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The relationship between malignant mesothelioma and an asbestos cement plant environmental risk: a spatial case–control study in the city of Bari (Italy)

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Abstract

Objectives   To estimate the mesothelioma risk and environmental asbestos exposure (EAE) due to an asbestos-cement plant.

Methods A spatial case–control study including 48 malignant mesothelioma (MM) cases occurred in the period 1993–2003 selected from the regional mesothelioma register (RMR) and 273 controls. The disease risk was estimated by means of a logistic-regression model, in which the probability of disease-occurrence is expressed as a function of the classes of distances. A non-parametric method was applied to estimate the full relative risk surface.

Results   Significant MM odds ratio of 5.29 (95 CI: 1.18–23.74) was found for people living within a range up to 500 m centered on the plant. The non-parametric estimation of relative risk surface unveiled a marked peak near the plant not paralleled by the spatial distribution of controls.

Conclusion   Evidence of an association between mesothelioma risk and EAE is highlighted. The role played by the RMR in increasing the public health local authorities awareness is stressed.

Keywords   Asbestos-cement plant · Environmental-neighborhood exposure · Mesothelioma register · Spatial case–control study · Public health · Italy

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Introduction

An increased mortality rate due to malignant mesothelioma (MM) was documented in many European nations and Italy during the 1990s that was related to the massive spread of asbestos used during the 1950s and the 1960s (Albin et al. 1999; Comba et al. 2005; Bianchi and Bianchi 2007). Some authors have estimated that the growing incidence of this tumor observed in the last decades will reach a peak between 2010 and 2020 (La Vecchia et al. 2000; Marinaccio et al. 2005; Pannelli et al. 2006). However, recent updates of predictions have shown a different picture, in some countries (i.e., Sweden) mesothelioma rates are leveling off (Burdorf et al. 2005). The onset of mesothelioma has been related to inhalation of asbestos fibers, and there is no evidence of a minimum exposure threshold below which there is no risk (Hillerdal 1999; Goldberg and Luce 2005).

After occupationally induced cases, environmental cases are being revealed at an ever increasing rate. Many studies have demonstrated an increased risk, even in the general population, associated with relatively low asbestos exposure of environmental type (Bourdes et al. 2000; Boffetta 2006). The environmental pollution was reported to be

derived from industrial sites or mines, from the presence of asbestos in buildings (asbestos in place), but also from natural contamination of the soil, in which case exposure can date right from birth (Pasetto et al. 2005).

An excess risk has been observed in populations living near asbestos cement factories (AC factories): on substantive evidences have been reported in studies from Great Britain (Newhouse and Thompson 1993), Germany (Schneider et al. 1996); Poland (Szeszenia-Dabrowska et al.1998) and in a multicentric study conducted in six areas of Italy, Spain and Switzerland (Magnani et al. 2000).

The Eternit was the largest asbestos cement manufacturing company in Europe (DeGiovanni et al. 2004) and in Italy. It has been shown that this production sector has caused an extension of the risk of tumors to the nonworking population living near production plants in many geographical areas: Casale Monferrato, Broni and Bari (Magnani et al. 2001; Amendola et al. 2003; Bilancia et al. 2003). The risk excess was found to be inversely correlated to the distance between the subject's residence and the factory. The same data were also reported recently by the National Register of Mesotheliomas (ReNaM-II Report 2006) (http://www.ispesl.it/ispesl/sitorenam).

This study analyzes the spatial distribution of residence of MM cases without occupational or domestic or household exposure in the city of Bari. An AC factory, named Fibronit in which was documented during 50 years of activity use of amphiboles, was located inside the urban area. The aim of this study is to verify whether there is evidence of a greater concentration of MM cases, due to environmental (neighborhood) exposure around the Fibronit AC plant, and to assess the influence, on mesothelioma onset, of the distance of subjects' residences from this factory.

Materials and methods

The factory and the town

The factory was active from 1934 to 1989 and then abandoned, but the area still has not been safely decontaminated and reclaimed. The size of the work force varied over time and never exceeded 450–500 workers. During the earliest years, from 1934, the plant was located outside the urban area, but later during the 1950s urban expansion progressively reduced the distance from the closest residential areas to less than 50 m. The factory produced plane and corrugated sheets, pipes and pressure pipes and special AC products; in 1974 the company notified the use of blending asbestos (about 80% chrysotile, and 20% amphiboles (15% crocidolite and 5% amosite).

Continuous airborne emissions of both chrysotile and amphiboles fibers were due to stack plume and dispersion from the plant area caused by wind. The data on environmental asbestos concentration inside the factory were not available until 1970 when up to 20 fibres per cubic centimeter (ff/cc) of airborne asbestos fibres (with length > 5 µm and diameter > 0.3 µm) were measured. In 1972 up to 10 ff/cc was found, and in 1974 after reclamation, concentrations ranging from 4 up to 19 ff/cc were reported (Coviello et al. 2002). However, the relevance of the environmental exposure outside the factory was not taken into account until the middle of the 1970s when environmental measurements were also taken close to the plant in nearby areas located far from the roads and not much polluted by the urban traffic; the mean concentration values equal to 16.06×10^{-4} "particles (<5 µm in size) per cc of air" were reported (Napoli 1975).

Besides AC production and related activities i.e., warehousing, transportation of raw asbestos and final finished products, no other noticeable sources of asbestos exposure of industrial origin were recorded in Bari. In today's urban environment asbestos exposure problems persist. Recently an area along the urban beach, named Torre Quetta, was identified, where waste materials from the AC plant have been unlawfully discharged for about 20 years (1950–1970).

Exposure assessment

No data on environmental asbestos concentration are available from the 1940s and 1960s, which was the full-production period of the factory, when considering mesothelioma latency the relevant exposures occurred. Consequently, regarding the expected dispersion of asbestos fibers from the plant over the relevant historic periods we have considered wind and weather patterns. A preliminary analysis of winds prevalent direction and force from 1961 to 1990 was performed, according to data provide by the Station Bari-Palese Air Force National Centre for Meteorology and Climatology Aeronautics. Monthly frequency distribution of winds at ground level for each synoptic hour (00, 03, 06, 09, 12, 15, 18, 21) were considered. No evidence of prevalent winds direction was found. Moreover the application of an anisotropic model for risk assessment as function of distance and direction of prevalent addresses not showed significant results. Therefore the residential history and the distance from the AC factory was considered as a proxy for environmental asbestos exposure in the current study.

In 1991, after the production ceased, the resident population in the three quarters bordering the factory

numbered 99.402 inhabitants, according to the census survey. As reported by the regional mesothelioma register during the last 20 years an increased number of MM among residents has been emphasised and endangerment of inhabitants health living closely to the Fibronit asbestos-cement factory, as well.

Study population

The study compares the distribution of addresses in the city of Bari between cases of malignant mesothelioma, resident in the same city at diagnosis, incident in 1993–2003 and dying before the time of the study with the corresponding distribution of controls from a random sample of decedents in Bari in the same calendar date. For each case the regional mesothelioma register verified the lack of any occupational asbestos exposure i.e., certain, probable or possible occupational exposure, as defined in the register guidelines [http://www.ispesl.it/ispesl/sitorenam/lineeguida.htm], so that only cases with nonoccupational exposure were included.

Cases

The records of the MM cases listed in the Apulia regional mesothelioma register from 1993 to 2003 were analyzed. The register ensures complete, quality information on exposure and diagnosis thanks to the adoption of operative guidelines agreed at national level. All the cases in the register were subjects with histological confirmed mesothelioma. Exposure to asbestos: occupational, household, neighborhood or environmental was assessed and classified by interviewing subjects affected by mesothelioma (or their relatives), during face-to-face interviews, with a standardized questionnaire following National Mesothelioma Register (ReNaM) guidelines [http://www.ispesl.it/ispesl/sitorenam/lineeguida.htm]. The questionnaire is designed to reconstruct demographic characteristics, life habits and, among the others, the lifelong occupational and residential histories. Information on residential locations includes the address and description of each dwelling and its neighbourhood environment. Moreover complete residential history were also retrieved for each case from Municipality Registries.

Of 108 MM cases, 48 nonoccupationally exposed cases incident in Bari during the period considered (1993–2003) i.e., 43% of incident cases, fulfilled the inclusion criteria. As a result MM cases admitted to the study were deceased cases with neither records of occupational nor domestic nor household exposure (i.e., subjects living with at least one worker with certain probable or possible occupational exposure or subjects exposed to asbestos or products containing asbestos, present in their home).

Controls

The controls were randomly selected from the births and deaths registry of the Bari municipality by calendar date of death among deaths due to causes other than mesothelioma. Data on sex, date and place of birth, date place, cause of death and complete residential history were retrieved for each control from municipality registries. No data on occupational or household or domestic asbestos exposure were available.

Matching for date of death, sex and date of birth, initially requested to Registry office staff failed because of noncomputerization of data before 1998. Matching was considered reliable only as regards the same calendar date of death for cases and controls (see Table 1 for the results of matching by date of death).

For the period 1993–2003, 48 cases referable to environmental (neighborhood) exposure and 273 nonmatched controls were available, cases and controls both with residential history provided by municipality records.

Due to the method of selection of controls, without matching for sex and age, these two variables were considered as confounding factors and expressed as covariates in the various parametric models used for producing risk estimates.

Residential history and geo-referencing

The complete residential history was available for each individual (cases and controls), corresponding to the residence addresses throughout the life of the individual, together with the date of taking up and leaving residence at each address.

All the addresses were geo-referenced as geographic coordinates (in sexadecimal degrees), precise to the third decimal figure, using the tool Maporama, information available online and collected in 2005 at the site http://www.maporama.com, the precision achieved by the mapping tool is comparable to that of a GPS system (i.e., about 5 m within urban areas). The geographic coordinates were transformed into metric coordinates (UTM-WGS 84), for graphic representation and calculation of the distances, using WinDatum conversion software.

The attribution of the residence address to each individual was made according to two criteria: considering the prevalent residence (i.e. the address where the individual lived for the longest time during her/his life) and the nearest residence to the source of environmental risk (i.e. the address closest to the AC factory). Both references are useful because the duration, as well as the intensity of exposure, influence the probability of contracting MM.

In any case the residence addresses of the last fifteen years before date of diagnosis for cases or before the date

of death for controls were excluded, in view of the minimal latency period of the disease. Herein we contemplate only results referred to the prevalent addresses for minimizing the number of false positives.

Statistical methods

The data in a spatial case–control study consist of two series of points corresponding to the spatial locations of cases of the disease in a given geographic area over a given period of time, and of a sample of controls extracted from the population at risk.

The spatial distribution of the points is considered as a realization of a spatial stochastic process (Gatrell et al. 1996). The spatial variations of the process generating the data can firstly be studied by considering its first order properties: the intensity function $\lambda(x)$ of the process corresponds to the mean number of events for an infinitesimal area dx, varying with the location x. In order to estimate such intensity functions for the two spatial processes corresponding to cases and controls, we used a Gaussian kernel density estimator depending on a common smoothing parameter named bandwidth (Rogerson 2006). For the critical issue of choosing such smoothing parameter a standard approach based on the minimization of the mean squared estimation error was used (Berman and Diggle 1989). Kernel density estimates can be used to produce smooth maps of the spatial variation in disease risk. While estimation of the intensity of a single point pattern of cases may shows area of low and high risk, its utility is limited because it may largely reflect the underlying pattern of the population at risk; the risk surface can then be assessed by plotting a log of the case to control estimated intensity ratio. This approach was not suitable for our data due to the control estimated intensity being often zero in under populated areas of the municipality. It is therefore preferable to consider the standardized difference between the two kernel estimates of the intensity functions, defined according to Han et al. 2005

$$\frac{\sqrt{\hat{\lambda}(x)_{\text{cases}}} - \sqrt{\hat{\lambda}(x)_{\text{cantrols}}}}{s.d.\left(\sqrt{\hat{\lambda}(x)_{\text{cases}}} - \sqrt{\hat{\lambda}(x)_{\text{cantrols}}}\right)} \qquad (1)$$

The above methods allow to produce a map of the relative risk surface and identify "peaks" and "troughs" in the data. Raw methods for the detection of clustering in relation to a pre-specified source rely on semi-parametric tests based on the distance of cases and controls from the source: the Cuzick and Edwards (CZ) test (Cuzick and Edwards 1990), for example, is a very simple procedure based on the count of the number of cases within the K nearest cases and controls of the source. Under the null

hypothesis of no clustering, the test statistic has an exact hypergeometric distribution: the parameter K is commonly set equal to a fraction of the total sampling dimension (5 or 10%). Other procedures for case–control data do exist (Morris and Wakefield 2000), although they have a low statistical power in common with the CZ test.

Isotropic focused analyses (Morris and Wakefield 2000) included the consideration of four circular bands, whose center coincide with the factory location, and having a width equal to 500 m. The risks (odds ratios) of each band were estimated using a logistic regression model in which the probability of disease occurrence is expressed as a function of the classes of distance (using distances greater than 2,000 m as the reference category), controlling for sex and age. The odds ratios and confidence intervals were obtained by exponential transformation of the corresponding parameter estimates in the logistic regression model.

We also estimated an extension of the previous logistic regression model, obtained without discretizing the distances from the putative source of risk. We defined the following additive log-linear models for disease odds at location x

$$\text{odds}(x; \theta) = \exp\left\{\theta_0 + \sum_{j=1}^{p} \theta_j z_j(x) + h(x)\right\} \qquad (2)$$

where $z_j(x)$ represent known risk factors associated to individual spatial locations (in our case sex and age class) and $h(x)$ is a non-linear function that describes the relation between the spatial odds and the distance from the putative risk source. The distance function adopted in this study has the following expression

$$h(x) = \log\left[1 + \alpha \exp\left(-\|x - x_0\|^2 \big/ \beta\right)\right] \qquad (3)$$

where α represents the relative increment of the risk of disease at the pollution source, $\|x - x_0\|$ is the distance of point x from the risk source x_0 and β describes the reduction of risk as the distance from the source increases (Diggle and Rowlingson 1994; Biggeri et al. 1996).

Maximum likelihood estimates of the relevant parameters were computed by the R function tribble2 (http://www.maths.lancs.ac.uk/~rowlings/Software/Tribble/) (Rogerson 2006, Diggle and Rowlingson 1994). We also carried out a likelihood ratio test that takes the absence of an effect of distance from the pollution source as the null hypothesis—i.e. $H_0 : h(x) = 0$. From this standpoint this likelihood ratio test takes on the specific meaning of a focused clustering test. Though the likelihood of the model (2) is very flat, we claim that this does not affect the use of the test, as it is only the ratio of the two likelihoods under the null and the alternative hypothesis that conveys the desired information (Biggeri et al. 1996).

Results

The complete data set and the distribution of sex and age classes for the cases and controls are shown in Tables 1 and 2, whereas the spatial distribution of the residence addresses and the empirical distribution functions of the distances—below 2,000 m—from the AC factory for cases and controls is shown in Fig. 1. The curve referring to the cases is almost invariably above the curve for controls, showing a tendency for the addresses of cases to be nearer to the AC factory than those of controls, although a two sample Kolmogorov–Smirnov test with unidirectional alternative was not statistically significant ($P = 0.32$).

Spatial exploratory data analysis is based on the standardized difference between the kernel intensity estimates for cases and controls. A preliminary analysis of the mean squared error of the kernel estimates allows the optimal bandwidth for the estimates to be determined; to facilitate the comparison the same 360 m bandwidth was considered for both cases and controls. The resulting map is reported in Fig. 2: the spatial pattern shows a peak near the factory, the addresses of the cases feature a spatial cluster near the AC factory, which is not paralleled by the spatial distribution of the controls, representing the overall mortality. However, observing the estimated risk surface it can be seen that there are other secondary peaks corresponding to

minor disease clusters: it is worth noticing that a cluster of six cases is located to the east of the plant location, close to the "Torre Quetta" urban beach, where during 1950–1970 years a not licensed waste disposal occurred. Excesses of background mortality (light grey areas) are observed around the city center where the highest population density occurs.

Preliminary focused analysis based on the CZ test was not able to give conclusive evidence: p-values for test statistics with K set equal to 5 or 10% of the total sampling dimension were, respectively, $p_{5\%} = 0.07$ and $p_{10\%} = 0.08$.

To analyze exposure effects as a function of the residential location, we classified subjects as residents in concentric bands at increasing distance from the AC factory. Table 3 shows the risk estimates in concentric geographic bands, obtained with the log-linear model that controls for the confounding variables (sex and age classes). A remarkable odds ratio (OR = 5.29, 95% CI: 1.18–23.74) was found within the band including distances up to 500 m: other odds ratio are above one, but their statistical significance is questionable. Results also show that the OR for the lowest exposure group (in terms of distance from the plant, 1,500–2,000 m) is considerably elevated (OR = 2.31, 95% CI: 0.88–6.06): a reasonable explanation is grounded on the fact that incident cases falling into this distance band include the secondary "Torre Quetta" cluster (see Figs. 1, 2). The estimated OR increases accordingly (with respect to the 1,000–1,500 m band), whereas the non significant P value points out that such raised incidence cannot be associated with the environmental pollution around the AC plant location.

Explicit testing of the presence of a spatial trend in the risk can be assessed by fitting the model described in expressions (2) and (3), which takes into account the distance from the factory in the calculation of the risk of mesothelioma and adjusts fr the effects of the confounding variables (Diggle and Rowlingson 1994). The likelihood

Table 1 Distribution of cases and controls and case to control ratio by year of death

Year of death	Cases	Controls	Ca/Co
1993–1994	10	45	0.22
1995–1997	9	51	0.18
1998–2000	20	108	0.19
2001–2003	9	69	0.13
Tot.	48	273	0.18

Table 2 Distribution of the 48 cases and 273 controls by sex and age classes at death

Age	Cases M	Cases F	Total cases	Controls M	Controls F	Total controls
≤49	1 (3.70)	4 (19.05)	5 (10.42)	7 (3.40)	3 (4.48)	10 (3.66)
50–54	1 (3.70)	3 (14.29)	4 (8.33)	4 (1.94)	2 (2.99)	6 (2.20)
55–59	4 (14.81)	1 (4.76)	5 (10.42)	18 (8.74)	2 (2.99)	20 (7.33)
60–64	3 (11.11)	5 (23.81)	8 (16.67)	15 (7.28)	2 (2.99)	17 (6.23)
65–69	2 (7.41)	2 (9.52)	4 (8.33)	20 (9.71)	3 (4.48)	23 (8.42)
70–74	4 (14.81)	1 (4.76)	5 (10.42)	15 (7.28)	6 (8.96)	21 (7.69)
75–79	5 (18.52)	2 (9.52)	7 (14.58)	39 (18.93)	5 (7.46)	44 (6.12)
80–84	4 (14.81)	2 (9.52)	6 (12.50)	37 (17.96)	16 (23.88)	53 (19.41)
85–89	2 (7.41)	0 (0.00)	2 (4.17)	31 (15.05)	12 (17.91)	43 (15.75)
≥90	1 (3.70)	1 (4.76)	2 (4.17)	20 (9.71)	16 (23.88)	36 (13.19)
TOT	27 (100)	21 (100)	48 (100)	206 (100)	67 (100)	273 (100)

Fig. 1 Map of residence addresses of cases and controls and distribution of cumulative frequencies of the distances from the asbestos-cement factory
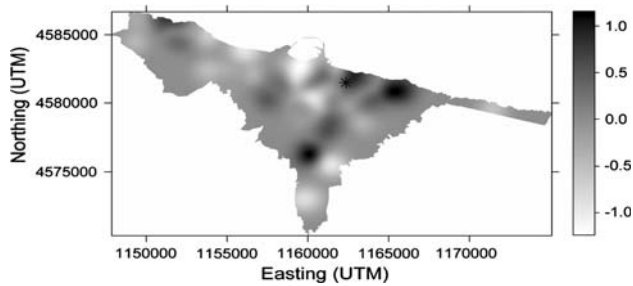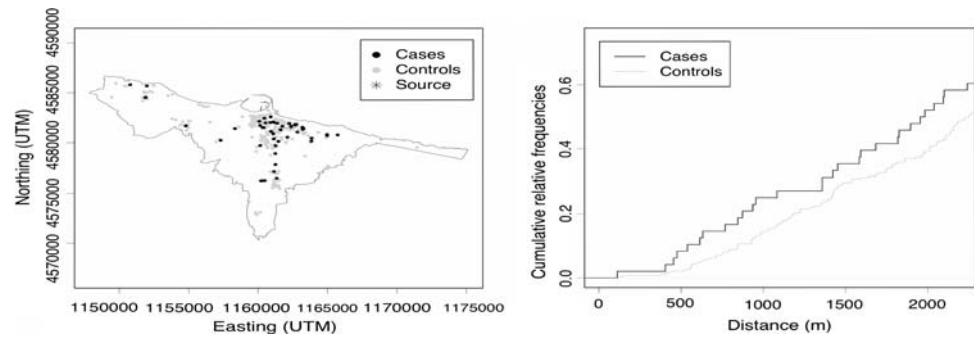

Fig. 2 Standardized difference between the kernel estimates of the intensity function for cases and controls

Table 3 Estimated risk and confidence intervals (CI) by classes of geographic distance in meters from the AC factory adjusted for sex and age

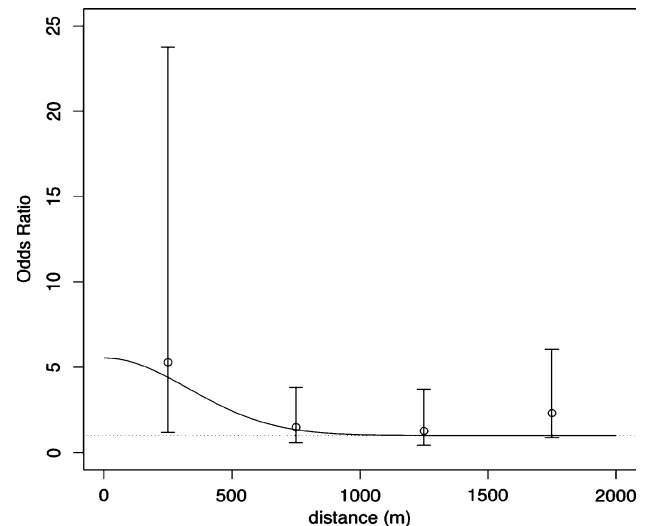| Distance	Cases		Controls		OR	95% CI
	n	Percentage	n	Percentage		
0–500	4	8.33	6	2.20	5.29	1.18–23.74
500–1,000	8	16.67	33	12.09	1.49	0.58–3.82
1,000–1,500	5	10.42	42	15.38	1.27	0.49–3.71
1,500–2,000	8	16.67	26	9.52	2.31	0.88–6.06
>2,000	23	47.91	166	60.81	REF	

Fig. 3 Risk estimates for mesothelioma adjusted for sex and age classes as a function of the distance from the AC factory, using Diggle and Rowlingson's model (*curve*) and odds ratios (*points*) with the logistic regression model (*arrows* indicate 95% confidence intervals)

ratio test, that hypothesizes the absence of an effect of distance from the pollution source under the null hypothesis ($H_0 : h(x) = 0$), shows strong evidence in favor of the model whereby the spatial odds depend on the distance ($P = 3.2 \times 10^{-5}$). The graph in Fig. 3 shows the function describing the behavior of the risk of mesothelioma, according to the distance from the AC factory, estimated with the above model, together with the odds ratios estimated with the logistic model shown in Table 3.

Discussion

This study extends our previous investigation (Bilancia et al. 2003) and in agreement with literature suggest the presence of an association between MM incidence and asbestos environmental pollution around the AC factory. The importance of non-occupational, domestic or environmental (neighbourhood) asbestos exposure has been underlined in many reports (Bourdes et al. 2000; Boffetta 2006; Pasetto et al. 2005; Magnani et al. 2000; Magnani et al. 2001; Maule et al. 2007). Our study is a further contribution to explain the asbestos drama in the city of Bari, the presence of the AC factory has been related with the onset of malignant mesothelioma among the neighboring resident population.

Environmental asbestos pollution can cause MM. In the epidemiological literature is clear that amphibole fibres cause mesothelioma after residential exposure (Reid et al. 2008, Osman et al 2007) while the debate regarding chrysotile as a risk factor for MM will likely continue for some time. Although a recent study (Mirabelli et al 2008) pointed out evidence to the carcinogenicity of chrysotile amphibole (tremolite) free and non occupational exposure. The Bari

AC factory reported the use, and therefore the released, of chrysotile certainly contaminated by amphibole. The blending asbestos used was composed of 80% chrysotile, and 20% amphiboles, so that during the '70 s years environmental measurements taken close to the plant reported mean concentration values equal to 16.06×10^{-4} "particles (≤ 5 µm in size) per cc. of air" (Napoli 1975).

About the design of this study it must be stressed that the role of geographical studies in environmental epidemiology and their importance in terms of public health has been firmly established in the literature: general purpose spatial statistical methods are available (Elliott and Wartenberg 2004, Mather et al. 2004), that can be easily integrated with in-depth analytical epidemiological studies (Bianchi et al. 2006). Geographic information systems (Nuckols et al. 2004 2004) as well as new methods for the analysis of disease risk as a function of the distance from a known source of risk (Biggeri et al. 1996; Vieira et al. 2002) contribute to provide evidences that environmental exposure from industrial sources increases cancer risk among neighboring residents (Comba et al. 2003). Evidence of the health effects of exposure to environmental asbestos from natural source and the odds of MM related to the distance from the nearest source of naturally occurring asbestos has been calculated by Pan et al. 2005. The importance from a public health point of view of non occupational asbestos exposure for the risk of mesothelioma has also been highlighted (Goldberg and Luce 2005).

Some limitations of this study, concerning the quality of data, should be discussed.

Despite the fact that the relationship between pleural mesothelioma and Fibronit company with the related occupational and environmental risk in the city of Bari is obvious, we used the available information on cases and controls residential histories in order to provide a detailed analysis of the spatial variation in the MM risk from environmental asbestos exposure. Our results were consistent with a similar study concerning another italian area (Casale Monferrato) with a large Eternit AC factory (Maule et al. 2007), although with an excess risk fewer than those observed by Maule due to the smaller number of cases in our study.

We have considered sex and age as confounding factors to be expressed as covariates in the various risk estimation models to avoid one limit of the study due to our inability to match cases and controls. Another limitation concerns the fact that the procedure used to select the controls did not enable us to verify lack of occupational exposure to asbestos and any other information on asbestos exposure except distance to the plant, although controls do not show a tendency to cluster around points of interest for asbestos exposure (factories, harbor etc). Notwithstanding these limitations the worst scenario is an underestimation of

mesotelioma risk, which makes our results valid from a conservative standpoint.

Despite the small number of cases in the sample the availability of lifetime residential history (historical certificates of residence) was a pre-requisite for admitting cases and controls to the study (Han et al. 2005; Jacquez et al. 2006). Moreover both cases and controls were included in the study if the residence in the city of Bari covered their entire residential history.

We have examined various criteria to select the addresses to be included in the spatial analysis in order to control for the various types of bias that could be introduced. The addresses taken into account were the prevalent ones (longest period of residence), to minimize the number of false positives.

Other important issues concern statistical methodologies used throughout the study. The use of a Gaussian kernel to estimate the risk surface is not crucial to our results, it is recognized in the literature on point processes that non parametric estimates of the intensity function are substantially independent of the choice of kernel function, the use of others kernel function yielded entirely comparable results to those presented in this paper (Diggle 2003).

Another choice that may appear arbitrary is the functional shape (3) used to model the risk as a function of the distance from the putative pollution source; however, this features an exponential fall of the risk as the distance increases, using a sufficiently flexible specification to fit any real situation (Dreassi et al. 2007). Moreover, in model the risk has the desirable property of tending toward 1 when the distance from the pollution source tends to infinity: this baseline value allows immediate identification of any excess or deficiency in the disease odds, within a finite distance from the putative risk source.

Focused analyses were made, in agreement with Maule et al. 2007, by using the distance from the factory as a proxy of the environmental exposure, in order to confirm the hypothesis of an increase of the disease incidence due to proximity to the risk source (AC factory). It is worth noticing that the odds ratio for the cases and controls falling in the distance band 0–500 m (OR = 5.29, 95% CI = 1.18–23.74) prompts for a significant increase of the MM risk: the effect of the modest sample size on the strength of conclusions, must be carefully evaluated in the light of statistical evidence produced by the diverse methods used in the study. The significant odds ratio among those living closest to the factory (0–500 m) can be considered as a validation of the risk peak observed around the plant location, a local excess that is apparent on the estimated risk surface (Fig. 2). These result are further strengthened by the highly significant P value ($P = 3.2 \times 10^{-5}$) obtained for the model (2) whereby the

spatial odds depend on distance, versus the null model not including the distance effect: this is a convincing evidence that the pattern of incident cases around the factory cannot be considered as completely random.

In any case, over the specific findings from this site, the potential applicability of this approach in other settings should be highlighted in line with the specific interest of environmental epidemiology to describe the spatial relationship between disease occurrence and a purported exposure source in the context of a registry-based case control study.

In conclusion, we believe that the intersection of all our results provides a little but decisive evidence in support of the existence of an association between MM incidence and asbestos environmental pollution around the AC plant. We have also verified the lack of strong potential confounders, no other known sources of asbestos pollution were present in the urban area. The diffusion process of the asbestos fibers from the factory to the surrounding zones was favored by physical mechanisms and this is strongly confirmed by tracing the progressive urbanization phenomenon of the city of Bari around the factory. Around the middle of the 1930s, when the factory was opened, the site was outside the urban weave; over the following 3–4 decades the city grew and incorporated the factory, continuing to expand in a southwards direction until the 1990 s. During the 1950s–1960 s years many council houses and low-cost flats were built in this zone and many workers moved near to the factory. Some workers with their families even lived inside the factory in the company flats (Musti et al. 2002).

Past intensive use of asbestos has implied severe public health consequences among Bari inhabitants. Results reported in our study support the evidence of an increased disease incidence around the Fibronit AC factory in Bari. From 2003 on other fifteen new MM cases with environmental exposure have been registered among residents close to the AC factory.

Failure to reclaim and safely decontaminate the industrial site present inside the urban weave is still a serious public health problem that should not be underestimated. It must also be stressed that the scientific support of the case series collected by our regional mesothelioma register, recording the number of cases among residents in the zone around the AC factory, has increased the awareness in the citizens of Bari and has induced the Authorities to schedule decontamination of the site taking an important step forward in safeguarding public health.

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