Original Article

Epidemiology of malignant mesothelioma in Italy: surveillance systems, territorial clusters and occupations involved

Alessandro Marinaccio, Alessandra Binazzi, Michela Bonafede, Davide Di Marzio, Alberto Scarselli; Regional Operating Centres

Occupational and Environmental Medicine, Epidemiology and Hygiene Department, Occupational and Environmental Epidemiology Unit, Italian Workers' Compensation Authority (INAIL), Rome, Italy

Contributions: (I) Conception and design: A Marinaccio; (II) Administrative support: D Di Marzio; (III) Provision of study materials or patients: Regional Operating Centres; (IV) Collection and assembly of data: A Binazzi, M Bonafede, D Di Marzio; (V) Data analysis and interpretation: A Scarselli, A Binazzi, A Marinaccio; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Alessandro Marinaccio. Epidemiology and Hygiene Department, Occupational and Environmental Epidemiology Unit, Italian Workers' Compensation Authority (INAIL), Via Stefano Gradi 55, 00143 Rome, Italy. Email: a.marinaccio@inail.it.

Background: As a legacy of the large asbestos consumption until the definitive ban in 1992, Italy is currently suffering a severe epidemic of asbestos related diseases. The aim of this paper is to describe the surveillance system for mesothelioma incidence and to provide evidences regarding the occurrence of the disease in Italy and the circumstances of asbestos exposure.

Methods: Italian National Register of Malignant Mesotheliomas (ReNaM) is a permanent surveillance system of mesothelioma incidence, with Regional Operating Centres (CORs) active in each Italian region, identifying incident malignant mesothelioma (MM) cases from health care structures. Occupational history, lifestyle habits and residential history are obtained using a standardised questionnaire, administered by a trained interviewer, to the subject or to the next of kin. Descriptive epidemiological figures, occupations involved in exposures and territorial maps of MM cases have been produced.

Results: At December 2016, ReNaM has collected 27,356 MM cases for the incidence period between 1993 and 2015. The modalities of exposure to asbestos have been investigated for 21,387 (78%) and an occupational exposure has been defined for around 70% of interviewed cases (14,818). Non-occupational exposure is still relevant with 4.9% and 4.4% of cases for which respectively a familial exposure (due to the cohabitation with an occupational exposed subject) and an environmental exposure (due to the residence near a contaminated site) has been detected.

Discussion: The epidemiological surveillance of MM incident cases, by the means of a national register for estimating the occurrence of the disease and identifying the circumstances of asbestos exposure, is a relevant tool for preventing asbestos exposure, for supporting the effectiveness of insurance system and for estimating reliable epidemiological figures.

Keywords: Mesothelioma; asbestos; Italy; surveillance system; occupational risk

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Introduction

Malignant mesothelioma (MM) is an aggressive tumour arising from the pleura and, less frequently, from the peritoneal and pericardial serous membranes and from the tunica vaginalis of testis. The causal association with asbestos exposure has been demonstrated and the International Agency for Research on Cancer provided

evidence that all forms of asbestos (amphiboles as actinolite, amosite, anthophyllite, crocidolite, tremolite and serpentine as chrysotile) are carcinogenic for humans (group 1) causing mesothelioma, as well as lung, laryngeal, and ovarian cancer (1-3). Several international authorities and agencies have produced calls and recommendations for the elimination of asbestos related disease, by globally banning the asbestos production and use (4-7). Asbestos production, trade and consumption currently affects a large part of the world population living in a consistent number of countries worldwide. In the last twenty years, the asbestos production has decreased worldwide, but not fallen below 2,000,000 tons of asbestos per year (8,9). Italy is one of the most involved and sensitive country in asbestos related diseases monitoring and control as a consequence of the large use of asbestos until the national bank in 1992 (3,748,550 tons of raw asbestos produced up to 1992, and a peak of more than 160,000 tons/year between 1976 and 1980 (10). Therefore, Italy (as several western countries) is currently suffering a severe epidemic of asbestos related diseases and the epidemiological surveillance of mesothelioma incidence is a real concern for monitoring, control and contrast the disease. In the international framework, specific surveillance systems of mesothelioma incident cases, with reliable information, exposure assessment and consistent territorial coverage, are scarce (11), currently ongoing only in Australia (12), France (13) and South Korea (14), and absent in countries with a current asbestos use and production.

The aim of this paper is to describe the epidemiological surveillance system active in Italy for MM incidence, to provide evidence regarding pleural mesothelioma occurrence discussing the modalities of asbestos exposure involved and finally to estimate the extent of direct and indirect costs of the diseases in terms of public health resources.

Methods

The epidemiology of MM in Italy can be described by the means of figures provided by the National Register of Malignant Mesotheliomas (Registro Nazionale dei Mesoteliomi, ReNaM in Italian). ReNaM is a national surveillance system of mesothelioma incidence, active with force of law since 2002, devoted to identify cases and to assess asbestos exposure. The structure is regional and an Operating Centre (COR) is now active in all 20 Italian regions. Each COR works applying the standardised methods described in the national Guidelines (15). Regional Operating Centres (CORs) actively search incident MM cases from health care institutions potentially involved in diagnosis (chest surgery wards, pathology and lung care units). Diagnostic coding criteria have been defined according to 3 classes of decreasing level of certainty: certain (if histological confirmation is available), probable (if cytological confirmation is available) and possible MM (only radiological and clinical evidences). The complete diagnosis coding system adopted in ReNaM has been previously described extensively (15,16). A trained interviewer administers a standardised questionnaire to the patient (or to the next of kin) for investigating the occupational history, the lifestyle habits and the residential history of the affected people. CORs regularly consult local health and safety agencies for retrieving supplementary information regarding occupations and residential history of the patients. An industrial hygienist, or a panel of industrial hygienists, based on the collected information, assigns an exposure code, according to the national coding system. Furthermore, Italian Workers' Compensation Authority (INAIL) provides CORs with information about occupational histories of mesothelioma cases, retrieving pension contributions from personal data, by the means of a structured collaboration with the Italian Social Security Institute (INPS). Occupational exposure classification is qualitative and classified in three levels: definite, probable or possible. Definite occupational exposure is assigned to the subjects for which there are sufficient information about the use of asbestos or materials containing asbestos. Probable occupational exposure is assigned to the subjects, who have worked in a firm where asbestos was used, but exposure cannot be directly documented, and possible occupational exposure to the subjects who have worked in an economic sector for which asbestos use is documented. The non-occupational modalities of exposure considered are: environmental exposure (residence near a source of asbestos pollution without work-related exposure), familial exposure (when patients have lived with a cohabitant occupationally exposed) and leisure activities exposures (other non-occupational exposures like those due to leisure-time activities). Territorial maps of MM cases have been produced referring to the municipality of residence at the diagnosis period. The maps presenting MM incidence rates have been produced excluding regions with a not complete incidence registration, therefore Sardegna, Calabria and Molise were not considered. With the aim of estimating the extent of costs of mesothelioma, public and social costs

Table 1 Italian National Mesothelioma Register (ReNaM) archives. Collected malignant mesothelioma cases by gender, age at diagnosis, period of incidence, anatomical site, diagnostic certainty level and morphology. ReNaM archives updated at December 2016, diagnosis period 1993–2015*, Italy

Variables	Men		Women		All	
	N	%	N	%	N	%
Age class						
≤44	326	1.7	166	2.1	492	1.8
45–64	5,343	27.2	1,856	24.0	7,199	26.3
65–74	7,360	37.5	2,477	32.1	9,837	36.0
≥75	6,604	33.6	3,224	41.7	9,828	35.9
Incidence period						
1993–2003	6,412	32.7	2,531	32.8	8,943	32.7
2004–2007	4,101	20.9	1,648	21.3	5,749	21.0
2008–2011	4,465	22.7	1,825	23.6	6,290	23.0
2012–2015 (on going)	4,655	23.7	1,719	22.3	6,374	23.3
Anatomical site						
Pleura	18,473	94.1	6,977	90.3	25,450	93.0
Peritoneum	1,042	5.3	727	9.4	1,769	6.5
Pericardium	39	0.2	19	0.2	58	0.2
Tunica vaginalis testis	79	0.4			79	0.3
Diagnostic evaluation						
Definite MM	16,075	81.9	5,928	76.8	22,003	80.4
Probable or possible MM	3,558	18.1	1,795	23.2	5,353	19.6
Morphology						
Epithelioid	1,0845	55.2	4,422	57.3	15,267	55.8
Biphasic	2,188	11.1	692	9.0	2,880	10.5
Fibrous	1,684	8.6	421	5.5	2,105	7.7
MM NOS*	2,469	12.6	986	12.8	3,455	12.6
Not available	2,447	12.4	1,202	15.5	3,649	13.3
Overall	19,633	100.0	7,723	100.0	27,356	100.0

*, incidence for year 2015 is not complete and collection of data is to be considered on going. MM, malignant mesothelioma; NOS, not otherwise specified.

have to be considered. The expenditure borne by the State and other public bodies (medical care cost, insurance cost, tax and benefit), but also the productivity loss suffered by the whole economy have been included in an econometric model. For the social costs estimation, the human capital approach has been used.

Results

At December 2016, ReNaM has collected 27,356 MM cases (*Table 1*), for the incidence period between 1993 and 2015, and the modalities of exposure to asbestos have been investigated for 21,387 (78%) of them (*Table 2*). Incident case list for 2015 is to be considered not complete

Table 2 Italian National Mesothelioma Register (ReNaM) archives. Collected malignant mesothelioma cases by modality of asbestos exposure and gender. ReNaM archives updated at December 2016, diagnosis period 1993–2015*, Italy

Modality of exposure	Incidence period (1993–2015)		
	Male (%)	Female (%)	Total (%)
Occupational, definite	9,300 (59.3)	987 (17.3)	10,287 (48.1)
Occupational, probable	1,358 (8.7)	191 (3.3)	1,549 (7.2)
Occupational, possible	2,246 (14.3)	736 (12.9)	2,982 (13.9)
Familial	152 (1.0)	895 (15.7)	1,047 (4.9)
Environmental	409 (2.6)	530 (9.3)	939 (4.4)
Other non-occupational	128 (0.8)	194 (3.4)	322 (1.5)
Unlikely	268 (1.7)	308 (5.4)	576 (2.7)
Unknown	1,824 (11.6)	1,861 (32.6)	3,685 (17.2)
Total defined	15,685 (100.0)	5,702 (100.0)	21,387 (100.0)
Total	19,633 (100.0)	7,723 (100.0)	27,356 (100.0)
Total defined	15,685 (79.9)	5,702 (73.8)	21,387 (78.2)
Total undefined	3,948 (20.1)	2,021 (26.2)	5,969 (21.8)

*, case list for year 2015 is not complete and collection of data is to be considered on going.

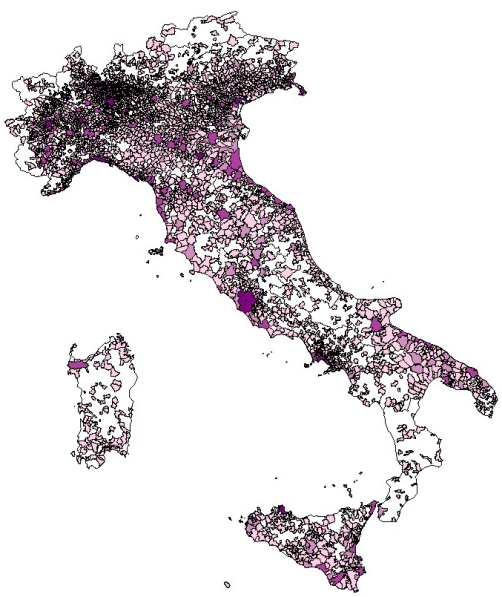

Figure 1 Italian National Mesothelioma Register (ReNaM) archives. Number of pleural MM cases for municipality of residence at the time of diagnosis. ReNaM archives updated at December 2016, diagnosis period 1993–2015*, men and women, Italy. MM, malignant mesothelioma; *, case list for year 2015 is not complete and collection of data is to be considered on going.

and ongoing. MM cases younger than 45 years at diagnosis are very rare (less than 2%) in ReNaM archives and mean age at diagnosis is around 70 years. More than 90% of collected cases are localized in the pleural cavities (93%), peritoneal MM cases are 6.5% (5.3% and 9.4% in men and women respectively) and pericardial and tunica vaginalis testis MM cases are very rare (58 and 79 collected cases respectively among the entire ReNaM archives). Morphology of more than half of caselist is epithelioid. Gender ratio is, constantly in time, equal to 2.54 (M/F) and to 2.64, if restricted to pleural cases. At the whole, CORs have interviewed 21,387 MM cases (78.2% of the whole caselist). Among them, an occupational exposure has been defined for around 70% of defined cases (14,818). Non-occupational exposure is still relevant with 4.9 % of cases for which a familial exposure (due to the cohabitation with an occupational exposed subject) has been detected and 4.4% of cases with an environmental exposure (due to the residence near a contaminated site). The epidemiological findings have been extensively described and discussed in ReNaM reports (17). The territorial distribution of MM incident cases for the whole ReNaM archives, according to the municipality of residence at the time of diagnosis, has been reported in *Figure 1*. *Figures 2* and *3* reported the raw incidence rates of pleural MM, respectively for men and women, only for

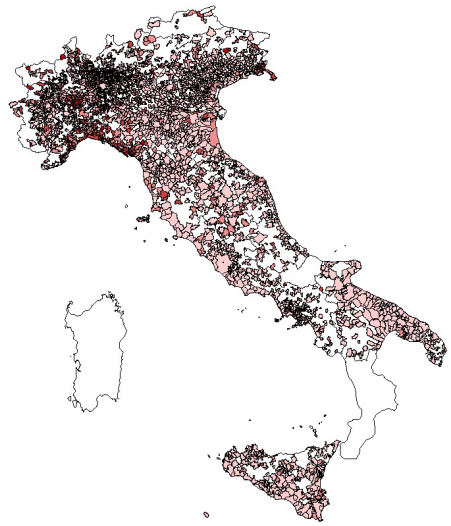

Figure 2 Italian National Mesothelioma Register (ReNaM) archives. Raw incidence rates of pleural MM for municipality of residence at the time of diagnosis. ReNaM archives updated at December 2016, diagnosis period 1993–2015*, men. Only Italian region with incidence figures (excluding Sardegna, Molise and Calabria). MM, malignant mesothelioma; *, case list for year 2015 is not complete and collection of data is to be considered on going.

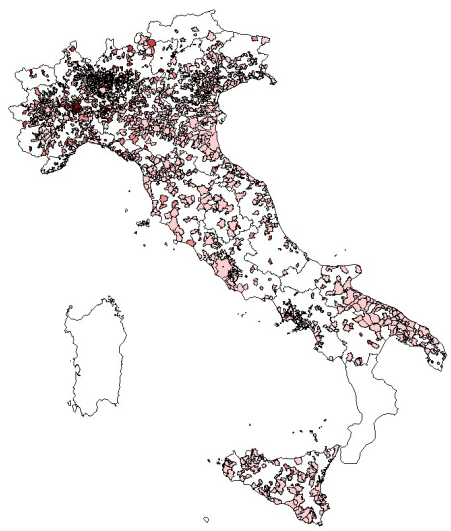

Figure 3 Italian National Mesothelioma Register (ReNaM) archives. Raw incidence rates of pleural MM for municipality of residence at the time of diagnosis. ReNaM archives updated at December 2016, diagnosis period 1993–2015 *, women. Only Italian region with incidence figures (excluding Sardegna, Molise and Calabria). MM, malignant mesothelioma; *, case list for year 2015 is not complete and collection of data is to be considered on going.

Italian regions with incidence data (excluding Sardegna, Molise and Calabria). The percentage of affected subjects for which the modalities of asbestos exposure have been investigated is around 78% in the pooled analyses, but with a great territorial variability and some regions (in particular in Southern Italy) have available interviews for less than half of detected cases.

Recently an extensive analysis of MM incidence in Italian national priority contaminated sites (NPCSs) has been performed (18), evidencing an overall excess of 1,531 cases in these areas. It is remarkable that mesothelioma occurrence resulted higher than expected also in sites for which asbestos was not explicitly cited as contaminant in the official documents. The analysis of Italian pool of asbestos exposed workers' cohorts (43 evaluated cohorts including 51,081 subjects) has provided evidence of a flattening of pleural MM mortality risk after long time since first exposure (around 40 years) (19). According to an inclusive econometric model, elsewhere described in details (20), an estimate of 33,000 and 25,000 euros per patient for medical care costs and for insurance and compensation costs respectively, has been provided. The most relevant extent of indirect costs, generally neglected, refers to productivity loss that can be quantified around 200,000 euros per patient.

Discussion

The epidemiological surveillance of MM incident cases, by the means of a national register, for estimating the occurrence of the disease and identifying the circumstances of asbestos exposure, is a relevant tool for preventing asbestos exposure, for supporting the effectiveness of insurance system, for estimating reliable epidemiological figures and for identifying possible sources of contamination still in place. The forecast scenarios for MM epidemic curve has been estimated according to a model including asbestos consumption before the ban (21), indicating the period of peak in mesothelioma mortality around 2015–2020. The territorial clustering of incident cases has been identified and discussed, based on collected cases and asbestos exposure qualitative assessment provided by CORs (22). The characteristics, and the extent of non-occupational exposure (above all environmental and familial modalities of exposure), have been estimated around 10% of cases (23) mainly due to the residence near asbestos cement plants and to the cohabitation with occupationally exposed subjects. The environmental exposure due to tremolite pollution in a rural area of Basilicata (Southern Italy) have

been documented (24). In the area of Biancavilla Etnea (Sicily, Southern Italy) the causal role of a mine extracting a fluoroedenite-contaminated material, massively used for construction and roads, has been discovered (25). The median period of latency (26) and survival rates for pleural and peritoneal mesothelioma cases have been estimated and discussed (27,28). The crucial role of epidemiologic findings to support and stimulate the reliability and effectiveness of the insurance system has been evidenced (29). The geographical distribution of MM cases is a sort of map of the industrial use of asbestos before the ban in 1992. The figures reported here and in previous papers (22,30) demonstrate how a higher than expected incidence (and mortality) in mesotheliomas has been observed in areas with direct use of asbestos as the naval shipyards, asbestos–cement plants and other industrial activities, such as railways carriages maintenances. In the interpretation of territorial maps, it is necessary to consider the possible source of bias due to the municipality of residence at the time of diagnosis taken as a proxy for exposure place. The extent of misclassification, due to the difference between the localization of suffered exposure and the residence of the subjects, is a real concern, according to the expected level of commuting. Asbestos exposure in civil buildings, such as public office or school, where subjects have no consciousness of contact with asbestos-containing material could be a still real concern, also where asbestos has been banned (31). The estimate of the financial burden of mesothelioma, in a framework of an inclusive econometric model, can enforce the awareness regarding the economic advantage of the ban in countries with still a current use of asbestos.

Finally, the epidemiological MM surveillance system findings, provided by countries with a MM efficient monitoring system, could represent a precious source of information, for countries where asbestos is still used, about the extent, the characteristics and the public health costs of asbestos related diseases.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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