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Epidemiological surveillance of mesothelioma mortality in Italy.

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ABSTRACT

Background: Malignant mesothelioma (MM) is causally linked to asbestos exposure with an estimated etiological fraction of 80% or more.

Methods: Standardized rates of all mesothelioma (C45, ICD-10) and malignant pleural mesothelioma (C45.0, ICD-10) mortality in Italy were computed at national and regional levels, for the period 2003–2014. Standardized Mortality Ratios (SMRs, with 95% Confidence Intervals) were calculated for each of the 8047 Italian municipalities, for both diseases, with respect to Regional figures. A geographical clustering analysis at municipal level was performed, applying SatScan methods.

Results: In Italy, 16,086 persons (about 1,340/year) died for MM, in analysed period.

National Standardized rates of MM mortality are 3.65/100,000 in men and 1.09/100,000 in women, with an increasing annual trend, among male population. The highest rates were found in men from Northern Regions. Significant clusters ($p < 0.10$) were found corresponding to areas that hosted major asbestos-cement plants, naval shipyards, petrochemical plants and refineries. Furthermore, excesses were found corresponding to chemical and textile industries; the latter involving, particularly, female population. Excesses were found also in areas near the chrysotile mine of Balangero, and in Biancavilla, a town with a stone quarry contaminated by fluoro-edenitic fibres; an excess of MM mortality was observed among male population living in a minor island where a Navy shipyard is located.

Conclusions: Mortality for mesothelioma in Italy is still increasing, twenty-six years after the asbestos ban. Epidemiological surveillance of mesothelioma mortality allows to detect the temporal trend of the disease and highlights previously unknown or underestimated sources of asbestos exposure.

1. Introduction

Malignant mesothelioma (MM) is causally linked to asbestos exposure with an etiological fraction of 80% or more.

In 2012 the International Agency of Research for Cancer (IARC), confirming the first evaluation [1], endorsed that there is sufficient evidence in humans for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite): asbestos causes extrapleural, as well as pleural, mesothelioma and cancer of the lung, larynx, and ovary. Limited evidence of the associations between all forms of asbestos and pharynx, stomach, and colorectum cancers was defined [2]. More recently, IARC has established the carcinogenicity of fluoro-edenitic fibres, because of sufficient evidence in humans with respect to MM [3].

The burden of MM at global level is unclear. The estimates of MM mortality, for 1994–2008 period, were reported from approximately 6,150cases/year [4] to 14,200 cases/year [5]. More recently, Odgerel et al. estimated the global mesothelioma burden in the range of 36,300 to 38,400 annual deaths, in 1994–2014 period for 230 countries [6].

The global burden of disease attributable to occupational asbestos exposure in 2004 was reported to be 107,000 deaths, of which 59,000 for MM [7]. Quantifying the proportion of cases attributable to environmental exposure is more difficult. The risk of pleural mesothelioma associated with exposure for living near an industrial asbestos source (mines, mills, asbestos processing plants) has been clearly confirmed; non-occupational exposure to asbestos may explain approximately 20% of mesothelioma in industrialized countries [8].

In Italy, the National Registry of Mesothelioma (ReNaM) reported 21,463 incident cases of MM in 1993–2012, about 1,073/year; out of them, 93% were pleural mesothelioma cases. The routes of exposure to

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asbestos was ascertained for 77% of MM cases: among those, 10.5% were non-occupational (including 4.2% environmental), whereas 69.5% were occupational exposures [9].

The World Health Organization (WHO) has declared that asbestos-related diseases should be eliminated throughout the world [10]. Developing national programmes to eliminate asbestos-related diseases was a point of the final Declaration of the Sixth Ministerial Conference on Environment and Health of WHO European Region, in order to achieve the health and well-being objectives of United Nations 2030 Agenda for Sustainable Development [11].

The purpose of the present paper is to show geographical distribution and temporal trend of mortality for all malignant mesothelioma (MM) and, specifically, for malignant pleural mesothelioma (MPM), in Italian Regions and municipalities. The investigation is part of a permanent epidemiological surveillance, that started at the beginning of the Nineties [12–16]. The estimates performed at national level could contribute to the estimates of the global burden of mesothelioma and of the health impact of asbestos in the world.

2. Materials and methods

We analyzed the data of municipal mortality for all malignant mesothelioma (MM, ICD-10 code: C45) and for malignant pleural mesothelioma (MPM, ICD-10 code: C45.0) separately, included in the cause-specific mortality database of Istituto Superiore di Sanità, based on mortality and population data provided by the Italian National Institute of Statistics (Istat).

We considered mortality in the time-window 2003–2014, the period of availability in Italy of data in ICD-10 code, that includes a specific diagnostic category of malignant mesothelioma.

Standardized Mortality rates (direct method, 2013 European population as reference) and their 95% Intervals of Confidence (95% CI), in the overall population and in the two genders separately, were computed for each of the 21 Italian Regions and Autonomous Provinces. Temporal trend of annual national and regional rates are reported.

We calculated the Standardized Mortality Ratios (SMRs), with the corresponding 95% CI, for each of the 8047 Italian municipalities, using the regional age-classes and gender specific rates to compute expected figures. The 95% CIs were estimated based on Poisson's distribution, if the observed cases were less than 100, otherwise on Byar method.

Furthermore, we performed a municipal clustering analysis to identify the areas with major departures from expected figures. This is less specific than SMR analysis, but it is less affected by random variation due to the low number of cases in individual municipalities. Given the different geographical distribution of all-causes mortality in the national territory, the country was divided into six geographical macro-areas, as defined by Istat: North-East, North-West, Centre, South and two main islands, Sicily and Sardenia, considered separately. These macro-areas also reflect the different industrial history, with a higher frequency of the main industrial settings in Northern Regions. Standardized rates and Standardized Rate Ratios (SRRs, 95% Confidence Intervals), with respect to the national rate, have been computed for each geographical macro-areas.

The analysis was performed according to the procedure Spatial Scan Statistics, using SatScan software (version 9.4.4), assuming a Poisson model for the distribution of the cases in each municipality. The procedure employs a circular window of varying radius from zero to some upper limit, which moves on the entire study area, centred at each step on one of the municipalities, identified by the x, y coordinates of the municipality's town hall (centroid). The radius of the circular window was fixed from 0 to 50% of population (in default) and to 10 km. The method creates an infinite number of distinct geographical circles with different sets of neighbouring data locations within them: each circle 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. The Relative Risk is the estimated risk within the cluster divided by that one outside of the cluster. Clusters of interest are selected on the basis of the p-value associated to their likelyhood under the null hypothesis ($p < 0.10$).

Lastly, we computed the sex ratio (Men/Women) of the cases deceased for MM and MPM in three classes of municipalities at different degrees of population density, like defined by EUROSTAT (http://ec.europa.eu/eurostat). The analysis was performed in Italy and in geographical macro-areas used in clustering analysis. The rationale of this analysis was to test a possible excess of female patients in urban areas reflecting a higher urban versus rural environmental asbestos concentrations (buildings, traffic).

3. Results

In Italy, between 2003 and 2014, 16,086 persons (about 1,340/year) died for MM, corresponding to 2.19/100,000 inhabitants (95% CI:2.15-2.22): 11,487 men (3.65/100,000) and 4599 women (1.09/100,000). Among those, we found 13,051 cases (1,087/year) of MPM (1.77/100,000): 9397 men and 3654 women, with a corresponding rate of 2.98/100,000 and 0.86/100,000. The remaining deaths for MM include mesothelioma of peritoneum, pericardium, other sites and unspecified mesothelioma (Table 1).

Temporal trends from 2003 to 2014 of the standardized rates of MM and MPM mortality are statistical significant increasing ($p \leq 0.001$) in the overall population and, particularly, in men (Fig. 1).

Figs. 2 and 3 show the distribution of regional standardized MM and MPM mortality rates in male and female population, separately. Northern Regions (Liguria, Piemonte, Friuli Venezia Giulia, Lombardia and Valle d'Aosta) have mortality rates for MM and MPM higher than the national ones.

In municipal SMRs' analysis, 247 municipalities showed significant excess of mortality (lower limit of SMR 95%CI > 100), based on 3 observed cases or more, for MM and 217 municipalities for MPM in the overall population. In the analysis by gender, we detected 212 municipalities with statistically significant increased SMR for MM, 196 for MPM in male population and 96 and 78 municipalities, respectively, among women.

Table 2 shows standardized rates and SRR for each geographical macro-areas used in cluster analysis.

Figs. 4 and 5 show the maps of significant clusters (p-value < 0.10) of MM and MPM mortality detected in the macro-areas, separately by gender. Their characteristics and the municipalities included in each cluster are described in Supplementary files (S1, S2, S3, S4).

Table 3 shows the sex ratio (male/female cases) of MPM deaths, in the three different classes of population density. The ratio Men/Women for MPM deaths in Italy is 2.58, with no differences between the three classes. This finding does not support the hypothesis of an excess risk of mesothelioma in women living in urban areas associated to asbestos exposure in dwellings or generated by traffic.

Table 1
Mortality for malignant mesotheliomain Italy, 2003–2014: number of cases and percentage with respect to all mesothelioma deaths.

Cause of death	ICD	Men: cases (%)	Women: cases (%)
Mesothelioma of pleura	C45.0	9397 (81.8)	3654 (79.5)
Mesothelioma of peritoneum	C45.1	464 (4)	283 (6.2)
Mesothelioma of pericardium	C45.2	12 (0.1)	7 (0.2)
Mesothelioma of other sites	C45.7	259 (2.3)	102 (2.2)
Mesothelioma, unspecified	C45.9	1,355 (11.8)	553 (12)
Mesothelioma (all)	C45	11,487 (100)	4599 (100)