MESOTHELIOMA MORTALITY SURVEILLANCE IN ITALY

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Introduction

The objective of the present study is 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). For a more detailed analyses of mesothelioma surveillance in Italy, the reader is referred to Fazzo *et al.* 2012 (4).

Materials and methods

The source of data was the national mortality database, which is managed by the Statistics Unit of the Istituto Superiore di Sanità (the National Health Institute in Italy) and based on data provided by ISTAT (National Statistics Institute in Italy). This database contains the underlying cause of death. Mortality from pleural mesothelioma was defined using the specific ICD-10 (International Classification of Diseases - 10th revision) 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 for which coded data are not yet available). 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 Intervals (CI), and the standardized mortality rates for each of the 21 Regions/Autonomous Provinces, using as standard population the national population according to the 2001 census. Standardized Mortality Ratios (SMRs) were calculated for each municipality. The age-specific and gender-specific expected mortality rates based on national or regional mortality rates with 90% CI were estimated based either on a Poisson distribution, if there were fewer than 100 observed cases, or using the Byar method, if there were more than 100 observed cases. The age-specific and gender-specific rates of each regional population were used as reference in calculating the expected mortality rates; for municipalities in Regions in which the standardized or crude rate was higher than the national rate, we used the national rate as reference, so as not to underestimate the SMRs. Given the rarity of mesothelioma, which results in a very low expected mortality in many municipalities, an SMR-based surveillance system may be affected by random variation and generate a number of positive results by chance. For this reason, and given the fact that asbestos facilities tend to be concentrated in specific geographic areas, we performed a municipal clustering analysis to identify the areas with major departures from expected mortality. For this analysis, the country was divided into geographic macro-areas, each

consisting of several Regions: North-West (Piemonte, Lombardia, Liguria, Valle d'Aosta); North-East (Veneto, Friuli-Venezia Giulia, Trento Province), Central (Emilia-Romagna, Toscana, Umbria, Marche, Lazio, Abruzzo); South (Molise, Campania, Puglia, Basilicata, Calabria); and the main islands, considered separately (Sicilia and Sardegna). The analysis was performed according to the procedure Spatial Scan Statistics (5), using SatScan software (version 6). 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. 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. 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 (6), a maximum radius of 11 km was fixed.

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).

Table 1. Mortality from pleural mesothelioma (ICD-10: C450) (2003-2009)

Age (yrs)		Men	Women	Total
0-39	Observed cases	8	7	15
	Standardized rates	0.01	0.01	0.01
	Lower 95% CI	0.005	0.004	0.01
	Upper 95% CI	0.02	0.02	0.02
40-75	Observed cases	2,427	800	3,227
	Standardized rates	4.60	1.34	2.84
	Lower 95% CI	4.37	1.23	2.72
	Upper 95% CI	4.84	1.46	2.97
76-99	Observed cases	1,270	672	1,942
	Standardized rates	13.78	4.17	7.70
	Lower 95% CI	13.02	3.83	7.35
	Upper 95% CI	14.58	4.51	8.06

Annual national age-class and gender-specific standardized mortality rates per 100,000 inhabitants.
CI. Confidence Interval

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 gender.

Table 2. Mortality from pleural mesothelioma (ICD-10: C450)

Region	Men					Women					Total				
	Cases		SR	95% CI		Cases		SR	95% CI		Cases		SR	95% CI	
	O	E		L	U	O	E		L	U	O	E		L	U
Abruzzo	37	88.4	1.2	0.8	1.6	13	34.3	0.3	0.1	0.5	50	121.1	0.7	0.5	0.9
Basilicata	14	37.9	1.0	0.6	1.8	6	14.2	0.4	0.1	0.9	20	51.1	0.7	0.4	1.1
Bolzano Province	19	26.7	2.0	1.2	3.6	2	10.5	0.1	0.0	0.5	21	37.2	1.0	0.6	1.5
Calabria	29	120.1	0.7	0.4	1.0	16	45.3	0.3	0.2	0.5	45	162.5	0.5	0.3	0.6
Campania	154	291.9	1.4	1.2	1.7	67	116.0	0.5	0.4	0.6	221	408.9	0.9	0.8	1.0
Emilia Romagna	289	299.9	2.7	2.4	3.0	101	119.1	0.7	0.6	0.9	390	416.2	1.6	1.4	1.7
Friuli-Venezia Giulia	182	84.3	6.1	5.2	7.1	32	35.4	0.8	0.5	1.1	214	121.1	3.0	2.6	3.4
Lazio	165	334.1	1.4	1.2	1.6	60	133.8	0.4	0.3	0.5	225	469.6	0.8	0.7	0.9
Liguria	493	126.7	10.8	9.9	11.9	114	53.1	1.6	1.3	2.0	607	181.4	5.4	5.0	5.9
Lombardia	758	580.5	3.7	3.4	4.0	430	239.2	1.5	1.3	1.6	1188	830.2	2.4	2.2	2.5
Marche	81	107.2	2.0	1.6	2.6	28	41.9	0.5	0.3	0.8	109	147.3	1.2	1.0	1.5
Molise	11	22.0	1.5	0.7	2.7	4	8.6	0.3	0.1	1.1	15	30.2	0.9	0.5	1.5
Piemonte	496	305.0	4.5	4.1	4.9	286	122.0	2.0	1.7	2.2	782	427.3	3.0	2.8	3.3
Puglia	163	232.9	1.9	1.6	2.3	70	89.9	0.7	0.5	0.8	233	320.4	1.2	1.1	1.4
Sardegna	63	99.1	1.8	1.4	2.3	17	37.8	0.4	0.2	0.6	80	135.5	1.0	0.8	1.2
Sicilia	178	292.7	1.7	1.4	1.9	51	113.5	0.4	0.3	0.5	229	402.8	0.9	0.8	1.1
Toscana	244	263.5	2.6	2.3	3.0	65	105.2	0.5	0.4	0.6	309	367.2	1.4	1.3	1.6
Trento Province	16	30.1	1.5	0.9	2.6	9	12.5	0.5	0.2	1.1	25	42.9	1.0	0.6	1.5
Umbria	38	63.5	1.7	1.2	2.4	9	25.0	0.3	0.2	0.7	47	87.7	1.0	0.7	1.3
Valle d'Aosta	6	8.1	2.2	0.8	12.2	1	3.2	0.2	0.0	1.8	7	11.3	1.0	0.4	2.2
Veneto	269	290.4	2.6	2.3	2.9	98	118.6	0.7	0.6	0.8	367	411.9	1.5	1.3	1.7
Italy	**3,705**	**3,705.0**	**2.8**	**2.7**	**2.9**	**1,479**	**1,479.0**	**0.8**	**0.8**	**0.9**	**5,184**	**5,184.0**	**1.7**	**1.6**	**1.7**

O: Observed; **E**: Expected; **SR**: Standardized rates; **95% CI**: 95% Confidence Interval; **L**: Lower; **U**: Upper
Annual standardized mortality rates per 100,000 inhabitants for each of the 20 regions. 2003-2009 years.

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).

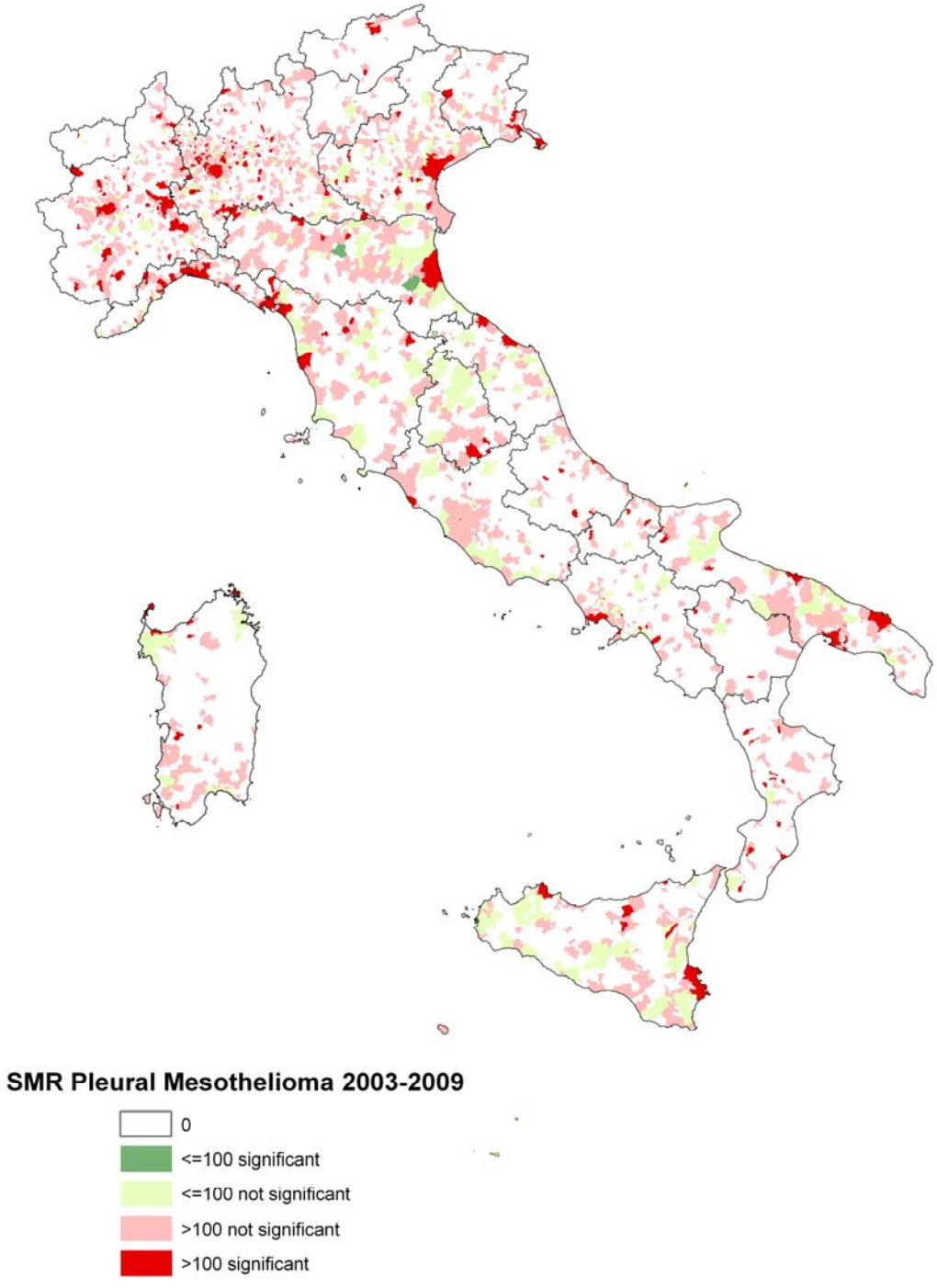
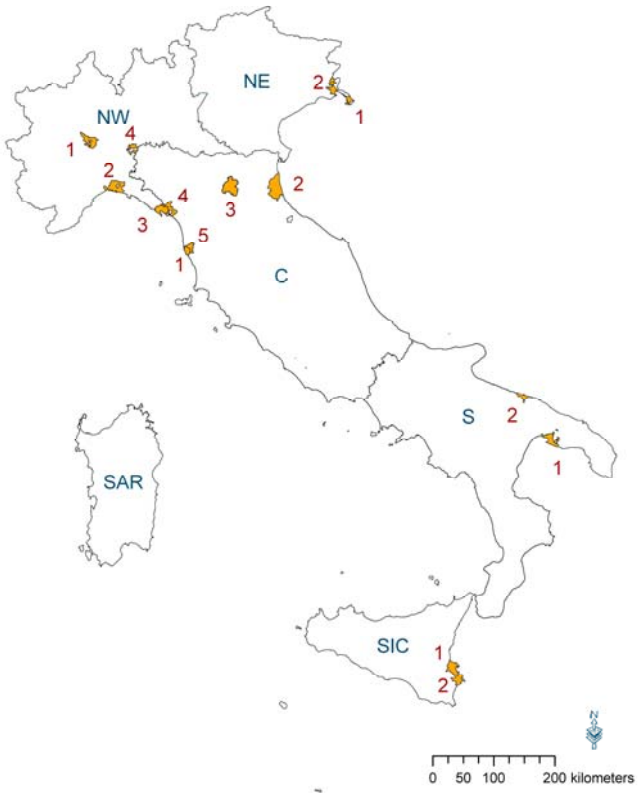


Figure 1. Pleural mesothelioma mortality in Italy (2003-2009)

Cluster analysis

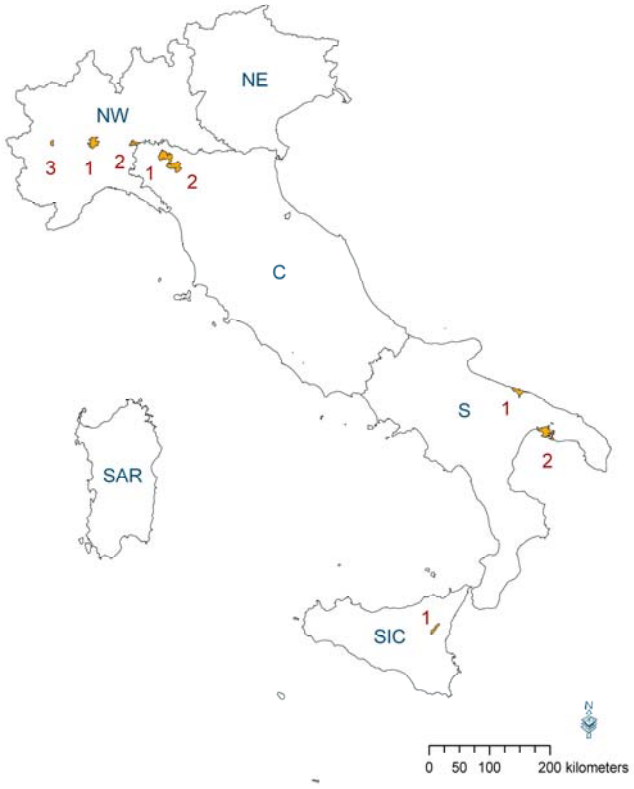
The significant clusters by macro-area and gender are shown in Figure 2 and 3.



Area	Cluster number	Ray (meters)	Number of municipalities	Observed cases	Expected cases	RR
NE	1	4796	2[a]	81	19.47	4.799
	2	9997	15[b]	51	8.04	6.976
NW	1	9343	14[c]	98	7.73	13.381
	2	8366	8[d]	259	86.77	3.331
	3	9639	11[e]	107	23.33	4.82
	4	8845	13[f]	29	6.05	4.685
C	1	-	1[g]	42	8.51	5.141
	2	-	1[h]	26	8	3.322
	3	10593	7[i]	55	27.24	2.089
	4	9916	3[j]	16	4.12	3.943
	5	-	1[k]	7	0.84	8.38
S	1	10667	3[l]	47	6.44	8.222
	2	-	1[m]	26	10.19	2.67
SIC	1	10513	3[n]	13	2.01	6.909
	2	-	1[o]	15	4.23	3.784

a: Muggia, Trieste; **b**: Gradisca d'Isonzo, Fogliano Redipuglia, Farra d'Isonzo, Mariano del Friuli, Romans d'Isonzo, San Pier d'Isonzo, Capriva del Friuli, Ronchi dei Legionari, Cormons, Campolongo Tapogliano, Turriaco, Ruda, San Canzian d'Isonzo, Monfalcone, Staranzano **c**: Morano sul Po, Pontestura, Balzola, San Giorgio Monferrato, Treville, Camino, Casale Monferrato, Trino, Rosignano Monferrato, Sala Monferrato, Cella Monte, Serralunga di Crea, Terruggia, Villanova Monferrato; **d** Sant'Olcese, Serra Riccò, Mignanego, Ceranesi, Casella, Campomorone, Montoggio, Genova: **e**La Spezia, Vezzano Ligure, Arcola, Portovenere, Follo, Lerici, Santo Stefano di Magra, Riccò del Golfo di Spezia, Riomaggiore, Sarzana, Bolano; **f** Canneto Pavese, Broni, Santa Maria della Versa, Zenevredo, Stradella, Rovescala, Santa Giulietta, Montalto Pavese, Barbianello, Campospinoso, Bosnasco, Portalbera, Corvino San Quirico; **g**Livorno; **h**Ravenna: **i**Casalecchio di Reno, Zola Predosa, Monte San Pietro, Bologna, Sasso Marconi, Calderara di Reno, Pianoro; **j** Carrara, Aulla; **k** FosdinovoCollesalvetti; **l** Taranto, Leporano, Pulsano; **m** Bari; **n** Augusta, Priolo Gargallo, Melilli; **o**Siracusa.

Figure 2. MEN: mortality from pleural mesothelioma, 2003-2009 (excluded 2004 and 2005). Significant clusters (p-value<0.10) in each macro-area



Area	Cluster number	Ray (meters)	Number of municipalities	Observed case	Expected cases	RR
NW	1	8677	11[a]	82	3.16	28.743
	2	5706	5[b]	28	1.69	17.115
	3	1132	2[c]	18	4.17	4.389
C	1	9153	4[d]	8	0.86	9.573
	2	6711	4[e]	6	0.54	11.3
S	1	-	1[f]	17	4.59	4.023
	2	8939	2[g]	13	3.19	4.342
SIC	1	-	1[h]	5	0.21	25.894

a: Terruggia, Rosignano Monferrato, San Giorgio Monferrato, Occimiano, Casale Monferrato, Borgo San Martino, Sala Monferrato, Conzano, Frassinello Monferrato, Camagna Monferrato, Ticineto**; b:** Stradella, San Cipriano Po, Arena Po, Bosnasco, Broni; **c:** Collegno, Grugliasco; **d**: Alseno, Fiorenzuola d'Arda, Castell'Arquato, Fidenza; **e**: Collecchio, Sala Baganza, Medesano, Felino; **f**: Bari; **g**: Taranto, San Giorgio Ionico; **h**: Biancavilla

Figure 3. WOMEN: mortality from pleural mesothelioma, 2003-2009 (excluded 2004 and 2005). Significant clusters (p-value<0.10) in each macro-area

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. 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 Sicilia 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.

Discussion

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 Northeastern clusters (Trieste and Monfalcone) has been attributed to the presence of a large shipbuilding industry (7-11).

In the North-western macro area, significant clusters have been identified that include one or more municipalities previously investigated: Casale Monferrato (asbestos-cement industry), (12-14), and Broni (asbestos-cement industry) (15, 16). Shipbuilding and repair industries are known sources of asbestos exposure in Genoa (17) and La Spezia (18, 19). In the Grugliasco area, mesothelioma in textile workers has been investigated (20, 21).

Some of the cluster areas in the Central macro area have already been investigated: Ravenna, where an harbour and a chemical industry are located (22), Carrara (asbestos-cement industry) (23), Livorno (shipbuilding and repair, harbour, oil refinery) (18, 24). 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 (25). 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 (14, 26-28). In 2009, Graziano *et al.* (29) studied the area of Taranto, included in a cluster, where shipbuilding and repair facility, a foundry and a refinery are located.

In Sicilia 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 (30).

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 (31).

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 country. The cluster analysis is more specific and less sensitive that 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.

Conclusion

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 led 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.

It is now 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.

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