Mesothelioma mortality surveillance and asbestos exposure tracking in Italy

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Abstract. Introduction. Spatial distribution of mortality from pleural mesothelioma (which in the ICD-10 Revision has a specific code: C45.0) in Italy for the period 2003-2009 is described. Previous mortality studies at national level employed the topographic code “Malignant neoplasms of pleura”, because of unavailability of a specific code in ICD-9 Revision for pleural mesothelioma. Methods. Standardized mortality ratios were computed for all municipalities, using each regional population as reference; for municipalities in Regions with rate higher than the national rate, the latter has been used as reference. SMRs were computed specifically also for each Italian Polluted Sites “of national concern for environmental remediation” (IPS) with asbestos exposure sources, composed by one or more municipalities, using regional rate as reference. Spatial Scan Statistics procedure, using SatScan software, was applied in cluster analysis: the country was divided into geographic macro-areas and the relative risks (RR) express the ratio of risk within the cluster to the risk of the macro-area outside the cluster. Clusters with p-value < 0.10 were selected.

Results. The national standardized annual mortality rate was 1.7 cases per 100,000. Several areas with evident burden of asbestos-related disease were detected. Significant clusters were found in correspondence to asbestos-cement industries (e.g. Casale Monferrato, women: RR = 28.7), shipyards (e.g. Trieste, men: RR = 4.8), petrochemical industries (e.g. Priolo, men: RR = 6.9) and a stone quarry contaminated by fluoro-edenite fibres (Biancavilla, women: RR = 25.9). Some of the increased clusters correspond to IPS.

Conclusions. The results may contribute to detect asbestos exposure and to set priorities for environmental remediation.

Key words: mesothelioma, geographic mortality, asbestos, polluted sites.

Riassunto (Analisi della mortalità per mesotelioma ed esposizione ad amianto in Italia). Introduzione. Viene illustrata la distribuzione spaziale in Italia della mortalità per mesotelioma pleurico (che nella decima revisione ICD ha un codice specifico: C45.0) per gli anni 2003-2009. Studi precedenti a livello nazionale avevano invece utilizzato il codice topografico “Tumori maligni della pleura”, in assenza di un codice specifico in Nona Revisione ICD per il mesotelioma pleurico. Metodi. I rapporti standardizzati di mortalità (SMR) sono stati calcolati per tutti i comuni, utilizzando la popolazione regionale come riferimento; per i comuni in Regioni con un tasso maggiore di quello nazionale, è stato utilizzato quel’ultimo come riferimento. SMR sono stati calcolati anche specificatamente per i siti di interesse nazionale per le bonifiche (SIN) con sorgenti di esposizione ad amianto, composti da uno o più comuni. Risultati. Il tasso standardizzato nazionale annuo è di 1,7 casi per 100,000. Alcuni cluster significativi sono stati identificati ad amianto. Conclusioni. I risultati contribuiscono a identificare esposizioni ad amianto prioritarie per la bonifica ambientale.

Parole chiave: mesotelioma, mortalità, amianto, siti inquinati.

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INTRODUCTION

The objective of the present study was to evaluate the geographic distribution in Italy of areas characterized by high mortality due to asbestos-related diseases. The importance of evaluating the distribution lies in the fact that it could contribute to detecting asbestos exposure and establishing priorities for environmental remediation, in the perspective of environmental public health tracking.

In this context, pleural mesothelioma is the main disease of interest, since it is induced almost exclusively by exposure to asbestos both occupational and environmental [1], and the only other known risk factors are exposure to erionite [2] and fluoro-edenite [3]. In Italy, pleural mesothelioma mortality has been extensively investigated at the municipality level [4-8] and the studies that have been conducted have ensured full coverage of the period 1980-2002. In 1980-2002 the 9th Revision of the International Classification of Disease (ICD) was used in Italy, and the topographic code for “Malignant neoplasms of pleura” (ICD 163.0-163.9) was employed as an indirect indicator for estimating occurrence of pleural mesothelioma. However, the use of this code resulted in a certain degree of misclassification at the individual level, though it was shown to be appropriate at the population level because of a sort of a kind of compensatory effect [9, 10]. Since 2003 Italy has adopted the 10th Revision of the ICD, which has an ad hoc morphologic code for pleural mesothelioma (C45.0). Subsequent to this change there were 20% fewer cases [8] and accuracy improved. The present study refers to the years 2003-2009, which is the most recent period for which mortality data are available (excluding the years 2004 and 2005, for which coded data are not yet available).

The National Mesothelioma Register (ReNaM), located at the former National Institute for Occupational Safety and Health (ISPESL) (currently known as the “Italian National Workers Compensation Authority”, INAIL), has existed since 1993, with the remit of estimating the incidence of malignant mesothelioma in Italy, investigating the occurrences of asbestos exposure, identifying any possible underrated or unknown source of asbestos contamination and promoting research. ReNaM has published data on incidence and on jobs associated with asbestos exposure [11], survival [12, 13], latency [14] and the predictions for mesothelioma deaths in the next years [15]. Currently, data on incident cases of mesothelioma (based on histologically confirmed diagnoses) are available for the period 2003-2008 for a large part of the country (more than 15 000 malignant mesothelioma cases at the whole). For more than 12 000 cases (76% of the incident cases recorded) data on occupational and residential history and lifestyle habits, have been collected.

Major developments in asbestos exposure mapping have also taken place in recent years because of the commitment of the Ministry of the Environment which identified a great number of sites (about 34 000) characterized by different amounts and modes of asbestos presence; these sites are currently candidates for remediation activities [16]. A limited number of sites (no. = 12) were recognized as being of national concern for environmental remediation because of a greater presence of asbestos and an ongoing health risk. The boundaries of Italian polluted sites (IPS) are defined on the basis of health, environmental and social criteria (Decree 152/06). In 2011, there were 57 IPSs, of which 44 were included in the SENTIERI Project which analyzed mortality among residents for the years 1995-2002. The results of the mortality analysis, including those for “Malignant neoplasms of pleura” (ICD 163.0-163.9) in each site and in all sites combined were published in 2011 [17].

In the present study, mortality for pleural mesothelioma (ICD-10 Rev: C45.0) was analysed for the period 2003-2009 (excluding the years 2004 and 2005) in the IPSs of the SENTIERI Project characterized by the presence of sources of asbestos exposure. As anticipated in the previous paragraph, asbestos was listed in the Decree for 12 out of 44 sites; in 6 sites only sources of asbestos/mineral fibers were listed: Emarese and Balangero (asbestos, quarry and dumping sites), Broni, Casale Monferrato and Bari-Fibronit (asbestos-cement factory), Biancavilla (fluoro-edenite quarry). In the remaining 6 sites, asbestos was recorded together with one or more other sources of environmental exposures (Area Litorale vesuvian, Aree industriali Val Basento, Massa Carrara, Pitelli, Priolo and Tito).

MATERIALS AND METHODS

The source of data was the National Mortality Database (NMD), which is managed by the Statistics Unit of the Istituto Superiore di Sanità (Italy’s National Health Institute) and based on data provided by ISTAT (Italy’s National Statistics Institute). This database contains the underlying cause of death, which until 2003 was coded using the Ninth Revision of ICD (ICD-9); since then, the 10th Revision (ICD-10) has been used (www.who.int/classifications/icd/en/). In the NMD, data are available from 1980 to 2009, except for the years 2004 and 2005, for which coded data are not yet available. Mortality from pleural mesothelioma was defined using the specific ICD-10 Code: C45.0.

The denominators used for the mortality rates are the sum of the annual residential populations for the considered study period (2003-2009, excluding 2004 and 2005).

The analysis was conducted for all 8094 municipalities in Italy. The number of observed deaths for pleural mesothelioma among residents in each municipality was compared to the expected number of deaths based on national and regional rates.

We calculated the national rates specific for age-class and gender and their corresponding 95% confidence
is a possible candidate for a cluster. Under the null hypothesis, the observed number of cases follows a uniform distribution, so that the expected number of cases in an area is proportional to its population size. Clusters of interest are selected on the basis of the p-value associated to their likelihood under the null hypothesis (p < 0.10). The relative risk is the estimated risk within the cluster divided by the estimated risk outside of the cluster.

On the basis of the studies of environmental risk for residents near an asbestos-cement facility in the town of Casale Monferrato [19], a maximum radius of 11 km was fixed.

In the analysis for IPSs the method used in the SENTIERI Project was applied. The SMRs for each IPS, which consist of one or more municipalities, were computed using regional rates.

### RESULTS

#### Standardized rates

The standardized annual mortality rates from pleural mesothelioma in Italy in the study period was 1.7 per 100,000 inhabitants; the rate was 4.60 among men and 1.34 among women in the 40-75 year age class (Table 1). The present results confirm the highest rates in some Northern Regions: Friuli-Venezia Giulia (3.0); Liguria (5.4), Lombardia (2.4) and Piemonte (3.0). Table 2 shows the annual regional rates by genders.

#### Standardized mortality ratios

Significantly increased SMRs were found in 263 municipalities, with a geographical distribution that confirms the well known north-southern gradient in pleural mesothelioma mortality in Italy (Figure 1).

#### Cluster analysis

The significant clusters by macro-area and gender are shown in Figures 2 and 3.

In all macro-areas, there were fewer municipalities that constituted significant clusters when the analysis was conducted among women, compared to men.

In the North-East, women did not show significant clusters; both significant clusters detected among men (Trieste and Monfalcone areas) corresponded to areas with harbour, shipbuilding and repair industries.
Table 2 | Mortality from pleural mesothelioma (ICD-10: C450). Annual age-class and gender-specific standardized mortality rates per 100,000 inhabitants for each of the 20 Regions, 2003-2009 years (excluded 2004 and 2005)

<table>
<thead>
<tr>
<th>Region</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed cases</td>
<td>Expected cases</td>
<td>Standardized rates</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
<td>Lower 95% CI</td>
</tr>
<tr>
<td>Abbruzzo</td>
<td>37</td>
<td>88.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Basilicata</td>
<td>14</td>
<td>37.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Bolzano Province</td>
<td>19</td>
<td>26.7</td>
<td>2.0</td>
</tr>
<tr>
<td>Calabria</td>
<td>29</td>
<td>120.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Campania</td>
<td>154</td>
<td>291.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Emilia-Romagna</td>
<td>289</td>
<td>299.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Friuli-Venezia Giulia</td>
<td>182</td>
<td>84.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Lazio</td>
<td>165</td>
<td>334.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Liguria</td>
<td>493</td>
<td>1267.9</td>
<td>10.8</td>
</tr>
<tr>
<td>Lombardia</td>
<td>758</td>
<td>580.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Marche</td>
<td>81</td>
<td>1072.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Molise</td>
<td>11</td>
<td>22.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Piemonte</td>
<td>496</td>
<td>305.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Puglia</td>
<td>163</td>
<td>232.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Sardegna</td>
<td>63</td>
<td>99.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Sicilia</td>
<td>178</td>
<td>292.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Toscana</td>
<td>244</td>
<td>263.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Trento Province</td>
<td>16</td>
<td>30.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Umbria</td>
<td>38</td>
<td>63.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Valle d’Aosta</td>
<td>6</td>
<td>8.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Veneto</td>
<td>269</td>
<td>290.4</td>
<td>2.6</td>
</tr>
<tr>
<td>Italy</td>
<td>3.705</td>
<td>2.8</td>
<td>2.7</td>
</tr>
</tbody>
</table>

CI: confidence interval.
In the North-West, three significant clusters were found for women and four for men. Two clusters found in both genders corresponded to the areas with major asbestos-cement industries (Casale Monferrato and Broni); two male clusters are located in Liguria, where harbour, shipbuilding and repair industries are present; oil refineries plants are also operating in these areas. In the Central Italy macro-area two significant clusters were detected in the analysis among women and five among men. Three of the latter are constituted by one municipality: Livorno (RR = 5.1), where a major harbour is located, Ravenna (RR = 3.3), with harbour and chemical industry site, and Collesalvetti (RR = 8.4); the latter is located close to Livorno, so that a common source of asbestos exposure may be hypothesized.

In the South, clusters in the same areas are present for both genders: Bari, with an asbestos-cement industry and Taranto, where a harbour, a large steel foundry and oil refinery are located.

In Sicily a significant cluster was found among women, corresponding to the Biancavilla municipality (RR = 25.9), characterized by the presence of a quarry contaminated by fluoro-edenite not detected as a cluster in previous national studies, but always expressing elevated SMRs. In men, one of the significant clusters includes the Priolo area, where an oil refinery and a petrochemical industry are operating; the other one is the Siracusa municipality (RR = 3.8), where an asbestos-cement industry was present. The latter one was not detected in the previous analysis.

No significant clusters were detected in Sardegna.

Table 3 shows mortality results in IPS with asbestos contamination for males and females in the period 1995-2002 [17] and the following period 2003-2009. A formal comparison is precluded by the change in the ICD Revision, but some comments are warranted.

Among males, in nine sites the increased risk is present in both periods; in one site (Area Val Basento) no cases were recorded in 1995-2002 and an increase is present in the most recent period (3 Obs; SMR 430; 90% CI 117-111).

For females in five sites the observed mortality is above expected in both periods; in one site (Area Litorale Vesuviano) an increase is present only in
In the 5 of the 6 IPSs where asbestos was recorded to together with one or more other environmental exposures mortality in 2003-2009 is lower than in 1995-2002; in two sites (Massa Carrara and Pitelli) an increased risk is registered only in 2003-2009, with the SMRs equal to, respectively, 127 (3 Obs; 90% CI 35-327) and 147 (4 Obs; 90% CI 77-518).
the overall cases where 641 in the 1995-2002 and 447 in 2003-2009 (excluding the years 2004 and 2005).

**DISCUSSION**

This is the first national level study of asbestos-related disease mortality, using the specific code of pleural mesothelioma, available in ICD-10, adopted in Italy since 2003. As described in the introduction, the code used until 2002 “pleural malignant neoplasms” implied an overestimation of pleural mesothelioma of about 20%. Thus, the present estimates are lower in absolute terms, yet the SMRs and RRs should be more accurate. The annual rate based on ICD-10 is 1.7 cases per 100,000, compared to the previous estimate of 1.9 cases per 100,000. Notwithstanding the possible underestimation, in the investigated IPSs the annual number of cases of pleural mesothelioma in the period 2003-2009 years (excluding 2004 and 2005) was 89, compared to the 80 cases per year of malignant neoplasms of pleura in the period in which ICD-9 was used. In a recent
paper on pleural mesothelioma mortality in Spain, both ICD revisions were used to estimate the impact of asbestos on health, and this is said to be the accepted way to complete the mortality series [20].

Several identified clusters are in areas already studied and the risk of mesothelioma was attributed to occupational or environmental asbestos exposure.

Increased risk for mesothelioma in the North-eastern clusters (Trieste and Monfalcone) has been attributed to the presence of a large shipbuilding industry [21-25].

In the North-western macro area, significant clusters have been identified that include one or more municipalities previously investigated: Casale Monferrato (asbestos-cement industry), [26-28], and Broni (asbestos-cement industry) [29, 30]. Shipbuilding and repair industries are known sources of asbestos exposure in Genoa and La Spezia (Genoa by Puntoni et al., 2001 [31]; La Spezia by Dodoli et al., 1992 [32] and Gennaro et al., 2000 [33]). In the Grugliasco area, mesothelioma in textile workers has been investigated [34, 35].

Some of the cluster areas in the Central macro area have already been investigated: Ravenna, where an harbour and a chemical industry are located [36], Carrara (asbestos-cement industry) [37], Livorno (shipbuilding and repair, harbour, oil refinery) [32, 10, 38]. On the other hand, no information is currently available to allow us to comment on the cluster of Collesalvetti (municipality close to Livorno). Pleural mesothelioma cases among workers in railway carriages construction and repair of Bologna were studied [39]. An old oil refinery is located in Fiorenzuola d’Arda.

In the South area a cluster is represented by a municipality (Bari), where a major asbestos-cement industry operated; this source of exposure was considered in studies conducted by different authors, with respect to both occupational and environmental exposures [40-42, 28]. Graziano et al., 2009 [43], studied the area of Taranto, included in a cluster, where shipbuilding and repair facility, a foundry and a refinery are located.

In Sicily three mesothelioma clusters were identified. The Biancavilla case, where no industrial activities related to asbestos had occurred, is well known because of an outbreak of mesothelioma. Previous studies suggested an etiological role of the asbestiform fiber found in a stone quarry whose products were used in the local building industry and in road paving. The fiber, a new mineral species named fluoro-edenite, was demonstrated to induce mesotheliomas in animals. The town of Biancavilla is still facing an epidemic of pleural mesothelioma as a consequence of the environmental exposure to fluoro-edenite [44]. The cluster identified among women corroborates the role of the environmental exposure to the fibre.

Clusters of Siracusa and Augusta, Priolo, Gargallo are located in a polluted site of national interest for remediation. Large refinery and petrochemical industry, asbestos-cement industry, shipbuilding and repair activities are located there. Data on mesothelioma cases have been already published [45].

The geographical distribution of municipal SMRs confirms the geographical North-South trend of past asbestos use: municipalities with significantly increased SMRs are mainly located in northern part of the coun-

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Mortality in Italian polluted sites (IPS) from malignant neoplasm of pleura (1995-2002) and pleural mesothelioma (2003-2009)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPS</td>
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<tr>
<td></td>
<td>Males</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant neoplasm of pleura ICD-9 163</td>
<td>Malignant neoplasm of pleura ICD-10 C45.0</td>
</tr>
<tr>
<td>Obs</td>
<td>SMR (90% CI)</td>
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<tr>
<td>------</td>
<td>---------------</td>
</tr>
<tr>
<td>Area Litorale vesuviano</td>
<td>49</td>
</tr>
<tr>
<td>Aree industriali Val Basento</td>
<td>--</td>
</tr>
<tr>
<td>Balangero</td>
<td>3</td>
</tr>
<tr>
<td>Bari - Fibronit</td>
<td>49</td>
</tr>
<tr>
<td>Biancavilla</td>
<td>6</td>
</tr>
<tr>
<td>Broni</td>
<td>22</td>
</tr>
<tr>
<td>Casale Monferrato</td>
<td>147</td>
</tr>
<tr>
<td>Emarese</td>
<td>--</td>
</tr>
<tr>
<td>Massa Carrara</td>
<td>29</td>
</tr>
<tr>
<td>Pitelli</td>
<td>104</td>
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<tr>
<td>Priolo</td>
<td>29</td>
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<tr>
<td>Tito</td>
<td>--</td>
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<tr>
<td></td>
<td>Obs: observed; SMR: standardized mortality ratio; CI: confidence interval; *excluded 2004 and 2005 years; ** &lt; 3 or 0.</td>
</tr>
</tbody>
</table>
try. The cluster analysis is more specific and less sensitive than SMR analysis and less influenced by chance, but it may not be able to detect individual municipalities with increased risk because of limited sample size.

The novel findings produced by the present study can thus be summarized as follows. In 2003-2009, excluding 2004 and 2005 years, 5,184 deaths per year from pleural mesothelioma occurred. The overall spatial distribution was consistent with previous findings, although some clusters were here reported for the first time and for some of them previous documentation of asbestos exposure was unavailable (i.e. Collesalvetti, Collecchio, Fidenza, Sala Baganza) so that ad hoc investigations are now specifically required in these contexts.

CONCLUSIONS

In light of the findings of the present study, and of the subsequent discussion, some conclusions are warranted.

The study of the geographic distribution of pleural mesothelioma in Italy, especially the cluster analysis, has lead to the detection of several areas of the country where the burden of asbestos-related disease is evident. Occupational and environmental asbestos exposures in these areas appear to have consistently been elevated and long-lasting.

Several among the clusters showed in Figures 2 and 3 (namely, Casale Monferrato, Broni, Carrara, Bari, Biancavilla, Augusta and Siracusa) are included among the sites of national concern for environmental remediation, because of the presence of asbestos (see Table 3). The clusters of Trieste, Livorno and Taranto correspond to IPSs where asbestos is not mentioned in the Decree, but characterized by the presence of harbour area; interestingly, in all three these sites, available epidemiological evidence strongly supports the presence of relevant occupational and environmental asbestos exposure.

As far as the remaining clusters are concerned, and in many individual municipalities characterized by high mesothelioma mortality rates, it is necessary to rank priorities of intervention and to evaluate the effectiveness of environmental remediation. This process requires an approach based on the integration of available environmental and health data, to be performed by an interdisciplinary working group including central and local institutions committed to environmental protection and public health.

This activity requires, beyond technical skill, both transparency and equity. Transparency implies involvement of the media and of various stakeholders, including environmental associations and representatives of affected communities, including victim organizations. Equity has to be pursued by ranking priorities in order to favour worst-off situations, in terms of exposure levels, health impacts, and socioeconomic deprivation. Environmental remediation might thus be experienced as a starting point of a global process of development for those communities that have been severely affected by the prevailing industrialization models of the past.

Conflict of interest statement

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

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