP; 2013



Stayner L, Welch LS, Lemen R. The worldwide pandemic of asbestos-related diseases. *Annu Rev Public Health* 2013;34:205-16.

Terracini B. The scientific basis of a total asbestos ban. *Med Lav* 2006;97:383-92.

Vandenbroucke JP, Pearce N. Incidence rates in dynamic populations. *Int J Epidemiol* 2012;41:1472-9.

Vianna NJ, Polan AK. Non-occupational exposure to asbestos and malignant mesothelioma in females. *Lancet* 1978;1:1061-3.

**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		Men			Women			Total		
	Male	Female	Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)
<b>All</b>			59	6.09	9.7 (7.4–12.5)	87	6.48	13.4 (10.8–16.6)	146	12.57	11.6 (9.8–13.7)
			54 pleural			84 pleural			138 pleural		
			5 peritoneal			3 peritoneal			8 peritoneal		
<b>Occupational</b>	1,254 <sup>a</sup>	42 <sup>a</sup>	30	0.62	48.4 (32.6–69.1)	6	0.02	300.0 (110.1–653.0)	36	0.64	56.3 (39.4–77.9)
			25 pleural			4 pleural			29 pleural		
			5 peritoneal			2 peritoneal			7 peritoneal		
<b>Familial</b>	3,240 <sup>b</sup>	3,240 <sup>b</sup>	5	1.59	3.1 (1.0–7.3)	32	1.44	22.2 (15.2–31.4)	37	3.03	12.2 (8.6–16.8)
			All pleural			31 pleural			36 pleural		
						1 peritoneal			1 peritoneal		
<b>Environmental</b>	25,327	27,126	24	3.88	6.2 (4.0–9.2)	49	5.02	9.8 (7.2–12.9)	73	8.90	8.2 (6.4–10.3)
			All pleural			All pleural			All pleural		
<b>Town of Broni</b>	9,704 <sup>c</sup>	10,888 <sup>c</sup>	19	1.28	14.8 (8.9–23.2)	28	1.74	16.1 (10.7–23.3)	47	3.02	15.6 (11.4–20.7)
<b>Adjacent towns</b>	8,773 <sup>d</sup>	9,398 <sup>d</sup>	3	1.12	2.7 (0.6–7.8)	17	1.44	11.8 (6.9–18.9)	20	2.56	7.8 (4.8–12.1)
Albaredo Arnaboldi	108	95	-	0.01		-	0.02		-	0.03	
Barbianello	411	435	-	0.05		-	0.07		-	0.12	
Campospinoso	409	438	-	0.05		-	0.08		-	0.13	

Canneto Pavese	699	712	-	0.10		2	0.11		2	0.21	
Cigognola	677	720	-	0.10		1	0.12		1	0.22	
Pietra De' Giorgi	444	420	1	0.06		-	0.07		-	0.13	
Redavalle	503	535	-	0.07		-	0.09		-	0.16	
San Cipriano Po	241	226	-	0.02		-	0.03		-	0.05	
Stradella	5,281	5,817	2	0.65		14	0.86		16	1.51	
<b>Surrounding towns</b>	12,143 <sup>d</sup>	12,779 <sup>d</sup>	2	1.48	1.4	4	1.84	2.2	6	3.32	1.8
					(0.2–4.9)			(0.6–5.6)			(0.7–3.9)
Arena Po	802	816	-	0.10		1	0.13		1	0.23	
Belgioioso	2,937	3,097	1	0.32		1	0.41		2	0.73	
Casanova Lonati	246	235	-	0.03		-	0.03		-	0.06	
Castana	363	378	-	0.05		-	0.06		-	0.11	
Linarolo	1,117	1,180	-	0.11		-	0.14		-	0.25	
Lirio	80	67	-	0.01		-	0.01		-	0.02	
Mezzanino	726	735	-	0.09		-	0.11		-	0.20	
Montalto Pavese	451	480	-	0.07		-	0.08		-	0.15	
Montescano	185	201	-	0.02		-	0.03		-	0.05	
Montù Beccaria	869	904	-	0.11		-	0.15		-	0.26	
Mornico Losana	368	358	-	0.05		-	0.06		-	0.11	
Pinarolo Po	776	835	-	0.11		-	0.11		-	0.22	
Portalbera	713	766	-	0.08		1	0.09		1	0.17	
Santa Giuletta	785	858	1	0.11		1	0.13		2	0.24	
Santa Maria della Versa	1,209	1,330	-	0.16		-	0.21		-	0.37	
Spessa	276	299	-	0.03		-	0.04		-	0.07	
Zenevredo	240	240	-	0.03		-	0.03		-	0.06	

Abbreviations: CI, confidence interval; Exp, expected; Obs, observed; SMR, standardised mortality ratio.

<sup>a</sup> For occupational exposure, the population was estimated using data of the cohort of workers of the Broni factory, which comprised 1,254 men and 42 women who were still working there in 1970 or who were hired subsequently (Oddone et al., 2014).

<sup>b</sup> For familial exposure, the population was estimated assuming five family members (equal number of men and women) for each worker at the Broni factory (1,296 subjects).

<sup>c</sup> For environmental exposure in Broni, we calculated the population at risk assuming a yearly 10% turnover of the population (4,411 males and 4,949 females on 1 January 2007).

<sup>d</sup> For environmental exposure in adjacent and surrounding towns, the population in each town on 1 January 2007 was used (source: AIRTum).

**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	
<b>Geographical studies</b>													
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
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, Bastida Pancarana, Canneto Pavese, Casteggio, Cigognola, Montù Beccaria, Pietra De' Giorgi, Redavalle, Stradella, Voghera, Altri
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	Broni (22 M, 13 F), Barbianello (2 M), Campospinoso (3 M), Casanova Lonati (1 M), Castana (1 F), Cigognola (2 M), Stradella (9 M, 10 F)
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**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 at the asbestos cement factory in Broni
		PRC	L	7	0.69	10.10	0	0.03	-	7	0.72	11.29	

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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.

**Figure 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.

