

Pleural malignant mesothelioma epidemic: incidence, modalities of asbestos exposure and occupations involved from the Italian National Register

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Due to the large scale use of asbestos (more than 3.5 million tons produced or imported until its definitive banning in 1992), a specific national surveillance system of mesothelioma incident cases is active in Italy, with direct and individual anamnestic etiological investigation. In the period between 1993 and 2004, a case-list of 8,868 pleural MM was recorded by the Italian National Register (ReNaM) and the modalities of exposure to asbestos fibres have been investigated for 6,603 of them. Standardized incidence rates are 3.49 (per 100,000 inhabitants) for men and 1.25 for women, with a wide regional variability. Occupational asbestos exposure was in 69.3% of interviewed subjects (N = 4,577 cases), while 4.4% was due to cohabitation with someone (generally, the husband) occupationally exposed, 4.7% by environmental exposure from living near a contamination source and 1.6% during a leisure activity. In the male group, 81.5% of interviewed subjects exhibit an occupational exposure. In the exposed workers, the median year of first exposure was 1957, and mean latency was 43.7 years. The analysis of exposures by industrial sector focuses on a decreasing trend for those traditionally signaled as "at risk" (asbestos-cement industry, shipbuilding and repair and railway carriages maintenance) and an increasing trend for the building construction sector. The systematic mesothelioma surveillance system is relevant for the prevention of the disease and for supporting an efficient compensation system. The existing experience on all-too-predictable asbestos effects should be transferred to developing countries where asbestos use is spreading.

Key words: asbestos, mesothelioma, pleural, national register, Italy

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Malignant mesothelioma (MM) is a tumor arising from the serous membranes of the pleura and, less frequently, of the peritoneal and pericardial cavities and from the tunica vaginalis testis. Prognosis is severe, and median survival for the pleural form is around 9 months from diagnosis in the population-based studies.¹ The etiological relationship with the inhalation of asbestos fibres is well documented, such as doseresponse parameters.² Asbestos is a natural occurring mineral, which was widely used in the construction and shipbuilding industries, especially in thermal and acoustic insulation, thanks to its unusual characteristics of plasticity and resistance and also for water-proofing and fire-proofing. Many western countries are currently suffering the MM epidemic, considering the extensive use of asbestos between the 1950s and the 1980s in several industrial applications and the long latency period (around 40 years) since the beginning of exposure. Forecasts of mesothelioma mortality have been estimated in Australia,³ Britain,⁴ France,⁵ Netherlands,⁶ Italy,⁷ Japan⁸ and Spain.⁹ A specific national MM incidence surveillance system with an individual and direct anamnestic etiological investigation is active in Australia,¹⁰ France¹¹ and Italy.¹² Up to the end of the 1980s, Italy was the second largest asbestos producer in Europe, after the Soviet Union, and the largest in the European Community. From the end of the Second World War to the asbestos ban in 1992, 3,748,550 tons of raw asbestos were produced, reaching its peak in the period between 1976 and 1980 at about 160,000 tons/year.7 Because of its previous high consumption, the wide spectrum of industries involved and the number of workers and nonworkers exposed, Italy is among these countries that are most sensitive to the prevention and control of asbestos related diseases, and it has a specific system of epidemiological surveillance of mesothelioma. The National Mesothelioma Register (ReNaM), kept at the National Institute for Occupational Safety and Health (ISPESL), has been in place since 1993 (by force of law since 2002) with the remit of estimating MM incidence in Italy, investigating occurrences of asbestos exposure, identifying any possible underrated or unknown source of asbestos contamination and promoting research. ReNaM has published figures for incidence, survival, latency and asbestos exposure.^{13–15}

The purpose of the study is to present data on pleural MM available from the ReNaM and to describe the occupations and economic sectors involved. The relevance of these evidences with respect to prevention and compensation activities is also discussed.

Material and Methods

The ReNaM has a regional structure with Operating Centres (COR) operating in 18 of the 19 Italian regions and one of the two autonomous provinces, so covering almost the whole Italy. Each COR acts independently by applying the standardized methods described in National Guidelines.¹⁶ CORs actively search for MM incident cases in health care institutions that diagnose and treat cases (especially pathology and histology units, pulmonology and chest surgery wards), analyze the pathology diagnosis and classify cases in four classes, according to the National Guidelines: certain MM, probable MM, possible MM and no MM. Subjects included in the first three groups are registered and transmitted to ReNaM. Currently, a panel of experts for the systematic pathology validation is not yet established, but a feedback of information between each COR is regularly functioning.

Data on occupational and residential history together with lifestyle habits, obtained using a standardized questionnaire administered by a trained interviewer, were reported directly from the subject (direct interview) or the next of kin (indirect interview). In few cases, the exposure can be ascertained through documents. CORs may consult public local health and safety agencies to gain supplementary information on occupational and residential exposure. ReNaM also has access to the pension contributions made to the Italian Social Security Institute and so can provide CORs with information about the occupational history of mesothelioma cases, either as a confirmation of information obtained from the subject or as the information source if no interview is possible. In each COR, an industrial hygienist (or sometimes a panel of industrial hygienists) classifies and codifies the exposure, after having examined the information.

Occupational exposure to asbestos is classified as definite, probable or possible. Definite occupational exposure is when the subject's work has involved the use of asbestos or materials containing asbestos; probable occupational exposure is when the subject has worked in a company or sector where asbestos was certainly used, but whose exposure cannot be documented; possible occupational exposure is when the subject has worked in a company or sector where asbestos might have been used. Data collected by each COR are periodically sent to ReNaM and stored in a centralized database.

Cases were assigned to a specific economic sector considering the whole occupational history, and if a multiple exposure was present, the longer was selected. Usually, the economic sectors involved in asbestos exposure are classified in 38 categories, but-exclusively for the aims of this analysis-a further classification in four macrogroups has been defined, according to the modalities of asbestos use: direct use (shipbuilding and repair, asbestos-cement industry, railways carriages construction and maintenance, asbestos mining, port handling, asbestos textile industry, friction materials production, gaskets and packings production); indirect use for insulation and auxiliary tools (metal and engineering, metallurgic, oil refineries, metal, food and drink industries, sugar refineries, organic and inorganic chemical plants, wood processing, tobacco, leather tanning, not asbestos textiles finishing, glass and ceramic, paper, jewellery, gas production, navy and military defence, power plants, heat and steam generators); construction sector (the whole building industry); accidental and unaware exposures (car mechanics, jute sacks recycling, agriculture, fishery, bar and restaurants, public administration, instruction, banks, post offices, health and social services). The rationale of this classification is an **Table 1.** Pleural malignant mesothelioma (*N*, %) collected in the Italian National Mesothelioma Register (ReNaM) by gender, age classes, period of diagnosis, level of diagnostic certainty, morphology and modalities of interview

		М	en	Women		
		N	%	N	%	
Age classes	0-44	125	1.9	64	2.7	
	45-64	2,254	34.9	708	29.3	
	65-74	2,273	35.2	768	31.8	
	75+	1,803	27.9	873	36.2	
Period of diagnosis	1993–1996	995	15.4	348	14.4	
	1997-2000	2,088	32.3	774	32.1	
	2001-2004	3,372	52.2	1291	53.5	
Diagnostic certainty	MM certain	5,038	78.0	1754	72.7	
	MM probable or possible	1,417	22.0	659	27.3	
Morphology	Epithelioid	3,210	49.7	1229	50.9	
	Biphasic	767	11.9	244	10.1	
	Sarcomatous	536	8.3	132	5.5	
	MM NOS ¹	1,060	16.4	404	16.7	
	Not available	882	13.7	404	16.7	
Exposure detection	Direct interview	2,547	39.5	752	31.2	
	Indirect interview	2,126	33.0	862	35.7	
	No interview	1,769	27.5	798	33.1	
Overall		6,455	100.0	2413	100.0	

Italy, 1993-2004.

¹NOS, not otherwise specified.

attempt to focus on the exposure modalities more than on the economic sector of activity.

To date, the ReNaM database has information on cases with a diagnosis of MM in the period 1993-2004 (transmission of incidence data in the period 2005-2009 is ongoing). Within this period, the data is not complete, depending on when each COR was set up: Piedmont, Veneto, Tuscany and Apulia have produced incidence regional case-lists starting since 1993; Liguria, Emilia-Romagna and Marche since 1996; Sicily since 1998; Lombardy, Friuli-Venezia Giulia and Valle D'Aosta since 2000 and Campania since 2001. Case-lists from Lazio, Abruzzo, Basilicata, Calabria and Sardinia cannot be considered complete at present, while Umbria and Molise and the two autonomous provinces of Trento and Bolzano did not transmit any data for 2004. The incidence rates specified below conform to the territories covered by incident data collection, as specified earlier. Exposure data pertain to the whole ReNaM database. Age standardized rates have been estimated by direct method using the resident Italian population database in the year 2001.

A geographical picture of MM occurrence and economic sectors of asbestos exposure has been produced, using the

town of residence at the time of diagnosis. The crude rates were calculated considering the period 1993–2004 for each Italian municipality (N = 8101). Furthermore, only for municipalities with more than 10 cases in the period and a crude rate higher than four per 100,000 inhabitants (36 municipalities selected with these criteria) the predominant industrial activities or environmental conditions have been detailed in the map.

Data about asbestos importation and production in Italy were obtained from reports published by the Italian Institute of Statistics, the Italian Foreign Trade Institute and the Italian General Direction of Mines of Ministry of Industry. Annual asbestos consumption data for United States of America, United Kingdom and Sweden have been obtained from the Open-file report 03-83 "Worldwide asbestos supply and consumption trends from 1900 to 2003" (United States Geological Survey).¹⁷ Figures were available for the years 1940, 1950, ..., 1990, and a linear interpolation function has been used to calculate intermediate years and to estimate the annual trend of consumptions in these countries. All statistical analyses have been carried out with SPSS software (ver. 17.0).

Results

In the period between 1993 and 2004, 9,544 MM cases were registered, and the modalities of exposure to asbestos fibers have been investigated for 7,044 of them. The tumor site is the pleura in 92.9% (8,868) of cases, the peritoneum in 6.4% (610), the pericardium in 0.4% (35) and the testis in 0.3% (31). In the pleural group, 72.8% (6,455) are men and 27.2% (2,413) are women with a mean age at diagnosis of respectively 68.3 (SD: ±10.6) years and 69.8 (SD: ±11.6); about half the cases are in the age range 62-77 years while cases under 45-years-old are only 2.4% of all pleural cases recorded. The number of cases diagnosed as certain were 6,792, as probable 1,057 and as possible 1,019 (Table 1). The mean ages within the three diagnosis groups were respectively 67.0 years (SD: ±10.4), 72.7 years (SD: ±10.7), and 75.9 years (SD: ± 10.6) with a significant difference of mean age resulting from the ANOVA test (F = 413.2; p value < 0.001). The standardized national incidence rates for pleural MM (certain, probable and possible) in 2004 are 3.49 (cases per 100,000 inhabitants) for men and 1.25 for women (Table 2) with a wide regional variability, with territorial peaks for men in Liguria (14.13), Friuli-Venezia Giulia (6.28) and Piedmont (5.56) and for women in Piedmont (3.18) and Liguria (2.23). If restricted only to the cases diagnosed as certain MM (excluding possible and probable cases), the incidence rates decrease by about 20%.

From the geographical map of crude incidence rates, the highest values have been found in areas, where asbestos industries laid, such as the asbestos cement production plants (Casale Monferrato in Piedmont and Broni in Lombardy), the shipbuilding and repair (La Spezia, Savona and Genova in Liguria; Trieste and Monfalcone in Friuli-Venezia Giulia; Venezia in Veneto; Livorno in Tuscany; Castellamare di

Table 2. Number of detected cases and age-standardized incidence rates (cases per 100,000 inhabitants) for certain, probable and possible	
pleural malignant mesothelioma (standard population: Italy 2001) by gender and Regions	

Regions	Territory (km²)	Inhabitants	Number of cases		Standardized incidence rates		
			Men	Women	Men	Women	Note ¹
Piedmont	25,400	4,330,172	120	74	5.56	3.18	I
Valle d'Aosta	3,260	122,868	3	1	4.71	1.41	I
Lombardy	23,862	9,393,092	180	91	3.84	1.87	I
AP Bolzano	7,400	477,067					NA
AP Trento	6,207	497,546					ND
Veneto	18,391	4,699,950	57	17	2.39	0.70	I
Friuli-Venezia Giulia	7,855	1,204,718	38	4	6.28	0.61	I
Liguria	5,420	1,592,309	109	19	14.13	2.23	I
Emilia-Romagna	22,450	4,151,369	88	25	4.35	1.16	I
Tuscany	22,997	3,598,269	46	14	2.63	0.75	L
Marche	9,695	858,938	18	6	2.45	0.73	I
Umbria	8,455	1,518,780					ND
Lazio	17,205	5,269,972	41	19	1.58	0.66	Р
Abruzzo	10,799	1,299,272	5	-	0.80	-	Р
Molise	4,438	321,953					NA
Campania	13,595	5,788,986	51	19	1.76	0.61	I
Apulia	19,360	4,068,167	22	6	1.05	0.27	I
Basilicata	9,992	596,546	4	1	1.24	0.33	I.
Calabria	15,081	2,009,268	3	1	0.29	0.10	Р
Sicily	25,710	5,013,081	58	25	2.30	0.92	I.
Sardinia	24,090	1,650,052	5	2	0.59	0.23	Р
Italy ²	301,662	58,462,375	848	324	3.49	1.25	

Italian National Mesothelioma Register (ReNaM), Italy, 2004.

¹I, Region trasmitting regional incidence data for 2004; NA, region not active in ReNaM; ND, region active in ReNaM but not transmitting data for 2004; P, region transmitting partial and nonincidence data for 2004. ²Incidence rates were estimated only for pooled "I" Regions.

Stabia in Campania and Taranto in Apulia), the asbestos textile manufactures (Grugliasco and Nole in Piedmont), the railway carriages maintenance and repair (Savigliano and Fossano in Piedmont), the iron and steel industry (Taranto), the petrochemical and oil refinery (Augusta in Sicily), and where environmental conditions of natural contamination have occurred (Biancavilla in Sicily) (Fig. 1).

Direct and indirect interviews were 48.8% and 44%, respectively, of all subjects with modalities of exposure ascertained (in some cases, defined by documented working files). For 6,603 (74%) of 8,868 pleural MM cases collected, the modalities of asbestos exposure have been defined in relation to the occupational, familial, residential and leisure history. The investigation is still ongoing for other 1,939 (22%) cases and not possible anymore for 326 (4%), so that their exposure is definitively considered not classifiable. An occupational asbestos exposure has been found in 69% of subjects with defined exposure modalities, whereas 4.4% presented an exposure due to the cohabitation with someone (generally the husband) occupationally exposed, 4.7% suffered an environ-

mental exposure living nearby a contamination source and 1.6% has been exposed during a leisure activity. Among the occupationally exposed group, the median year of first exposure was 1957 (SD: ±11.8), and about half of the whole group was exposed occasionally between 1949 and 1964. For a large amount of pleural MM cases with definite exposure (20%, 1,321 of 6,603 subjects), the modalities of exposure were unknown or unlikely. The distribution by exposure modalities is particularly different for men and women, and the identification of the source of exposure is more difficult for women (Fig. 2). The modalities of investigation are very important with respect to the ability of identifying the source of contamination. After a direct interview, the modality of asbestos exposure is unknown for only 10.8% of the interviewed subjects (355 of 3,299), whereas the figure is 22.1% (660 of 2,988) after an indirect interview.

The analysis of exposures for the period 1993–2004 shows that the largest number of cases with pleural MM of occupational origin was where asbestos was used for insulation (Fig. 3). The direct use of raw asbestos in the shipbuilding

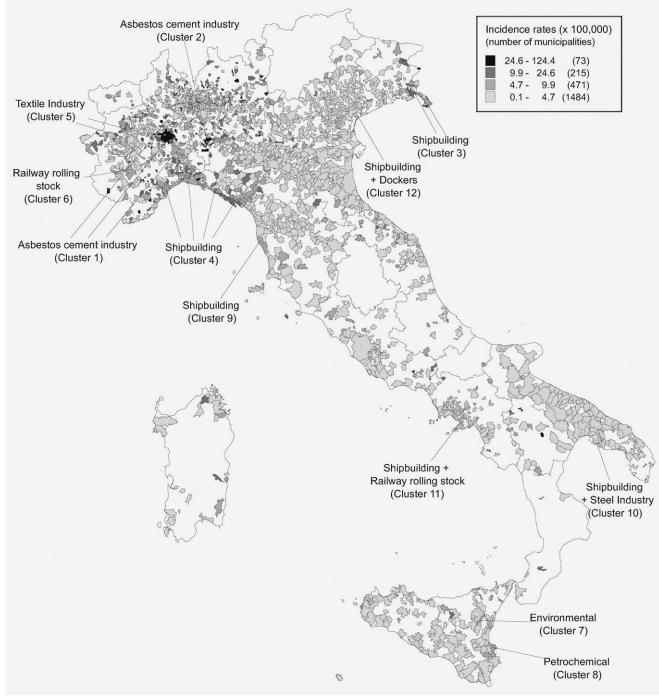


Figure 1. Crude incidence rates (CR) of pleural malignant mesothelioma (PMM) cases by Italian municipalities (n = 8,101)*. Italian National Mesothelioma Register (ReNaM). Italy, men and women, 1993–2004 * Municipalities (n = 36) with CR > 4 (*100,000 inhabitants) and PMM cases > 10 are labeled with the predominant economic sector of asbestos exposure. Cluster 1 (municipalities: Casale Monferrato, S. Giorgio Monferrato, Villanova Monferrato, Alessandria and Vercelli); C2 (Broni and Stradella); C3 (Muggia, Staranzano, Monfalcone, Ronchi dei Legionari and Trieste); C4 (Lerici, La Spezia, Arcola, Sestri Levante, Genova, Sarzana, Chiavari, Cairo Montenotte, Rapallo and Savona); C5 (Nole, Collegno, Grugliasco, Ciriè and Rivoli); C6 (Biancavilla Etnea); C7 (Savigliano and Fossano); C8 (Augusta); C9 (Rosignano marittimo and Livorno); C10 (Taranto); C11 (Castellamare di Stabia); C12 (Venezia).

and repair, in the asbestos cement industry and in the railways carriage maintenance, was responsible for 23% of cases, with a decreasing trend over the period, and in the construction for 15% over the same period but with a significant increasing trend, rising from 16% in the period 1993–1998 to 25% in the more recent years (1999–2004). A relevant

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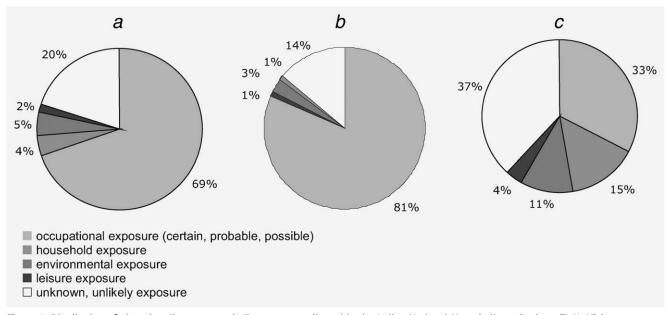


Figure 2. Distribution of pleural malignant mesothelioma cases collected in the Italian National Mesothelioma Register (ReNaM) by modalities of asbestos exposure, into selected groups: (*a*) all (N = 6,603); (*b*) men (N = 4,957); (*c*) women (N = 1,646). Italy, 1993–2004.

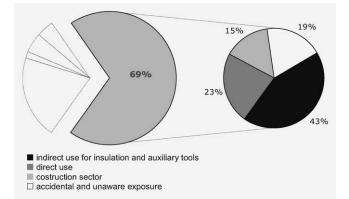


Figure 3. Distribution of pleural malignant mesothelioma cases occupationally exposed collected in the Italian National Mesothelioma Register (ReNaM) by asbestos use and exposure modalities, men and women, Italy, 1993–2004. (N=4577).

number of subjects (19%) are in the category of accidental or unaware exposure during a job generally not considered at risk and where asbestos exposure has to be considered absolutely unexpected and surprising. This category includes car mechanics, people who used jute sacks (for recycling or in agriculture) previously containing asbestos and still polluted by fibers, and people employed in the service industry whose exposure was due to the presence of asbestos in the working place.

The trend in asbestos consumption shows a time-lag in Italy compared to other industrialized states, peaking in the early 1980s (similar to France⁵), whereas in the United States, the United Kingdom and Nordic countries, consumption peaked much earlier (Fig. 4). Italy has been the only European western country increasing the asbestos consumption during the period 1975–1985.

Discussion

ReNaM is one of the largest extent system of epidemiological surveillance for MM, and, in the field of occupational disease monitoring, it is a success story when considering the quantity of data collected, the territory covered and the scientific reliability of results. Unfortunately, while in the United States, the United Kingdom and Nordic countries, asbestos consumption was already decreasing by the early 1960s, in Italy consumption rose in the same period and started to decrease only when it was known a ban would be put in place. In the 1977-1978, asbestos consumption in Italy actually overtook that of the United States, the United Kingdom and Scandinavian countries, and it remained over the symbolic threshold of 1 kg per capita almost until the actual ban in 1992, whereas, in other countries, consumption had been below this level for 15-20 years. The National programme of MM epidemiological surveillance in Italy is of great importance, with more than 340 million person-years of observations. It involves a large part of the country, including some areas with a high-direct industrial usage of asbestos (in shipbuilding, in railway carriage production and maintenance, in the asbestos-cement industry and in construction). At present, mesothelioma mortality surveillance is based on death certificates in Great Britain,¹⁸ on territorial cancer registries in Germany¹⁹ and on both in the United States,^{20,21} while in the Nordic countries the development of a complete national cancer incidence registry allows

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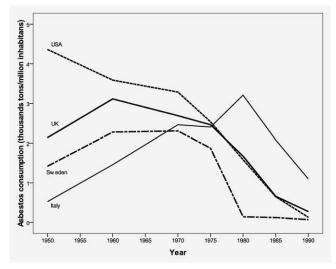


Figure 4. Asbestos consumption of United States, United Kingdom, Sweden and Italy. Thousands of tons per million of inhabitants, 1950–1990.

systematic linkage with occupational information archives.^{22–24} A specific registration activity based on active research and individual analysis through interview of occupational history of each case is ongoing only in Italy, France¹¹ and Australia.¹⁰

There are some critical limitations in the ReNaM dataset as its development has not been homogenous. As previously mentioned, some regions collected incidence cases even before the beginning of the national register in 1993, others started later and some others do not yet participate. Furthermore, data collection was not consistent between the regions, depending on the available resources and knowledge. The National Guidelines for the standardization of mesothelioma case recording have reduced such inconsistencies, but not totally as yet. Any trend evaluations in MM incidence are therefore strongly limited. To reduce the heterogeneity in COR practices, the establishment of a national panel of pathologists to validate and classify cases with an uncertain diagnosis has been scheduled.

The risk for asbestos-exposed subjects is related to the duration and intensity of the exposure; however, there is no scientific evidence of a threshold value below which there is no effect of asbestos fibres, so that their carcinogenic power cannot be excluded even after a short and not particularly heavy exposure.^{2,25–27} Observed clusters of MM cases, which cannot be attributed to exposure from intensive and direct use of asbestos, must be from environmental or not well-recognized sources of contamination. In fact, the large amount of raw asbestos consumption in Italy does not permit investigation to be limited only to the sectors traditionally involved, and systematic surveillance has identified a large number of unexpected sources, some of which are still extent. Recently, previously unknown sources of asbestos contamination have been revealed in oil production,²⁸ textiles,²⁹ lift and elevator

workers.^{30,31} Even more recently, cases of exposure in public places (theatres, bars and restaurants) have been identified.¹² Systematic MM surveillance and the registration of mesothelioma cases are fundamental not only from an epidemiological point of view, but also for the prevention of the disease where asbestos has already been banned. The theme of "other than occupational" exposures is not a mere academic issue if we take into account the total unawareness of the risk taken by many people, the consequences of a MM epidemic in the future and the absence of any form of compensation.

The reconstruction of the modalities of exposure, which is at the core of ReNaM, is made more difficult by the long latency period of the disease (generally around 40 years), by the variety of occupations involved and by the absence of a threshold level. A large amount of exposures are ascertained not by a direct interview, but-often because of a bad health status-by an interview to the patient's relatives, with a loss in the quality of information useful to the assignment of asbestos exposure. It depends on the rate of identification of MM cases and their following interview that, unfortunately, is still a weak spot in the Register. Furthermore, the choice to assign the sector with the longest exposure duration could induce an underestimation of other jobs performed with shorter or even occasional exposures. An "ever-never" classification in the future could be introduced for limiting this bias. The gender difference in unknown or unlikely exposures, more frequent in females than in males, advices caution in deciding that a mesothelioma case is without asbestos exposure, because, in many subjects, a lack in the investigation tools seems more possible than a real absence of exposure.

The analysis of asbestos exposure for MM patients shows changing patterns in time. The prevalence of exposure in the "traditional" sectors as the asbestos-cement industry, railway carriage maintenance, shipbuilding and repair has been reducing during recent years, and now exposure contexts seem more fragmented, involving many unexpected sources. This could be because the effects of the heavy and long exposure in the 1950s and 1960s are decreasing, but this hypothesis should be confirmed including an evaluation of MM relative risks by industrial sectors and with respect to the number of employments in the past, that is still not available in Italy at the present. Furthermore, the not homogeneous development of ReNaM territorial coverage could induce a bias in comparing sectors of asbestos exposure over time. The fragmentation of job involved in exposure is important to consider for compensation criteria, which should become wider and more flexible. At present, the most active industry within the MM surveillance program is the construction sector, where asbestos has been used as fireproofing and acoustic insulator, mixed with cements or plastics and also for the vinyl flooring. As a result, construction workers could currently be at risk from asbestos exposure during maintenance and restructuring activities.³² The circumstances of asbestos exposure in the construction sector are generally not evident

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and not easy to be defined correctly, especially when a direct interview is not possible. In Italy, probably as a consequence of these difficulties, there is a gap between epidemiological findings about mesothelioma risk and compensation figures for construction workers.³³ Other active sectors of exposure are the metal-mechanical and the steel and iron industry, followed by the textiles and the armed forces (principally the Navy), while shipbuilding, railways and the asbestos-cement industry still remain a large source of cases. From a preventive and compensatory point of view, the increasing weight of the unexpected exposures circumstances must be underlined. The MM surveillance system, reporting almost 20% of cases with an occupational origin in unaware and unexpected circumstances, is an auxiliary tool to identify unknown sources of contamination and to improve the insurance system efficiency. The known remaining activities connected with asbestos exposures are stripping/removal techniques and abatement/remediation. Recently, the first cohort study on asbestos removal workers has been published, with figures of relative risks higher than expected for mesothelioma and larynx and lung cancers.³⁴ At the whole and in comparison with other findings from case-control studies recently reported,^{18,35} the Italian pattern of economic sectors involved in asbestos exposure as detected by a surveillance system shows a large presence of asbestos cement industry, shipbuilding and construction, reflecting the historical national industrial development, but also a wide spectrum of less expected jobs.

Compensation is difficult to obtain in Italy for occupational cancer due to the difficulties of finding a causal relationship with the occupation, taking into account the long la-

Pleural MM in Italy

tency time of neoplasms and the multiplicity of their causes.³⁶ Currently, around 550–600 cases have been compensated in Italy by the Italian National Compensation Institute as "asbestos-related neoplasms"³⁷ and 71% of these are mesotheliomas (in the period 1994–2006). It is a widespread opinion that the systematic information availability about incidence and exposure of MM cases recognized by ReNaM has promoted and facilitated insurance activities.

In Italy, up to now, only a partial amount of occupational lung cancer cases are compensated, and the underestimation of asbestos-related lung cancer cases is confirmed by a compensation ratio of 0.39:1 between lung cancer and mesothelioma, when the epidemiological estimates provide a ratio of $1:1.^{38}$

The Italian mesothelioma Register shows a number of cases due to a nonoccupational asbestos exposure for relatives of occupational exposed workers and for those living around factories using asbestos, as discussed in previous studies.^{39–43} There is no kind of compensation for these people while in France there is a fund (FIVA) for asbestos victims, established in 2000, which compensates victims of mesothelioma and asbestosis, irrespective of any causal relationship with occupational exposure.⁴⁴ The epidemiological findings here reported help toward the proposal to introduce a similar fund in Italy, and so reducing the disparity between occupational and nonoccupational-exposed subjects. This could also lead to a reduction in the number of legal actions brought to obtain compensation.

Epidemiological surveillance system for occupational diseases helps compensation systems to focus on more recent exposure patterns and sources and to adjust compensation criteria accordingly.

References

- Montanaro F, Rosato R, Gangemi M, Roberti S, Ricceri F, Merler E, Gennaro V, Romanelli A, Chellini E, Pascucci C, Musti M, Nicita C, et al. Survival of pleural malignant mesothelioma in Italy: a population-based study. *Int J Cancer* 2009; 124:201–7.
- Boffetta P. Health effects of asbestos exposure in humans: a quantitative assessment. *Med Lav* 1998;89:471–80.
- Clements M, Berry G, Shi J, Ware S, Yates D, Johnson A. Projected mesothelioma incidence in men in New South Wales. Occup Environ Med 2007;64:747–52.
- Tan E, Warren N, Darnton AJ, Hodgson JT. Projection of mesothelioma mortality in Britain using Bayesian methods. *Br J Cancer* 2010;103:430–6.
- Le Stang N, Belot A, Ilg AGS, Rolland P, Astoul P, Bara S, Brochard P, Danzon A, Delafosse P, Grosclaude P, Guizard AV, Imbernon E, et al. Evolution of pleural cancers and malignant pleural mesothelioma incidence in France between 1980 and 2005. *Int J Cancer* 2010;126:232–8.

- Segura O, Burdorf A, Looman C. Update of predictions of mortality from pleural mesothelioma in the Netherlands. Occup Environ Med 2003;60:50–5.
- Marinaccio A, Montanaro F, Mastrantonio M, Uccelli R, Altavista P, Nesti M, Costantini AS, Gorini G. Predictions of mortality from pleural mesothelioma in Italy: a model based on asbestos consumption figures supports results from age-period-cohort models. *Int J Cancer* 2005;115:142.
- Murayama T, Takahashi K, Natori Y, Kurumatani N. Estimation of future mortality from pleural malignant mesothelioma in Japan based on an agecohort model. *Am J Ind Med* 2006;49:1–7.
- Pitarque S, Clèries R, Martínez JM, López-Abente G, Kogevinas M, Benavides FG. Mesothelioma mortality in men: trends during 1977-2001 and projections for 2002-2016 in Spain. Occup Environ Med 2008;65:279–82.
- Leigh J, Driscoll T. Malignant mesothelioma in Australia, 1945-2002. Int J Occup Environ Health 2003;9:206–17.

- Goldberg M, Imbernon E, Rolland P, Ilg AGS, Savès M, de Quillacq A, Frenay C, Chamming's S, Arveux P, Boutin C, Launoy G, Pairon JC, et al. The French National Mesothelioma Surveillance Program. Occup Environ Med 2006;63:390–5.
- Marinaccio A, Binazzi A, Di Marzio D, Scarselli A, Verardo M, Mirabelli D, Gennaro V, Mensi C, Merler E, De Zotti R, Romanelli A, Chellini E, eds. Italian National Mesothelioma Register, Third Report. Rome, Italy: ISPESL, 2010. Available at www.ispesl.it/renam [in italian].
- Nesti M, Marinaccio A, Chellini E, Regional Operative Centers. Malignant mesothelioma in Italy, 1997. *Am J Ind Med* 2004;45:55–62.
- Marinaccio A, Nesti M, Regional Operational Centers. Analysis of survival for mesothelioma cases in the Italian register (ReNaM). Eur J Cancer 2003;39: 1290–5.
- 15. Marinaccio A, Binazzi A, Cauzillo G, Cavone D, Zotti RD, Ferrante P, Gennaro

V, Gorini G, Menegozzo M, Mensi C, Merler E, Mirabelli D, et al. Analysis of latency time and its determinants in asbestos related malignant mesothelioma cases of the Italian register. *Eur J Cancer* 2007;43:2722–8.

- 16. Nesti M, Adamoli S, Ammirabile F, Ascoli V, Barbieri PG, Cacciarini V, Candela S, Cavone D, Cauzillo G, Chellini E, Chiappino G, Convertini L. eds. Italian National Institute for Occupational Safety and Prevention (ISPESL). Linee guida per la rilevazione e la definizione dei casi di mesotelioma maligno e la trasmissione delle informazioni all'ISPESL da parte dei centri operativi regionali, ISPESL 2003, Rome Italy. Available at: http:// www.ispesl.it/dml/leo/download/RenamLineeGuida.pdf (last accessed May 5, 2010) (in Italian).
- Virta RL. Worldwide asbestos supply and consumptions trends from 1900 to 2000. Open-file report 03-83. U.S. Department of interior—U.S. Geological Survey, 2006.
- Rake C, Gilham C, Hatch J, Darnton A, Hodgson J, Peto J. Occupational, domestic and environmental mesothelioma risks in the British population: a case-control study. Br J Cancer 2009;100:1175–83.
- Bang KM, Pinheiro GA, Wood JM, Syamlal G. Malignant mesothelioma mortality in the United States, 1999-2001. *Int J Occup Environ Health* 2006;12:9–15.
- 20. Moolgavkar SH, Meza R, Turim J. Pleural and peritoneal mesotheliomas in SEER: age effects and temporal trends, 1973-2005. *Cancer Causes Control* 2009;20:935–44.
- Neuman V, Gunter S, Muller KM, Fisher M. Malignant mesothelioma. German mesothelioma register 1987-1999. Int Arch Occup Environ Health 2002;74:383–95.
- Pukkala E, Martinsen JI, Lynge E, Gunnarsdottir HK, Sparén P, Tryggvadottir L, Weiderpass E, Kjaerheim K. Occupation and cancer—follow-up of 15 million people in five Nordic countries. *Acta Oncol* 2009; 48:646–790.
- Karjalainen A, Pukkala E, Mattson K, Tammilehto L, Vainio H. Trends in mesothelioma incidence and occupational mesotheliomas in Finland in 1960-1995. *Scand J Work Environ Health* 1997;23: 266–70.
- 24. Kjaergaard J, Andersson M. Incidence rates of malignant mesothelioma in Denmark and predicted future number of cases

among men. *Scand J Work Environ Health* 2000;26:112–7.

- 25. Iwatsubo Y, Pairon JC, Boutin C, Ménard O, Massin N, Caillaud D, Orlowski E, Galateau-Salle F, Bignon J, Brochard P. Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study. *Am J Epidemiol* 1998;148:133–42.
- Berry G. Models for mesothelioma incidence following exposure to fibers in terms of timing and duration of exposure and the biopersistence of the fibers. *Inhal Toxicol* 1999;11:111–30.
- Hillerdal G. Mesothelioma: cases associated with non-occupational and low dose exposures. Occup Environ Med 1999;56: 505–13.
- Petazzi A, Gaudiello F, Canti Z, Mensi C. Cluster cases of malignant pleural mesothelioma in an oil factory. *Med Lav* 2005;96:440–4.
- Chiappino G, Mensi C, Riboldi L, Rivolta G. Asbestos risk in the textile industry: final confirmation of data from the Lombardy Mesothelioma Registry. *Med Lav* 2003;94:521–30.
- Bianchi C, Bianchi T, Tommasi M. Mesothelioma of the pleura in the Province of Trieste. *Med Lav* 2007;98: 374–80.
- Huncharek M, Muscat J, Capotorto J. Pleural mesothelioma in a lift mechanic. Br J Ind Med 1989;46:500–1.
- U.S. Department of Labor. Occupational Safety & Health Administration (OSHA): asbestos safety and health topics. Available at: http://www.osha.gov/SLTC/asbestos/ construction.html (last accessed May 5, 2010).
- 33. Merler E, Bressan V, Somigliana A; Gruppo Regionale Veneto Sui Mesoteliomi Maligni.Mesothelioma in construction workers: risk estimate, lung content of asbestos fibres, claims for compensation for occupational disease in the Veneto Region mesothelioma register. *Med Lav* 2009;100: 120–32.
- 34. Frost G, Harding AH, Darnton A, McElvenny D, Morgan D. Occupational exposure to asbestos and mortality among asbestos removal workers: a Poisson regression analysis. Br J Cancer 2008;99:822–9.
- Rolland P, Gramond C, Lacourt A, Astoul P, Chamming's S, Ducamp S, Frenay C, Galateau-Salle F, Ilg AG, Imbernon E, Le

Stang N, Pairon JC, et al.; PNSM Study Group.Occupations and industries in France at high risk for pleural mesothelioma: a population-based casecontrol study (1998-2002). *Am J Ind Med* 2010;53:1207–19.

- Marinaccio A. Scientific research, epidemiologic surveillance, and compensation criteria for asbestos-related diseases. *Med Lav* 2010;101:146–8.
- Scarselli A, Scano P, Marinaccio A, Iavicoli S. Occupational cancer in Italy: evaluating the extent of compensated cases in the period 1994-2006. *Am J Ind Med* 2009;52: 859–67.
- Marinaccio A, Scarselli A, Binazzi A, Mastrantonio M, Ferrante P, Iavicoli S. Magnitude of asbestos-related lung cancer mortality in Italy. *Br J Cancer* 2008;99: 173–5.
- 39. Magnani C, Agudo A, González CA, Andrion A, Calleja A, Chellini E, Dalmasso P, Escolar A, Hernandez S, Ivaldi C, Mirabelli D, Ramirez J, et al. Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos. *Br J Cancer* 2000;83:104–11.
- 40. Ferrante D, Bertolotti M, Todesco A, Mirabelli D, Terracini B, Magnani C. Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. *Environ Health Perspect* 2007;115: 1401–5.
- Maule MM, Magnani C, Dalmasso P, Mirabelli D, Merletti F, Biggeri A. Modeling mesothelioma risk associated with environmental asbestos exposure. *Environ Health Perspect* 2007;115:1066–71.
- 42. Musti M, Pollice A, Cavone D, Dragonieri S, Bilancia M. The relationship between malignant mesothelioma and an asbestos cement plant environmental risk: a spatial case-control study in the city of Bari (Italy). Int Arch Occup Environ Health 2009;82:489–97.
- Mirabelli D, Cavone D, Merler E, Gennaro V, Romanelli A, Mensi C, Chellini E, Nicita C, Marinaccio A, Magnani C, Musti M. Non-occupational exposure to asbestos and malignant mesothelioma in the Italian National Registry of Mesotheliomas. Occup Environ Med 2010;67:792–4.
- Goldberg M. Compensating asbestos victims: the French model. *Epidemiol Prev* 2008;32:129–31.