Original research

Incidence of mesothelioma in young people and causal exposure to asbestos in the Italian national mesothelioma registry (ReNaM)

Alessandro Marinaccio ,[1] Davide Di Marzio,[1] Carolina Mensi ,[2] Dario Consonni ,[2] Carmela Gioscia,[3] Enrica Migliore,[4] Carlo Genova,[5] Roberta Rossetto Giaccherino,[5] Silvia Eccher,[6] Stefano Murano,[7] Vera Comiati,[8] Veronica Casotto,[8] Corrado Negro,[9] Lucia Mangone,[10] Lucia Miligi,[11] Sara Piro,[11] Alessia Angelini,[11] Iolanda Grappasonni,[12] Gabriella Madeo,[13] Ilaria Cozzi,[14] Laura Ancona,[14] Tommaso Staniscia,[15] Francesco Carrozza,[16] Domenica Cavone,[17] Luigi Vimercati ,[17] Michele Labianca,[18] Federico Tallarigo,[19] Giuseppe Cascone,[20] Massimo Melis,[21] Michela Bonafede,[1] Alberto Scarselli ,[1] Alessandra Binazzi [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Alessandro Marinaccio, Occupational Medicine Department, Italian Workers' Compensation Authority (INAIL), Rome, Italy;
a.marinaccio@inail.it

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ABSTRACT

Introduction The epidemiological surveillance of mesothelioma incidence is a crucial key for investigating the occupational and environmental sources of asbestos exposure. The median age at diagnosis is generally high, according to the long latency of the disease. The purposes of this study are to analyse the incidence of mesothelioma in young people and to evaluate the modalities of asbestos exposure.

Methods Incident malignant mesothelioma (MM) cases in the period 1993–2018 were retrieved from Italian national mesothelioma registry and analysed for gender, incidence period, morphology and exposure. Age-standardised rates have been calculated and the multiple correspondence analysis has been performed. The association between age and asbestos exposure has been tested by χ^2 test.

Results From 1993 to 2018, 30 828 incident MM cases have been collected and 1278 (4.1%) presented diagnosis at early age (≤50 years). There is a substantial association between age at diagnosis and the type of asbestos exposure and a significantly lower frequency of cases with occupational exposure to asbestos (497 cases vs 701 expected) in young people has been documented. Paraoccupational and environmental exposure to asbestos have been found more frequent in young MM cases (85 and 93 observed cases vs 52 and 44 expected cases, respectively).

Conclusions Mesothelioma incidence surveillance at population level and the anamnestic individual research of asbestos exposure is a fundamental tool for monitoring asbestos exposure health effects, supporting the exposure risks prevention policies. Clusters of mesothelioma incident cases in young people are a significant signal of a potential non-occupational exposure to asbestos.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Malignant mesothelioma (MM) is a rare tumour, prevalently due to occupational and environmental exposure to asbestos, characterised by a long latency and poor prognosis.

WHAT THIS STUDY ADDS

⇒ In Italy, a permanent surveillance system for mesothelioma incidence is active with a case list of 30 828 MM cases collected in the period between 1993 and 2018 and the 4.1% of registered cases are <50 years old at diagnosis.

⇒ A substantial lower frequency of cases with occupational exposure to asbestos (497 cases vs 701 expected) has been found in the group of younger subjects. At the opposite, 85 observed cases (52 expected) with paraoccupational exposure (due to the cohabitation with an exposed subject), and 93 observed MM cases (44 expected) with environmental exposure.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clusters of mesothelioma incident cases in young people are a significant signal of a potential non-occupational exposure to asbestos.

⇒ The epidemiological surveillance is crucial for monitoring MM incidence in young people supporting the environmental asbestos exposure prevention and promoting the compensation system efficiency.

INTRODUCTION

Malignant mesothelioma (MM) is a rare neoplasm characterised by high lethality, long latency and high aetiological fraction due to occupational exposure to asbestos. More than 80% of cases arise from the pleura, but peritoneum, pericardium and the tunica vaginalis of testis can be involved. The International Agency for Research on Cancer has

repeatedly confirmed the causal association with all forms of asbestos (amphiboles as actinolite, amosite, anthophyllite, crocidolite, tremolite and serpentine as chrysotile) for mesothelioma in humans (group 1), as well as lung, larynx and ovary cancer. Limited evidence has been established for the associations between exposure to all forms of asbestos and pharynx, stomach and colorectal cancers.[1]

Asbestos has been used in a large spectrum of industrial activities and in the construction sector due to its thermal and chemical resistance. In almost all Western countries, asbestos has been intensively used during 1950–1980, but it is now banned, whereas it is still extracted and processed in many countries of Asia, South America, Africa and in the Former Soviet Union.[2 3] The WHO has estimated 125 million of currently exposed workers and the Global Burden of Diseases research project calculated around 27 000 deaths annually for mesothelioma.[4]

The latency from the beginning of exposure to diagnosis or death is extremely long for mesothelioma, reaching 40 years or more.[5] As a consequence, the median age at diagnosis is generally high and the Italian national mesothelioma register (ReNaM) has provided evidence of 78 years as the median age of onset.[6] Early incidence of mesothelioma is generally considered as a warning of environmental contamination by asbestos exposure before working age. From a public health point of view, the surveillance of mesothelioma incidence in childhood or adolescence is crucial for monitoring the potential unknown environmental sources of contamination and for the concerns about the lack of awareness and vulnerability of exposed young people.[7]

In Italy, the epidemiological surveillance of the disease is working by means of a national MM Registry (Registro Nazionale dei Mesoteliomi, ReNaM in Italian). ReNaM is devoted to provide estimates of the incidence of MM, to define and record asbestos exposures, to assess the impact of the disease at the population level and to identify any possible underestimated or unknown source of asbestos contamination. ReNaM has been in force since 2003 and up to now published figures for incidence, survival, latency and asbestos exposure of subjects with mesothelioma, providing evidence of MM incidence in women[8] and in specific occupational settings.[9]

The purposes of this study are to analyse the incidence of mesothelioma in subjects ≤50 years old at diagnosis, to evaluate the modalities of asbestos exposure in this group compared with older patients, to assess specific territorial patterns of incidence in young populations and to discuss the epidemiological findings in a context of public health utility for the prevention of exposure.

METHODS

MM incident cases have been selected by ReNaM for the diagnostic period between 1993 and 2018. ReNaM is a national surveillance system of mesothelioma incidence, established with force of law since 1991, devoted to identify cases and to assess the modalities of asbestos exposure. In 2002 the aims, the methods and the epidemiological procedures have been definitively fixed (Italian law n. 308/2002). The structure is regional and the regional operating centres (Centro Operativo Regionale (COR), in Italian) have been gradually established as mapped in of the online supplemental figure SM1. At the present, case lists from three Italian regions (Calabria, Sardinia and Molise) cannot be considered complete yet. Recently, Abruzzo and Campania regions have suspended their activities and their data are lacking for the period 2016–2018. The two fundamental focuses of COR are (1) the active search of MM incident cases and (2) the analysis of occupational history, lifestyle habits and residence for each affected subject. Each COR actively searchs incident MM cases from healthcare institutions potentially involved in diagnosis (chest surgery wards, pathology and lung care units). According to the specific regional contexts, CORs access directly to electronic medical records or periodically contact all the involved medical wards and units to retrieve the clinical records. Mortality and hospital discharge data have been regularly used to verify the completeness of recognised case list. MM cases have been classified into three categories according to the level of diagnostic certainty: certain (with cytohistological confirmation), probable (with not definitive cytological or histological examination) and possible mesothelioma (with radiological and clinical evidence only). A trained interviewer administers a standardised questionnaire to the patient or to the next of kin (55.4% and 42.1% of interviewed patients, respectively) for investigating the occupational history, the lifestyle habits and the residential history of the affected people. Sporadically, in the absence of questionnaire, the exposure can be assessed by consulting the documentation held by the last company in which the patient worked (2.5% of cases) and confirmed through cooperation with public local health agencies. The interview is generally in person, and only sporadically on telephone (13%). Training courses focused on the potential modalities of exposure to asbestos and the ReNaM questionnaire are regularly performed for the interviewers at national and regional level. The informed consent is always obtained for interviewed patients.[10] Furthermore, 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 and unique exposure coding system adopted in the ReNaM network. Occupational exposure classification is qualitative and the non-occupational modalities of exposure considered are: 'environmental' exposure (residence near a source of asbestos pollution without work-related exposure), 'paraoccupational' exposure (exposure of family members living with someone who was occupationally exposed to asbestos) and 'leisure activities' exposures (other non-occupational exposures to asbestos containing material, like those during plumbing or electrical repairs or during thermal insulation work at home, or due to the use of baking glovers or steam iron boards containing asbestos, or in general during hobby activities).The potential sources of environmental contamination that are reported in ReNaM national guidelines and investigated by the questionnaire are: chemical/petrochemical plant, thermoelectric power plant, port/harbour, shipyards, asbestos-cement production plants (Eternit), railway production and repair plants, quarry or mine, railway line/station, incinerator, waste disposal site. The distance between the residence of the affected subject and each potential source is evaluated. Other details about MM diagnosis and asbestos exposure coding system adopted in ReNaM are extensively described elsewhere.[10–12] The CORs periodically transmit the collected case lists to ReNaM that performes the epidemiological aggregate analyses and promotes specific research projects in synergy with regions.

For the aim of this study, incident cases available to ReNaM in the period 1993–2018 have been considered according to the three diagnostic certainty levels and the anatomical site (pleura, peritoneum, pericardium and tunica vaginalis of testis). Mesothelioma in young people has been defined if the affected subject was <50 years old at diagnosis.[7] Analysed information regarded gender, incidence periods (1993–1998, 1999–2003, 2004–2008,

2009–2013 and 2014–2018), morphology (epithelioid, biphasic, sarcomatous and mesothelioma not otherwise specified); exposure detection modalities (interview to the patient or to a relative). The nationality of affected people distinguishing between Italian, other European countries and non-European countries nationality has been evaluated.

A multiple correspondence analysis (MCA) has been performed to detect and represent the underlying structure of data, searching for the basilar dimensions of the case list and analysing the structure of associations with age in a multilevel approach. Variables included in the MCA models are: age at diagnosis (≤50 years old as 'young' and other as 'not young); anatomical site (pleural and extrapleural), the level of diagnostic certainty (definite MM, probable or possible MM); exposure to asbestos (occupational, non-occupational, other or undefined), gender (men and women); modality of interview (direct interview to the subject, other). MCA allows identifying the patterns of association between the original variables in the space of two (or more) factorial axes. Age-standardised incidence rates have been calculated using the Italian standard population (2001 census), separately for pleural and peritoneal MM, for 'young' and 'not young' MM, by year (period: 1993–2017). The association between these two age categories and the asbestos exposure modalities has been tested by χ^2 test, by computing expected cases for all combinations of age and exposure. The territorial distribution of young mesothelioma cases according to the region of residence at diagnosis has been mapped calculating the percentage of young cases with respect to the entire case list for each region.

Patient and public involvement

All mesothelioma patients have been involved and informed about the background, the research design and the conduct of ReNaM activities. The results of the Italian surveillance system of mesothelioma incidence are regularly presented and discussed in a large spectre of public events, including meetings with the affected subjects, next of kin or asbestos exposed workers and victims associations.

All analyses have been performed by IBM SPSS, V.25.0 (IBMSPSS) packages for statistical analysis, 'data reduction' procedure considering each MM case as the unit of analysis.

RESULTS

From 1993 to 2018, 30 828 incident MM cases have been collected by the Italian surveillance system and 1278 of them (4.1%) with diagnosis at age ≤50 years old (0.7% in the 15–39 and 3.5% in the 40–50 age classes, respectively). Gender ratio (M/F) in young MM was lower than in not young MM (1.88 and 2.60, respectively) with a substantial proportion of young women (34.7% of the total young affected people).

Characteristics of young and eldest MM cases are reported in table 1. Extrapleural sites were more represented in the young group (17.2 %) than in the older one (6.4%), in particular peritoneal mesothelioma (15.2%). The proportion of young people with mesothelioma decreased in the considered period, from 26.4% in 1999–2003 to 12.9% in 2014–2018, but this evidence must be analysed with caution according to the different territorial coverage of the surveillance system (reported in details in of online supplemental figure SM1). The level of diagnostic certainty was quite different in the two considered groups. In the

Table 1 Malignant mesothelioma (MM) cases in young (≤50 years old at diagnosis) and eldest adults (>50 years) by gender, anatomical site, incidence period, diagnostic certainty, morphology and modalities of exposure detection

		MM cases (≤50 years old)		MM cases (>50 years old)	
		N.	%	N.	%
Gender	Women	443	34.7	8214	27.8
	Men	835	65.3	21 336	72.2
Anatomical site	Pleura	1058	82.8	27 685	93.7
	Peritoneum	194	15.2	1742	5.9
	Pericardium	13	1.0	48	0.2
	Tunica vaginalis of testis	13	1.0	75	0.3
Incidence period	1993–1998	214	16.7	2545	8.6
	1999–2003	338	26.4	5428	18.4
	2004–2008	298	23.3	6854	23.2
	2009–2013	263	20.6	7889	26.7
	2014–2018	165	12.9	6834	23.1
Diagnostic certainty	Defined MM	1167	91.3	23 821	80.6
	Probable or possible MM	111	8.7	5729	19.4
Morphology*	Epithelioid	805	69.0	16 338	68.6
	Biphasic	182	15.6	2947	12.4
	Sarcomatous	59	5.1	2112	8.9
	MM NOS	121	10.4	2424	10.2
Exposure detection	Interview to the patient	697	54.5	12 933	43.8
	Interview to a relative	299	23.4	10 148	34.3
	Other	2	0.2	150	0.5
	No interview	280	21.9	6319	21.4
Overall		1278		29 550	

Italian national mesothelioma registry (ReNaM), 1993–2018.
*Only defined MM.
NOS, not otherwise specified.

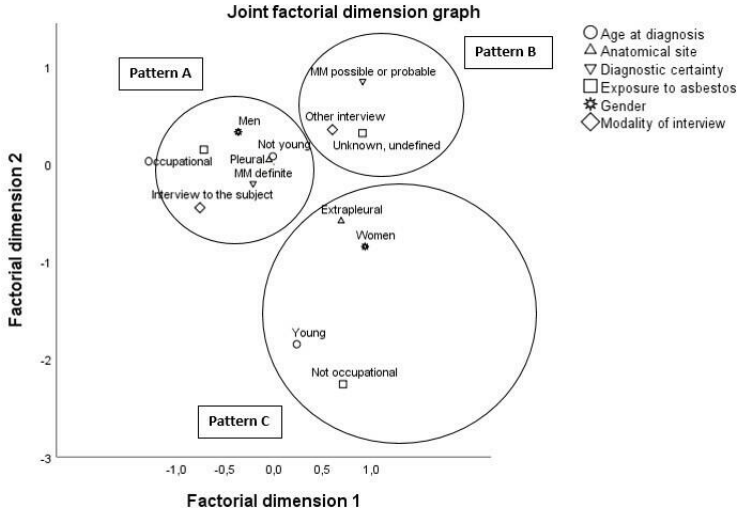

Figure 1 Multiple correspondence analysis for malignant mesothelioma cases (N: 30 828) by gender, age at diagnosis, anatomical site, diagnostic certainty, exposure to asbestos and modality of interview. First two-factorial dimensions selected (explained variance 48.7%; 27.5% and 21.2% for factors 1 and 2,respectively). Italy, Italian national mesothelioma registry, 1993–2018.

older patients, the diagnosis was on average less defined, with a consistent quota of probable and possible MM (19.4%). This percentage was only 8.7% among younger MM patients. In the entire case list, the distribution of nationality is 97.6%, 1.8%, 0.7% for Italian, other European countries and non-European countries nationality, respectively. In the subset of young mesothelioma cases the proportion of not Italian nationality reaches 5.6% (3.4% and 2.1%, European and extra European countries nationality, respectively).

With regard to the modalities of interview, the direct one to the affected subjects in the young MM patients was prevalent. In ReNaM procedures, the interview with the affected subjects' relatives is a second choice, if there is a concrete impediment for talking with the patients directly. Median year of first exposure is 1975 in young MM patients, whereas it is 1959 in the group of cases older than 50 years at diagnosis. The median age of first exposure is 18 years old in young patients and 22 years in older patients.

The multivariate analysis (MCA) allowed identifying homogeneous patterns in MM cases, detecting specific profiles in the joint graph (figure 1). The first two factorial dimensions explained 48.7% of the total variance (27.5% and 21.2% for the first and second axes, respectively). Three patterns seemed to be recognised by the multivariate analyses: the first (pattern A) was characterised by pleural MM cases in males with occupational exposure and with high level of available information for diagnosis (defined MM) and exposure (interview to the subject). The second pattern (B) presented a low level of definition, referring both to diagnosis and exposure. The third (C) was characterised by female MM cases with extrapleural localisation of the disease, young age and not occupational exposure to asbestos.

The temporal trend of pleural MM incidence standardised rates in ≤50 years old population evidenced a negative slope, much stronger in males (online supplemental figure SM2), while in the older population (>50 years old) the trend is positive for males, and quite flat in females (online supplemental figure SM3). With regard to peritoneal MM, there is large variability due to low numbers in young cases (online supplemental figure SM4), while rates seem rather stable in the older age group (online supplemental figure SM5), for both genders.

The strong association between the age at diagnosis and the type of asbestos exposure in MM patients collected by ReNaM was confirmed by contingency table analysis (table 2). In the group of younger subjects, we found a substantial lower frequency of cases with occupational exposure to asbestos (497 cases vs 701 expected in the hypothesis of equal distribution) and, as a consequence, a higher frequency of non-occupational exposure. In particular, 85 observed cases (52 expected) with an exposure due to the cohabitation with an exposed subject (generally the husband) and 93 observed MM cases with environmental exposure, vs 44 expected. Young people also showed a much higher proportion of unlikely exposure (302 against 202

Table 2 Malignant mesothelioma (MM) cases in young (≤50 years old at diagnosis) and not young adults (>50 years) by modality of asbestos exposure in the Italian national mesothelioma registry (ReNaM), Italy, 1993–2018

		MM cases (≤50 years old)		MM cases (>50 years old)	
		Observed	Expected	Observed	Expected
Asbestos exposure	Occupational	497	700.6	16 403	16 199.3
	Paraoccupational	85	52.4	1180	1212.6
	Environmental	93	44.0	969	1018.0
	Leisure activities related	26	15.3	343	353.7
	Unknown, unlikely	302	202.3	4579	4678.7
	Not defined	275	263.3	6076	6087.7
Overall		1278		29 550	

Observed cases and expected cases in the hypothesis of independence.

expected), more evident in young females (43.3% vs 36.8% in the older age group) than in young males (27.5% vs 13.3%). The group of MM cases with less than 50 years old at diagnosis counted for 4.3% for Italy with a great geographical variability and a higher percentage in the Southern Italy regions.

DISCUSSION

MM incidence in young people is a substantial issue for epidemiological, research, public health and social reasons. According to the high occupational aetiological fraction, to the selective association with asbestos exposure and the long latency of the diseases, the occurrence of mesothelioma in subjects with age at diagnosis less than 50 years is expected to be infrequent and deserves specific attention.

Due to the long-term epidemiological surveillance of MM, which covers almost completely the Italian territory in a large observational period, our study provided evidence of the rarity of mesothelioma occurrence in young people, representing 4.1% (1278/30 828 MM cases) of the entire case list recorded in 1993–2018, but a great variability has been observed according to demographic, pathological and anamnestic factors. Female gender and extrapleural localisation of the disease appeared associated with the young age at onset.[13] The coexistence of MM clusters in young people with a substantial proportion of women has been previously observed in a Danish context of asbestos environmental contamination[14] and has been also reported among the residents near a large Colombian asbestos cement plan in Sibatè.[15] In Italy, an environmental contamination by fluoroedenite had been identified in the town of Biancavilla (quarry of Mount Calvario, Sicily, in Southern Italy) starting from the epidemiological evidence of a cluster of MM deaths characterised by young age and the gender ratio near the unity.[16 17]

The percentage of probable or possible MM is 18.9% (5840/30 828 cases) in the entire ReNaM case list. This percentage is distributed with a clear gradient by age at diagnosis (8.7% in young patients and 19.4% in not young patients). Evaluating by the anatomical site, in the pleural form, we have 19.2% (8.6% and 19.6% in young and not young patients, respectively); in the peritoneal form we have 16.2% (9.8% and 16.8%). The distinct features of the young MM trend probably take into account of the higher peritoneal cases in women that could be interpreted in the light of the recognised level of misdiagnosis for women with abdominal neoplasms and ovarian serous carcinoma,[18 19] but the high frequency of definite peritoneal MM in ReNaM network has to be considered.

In this study, the multivariate analyses allowed us to recognise a pattern of cases with insufficient available information for a definite diagnosis and a solid assessment of asbestos exposure modalities. The inverse association between age at diagnosis and level of diagnostic certainty in MM patients, as repeatedly evidenced in ReNaM,[20 21] is explained by the avoidance of the invasive diagnostic examinations in the elderly, when not strictly necessary.

The decline observed in the incidence of young individuals with MM provides further evidence of their limited occupational exposure. This is a consequence of the asbestos ban in 1992[22] and supports the opportunity of using MM surveillance in young people as a tool for identifying asbestos environmental sources of contamination.[23] The substantial percentage of young MM cases with not Italian nationality (higher than in the entire case list) enforces the need to evaluate specific formation policies for migrant young workers involved in activities potentially at risk of exposure (particularly in maintenance and renovation of old buildings).

At this regard, two recent studies found an increased risk of MM in former school children exposed to environmental asbestos in childhood (Standardised Incidence Ratio (SIR) 8.77, 95% CI 6.38 to 12.05)[24] and particularly in a cohort of former female school children (SIR 7.26, 95% CI 3.26 to 16.15) who lived and attended school in close proximity to a large asbestos-cement plant.[25] These results confirm the harmful effects of environmental asbestos in young people. Despite in Italy, the use and the production was banned in 1992, asbestos remains a hazard to human health because most of asbestos-containing materials (ACM) have not been removed and are still in the original place, often public buildings, such as schools and hospitals. Depending on how much is strongly stuck, ACM may be a source of airborne asbestos in the environment. The longer life expectancy of younger subjects compared with the adults implies a higher potential environmental exposure to asbestos and chance to develop over time asbestos-related diseases that may occur also a long time after exposure to asbestos has finished. Biological factors of young population, for example, the higher lung ventilation that may allow the fibres to lay down more quickly, and behavioural factors—like playing for a long time in possibly contaminated areas—should also be considered. In this context, also the current asbestos exposure assessment of children in school building is a real concern. A recent estimate in Rome (Italy) identified ACM in about 16% of the inspected schools, primarily in vinyl floor tiles.[26] In the population-based case–control study of pleural MM incident cases between 1987 and 1993 in Casale Monferrato (Torino, North Western Italy), Magnani *et al* showed an increased risk in subjects attending grammar school in the town (OR 3.3; 95% CI 1.4 to 7.7) due to the environmental exposure to asbestos.[27] Exposure to blue asbestos in childhood has been demonstrated to be associated with an increased risk of cancer and mortality in a cohort of adults that had lived in an asbestos mining town (Wittenoom, Australia) during their childhood.[28] The same authors have discussed the evidence of no greater susceptibility to mesothelioma among those first exposed to asbestos as children than those first exposed as adults, but, according to the long latency, the early exposure to asbestos is a great concern.[29]

With concern to tumours manifesting at earlier ages, a large amount of data is reporting new genes and their alterations involved in the development of mesothelioma and in the predisposition to develop this pathology among carriers.[30 31] Cases in young adults under the age of 50 have been reported in the Italian case series relating to consanguineous family groups and heavy exposure, in some cases also with identification of genetic alterations and long survival.[32 33]

Some limitations of the study must be evidenced. The Italian epidemiological surveillance system of mesothelioma incidence has a regional architecture, but the CORs were not established at the same time and this could introduce a bias in the findings, due to the different spatial distribution of the industrial contaminated sites and the environmental sources of asbestos fibres dispersion. In northern Italy, the occurrence of mesothelioma in elderly people was consistently higher than in young people. In these areas, the incidence of mesothelioma has been linked to specific industries, such as metallurgical industries, insulation companies, docks and shipyards, where several occupational groups (mainly men) have been exposed to asbestos, especially in the past. Furthermore, regions presented different levels of exposure assessment, with a percentage of collected exposure histories through the questionnaire that, in some cases, is less

than 50% of collected cases.[6] Unfortunately, the current suspension of the epidemiological activities in Campania region remains a strong concern. Finally, there is a substantial effort to improve the homogeneity among CORs in classifying and coding diagnoses and exposures (an updated version of the national guidelines is currently in preparation, with the aim to standardise the procedures and implement tighten quality checks of data), but the capacity in recognising incident cases and in exposure assessment is still not fully consistent across the territorial contexts.

The systematic surveillance of mesothelioma incidence in young people, including the evaluation of the occupational and not occupational sources of contamination of each affected subject, is a precious tool for stimulating the protection from unaware exposure to environmental risk factors in children. The potential high susceptibility, the substantial lack of unawareness, the weakness of social and working protection contribute to make the prevention of the risk of MM in young people a sensitive issue for public health systems.

In conclusion, our study provides evidence of a consistent proportion of mesothelioma cases occurring in young people in Italy, demonstrating a recognised association with non-occupational exposure to asbestos. The MM incidence surveillance at population level (not only in workers) and the anamnestic individual research is a fundamental tool for monitoring the presence of MM clusters in young people, supporting the exposure risks prevention policies. The legacy of asbestos industrial massive use is still dramatic in Italy, as in other countries. As repeatedly WHO stated that the best way to eliminate asbestos-related diseases is the international ban.[2 34 35]

Author affiliations
[1]Occupational and Environmental Medicine, Epidemiology and Hygiene Department, Italian Workers' Compensation Authority (INAIL), Rome, Italy
[2]Epidemiology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[3]Valle d'Aosta Health Local Unit, Valle d'Aosta Region, Aosta, Italy
[4]COR Piemonte, Unit of Cancer Epidemiology, University of Turin and CPO-Piemonte, Torino, Italy
[5]Internal Medicine Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy
[6]Provincial Unit of Health Hygiene and Occupational Medicine, COR Province of Trento- APSS, Trento, Italy
[7]Occupational Medicine Unit, COR PA Bolzano, Bolzano, Italy
[8]COR Veneto, Azienda Zero, Veneto Region, Padova, Italy
[9]COR Friuli Venezia Giulia, Unit of Occupational Medicine, University of Trieste, Trieste Hospital, Trieste, Italy
[10]COR Emilia-Romagna, Reggio Emilia, Italy
[11]ISPRO, COR Toscana, Florence, Italy
[12]COR Marche, University of Camerino, School of Pharmacy, Camerino, Italy
[13]COR Umbria, Umbria Region, Perugia, Italy
[14]COR Lazio, Department of Epidemiology, Lazio Regional Health Service, ASL Roma1, Rome, Italy
[15]COR Abruzzo, Abruzzo Regional Health Agency (ASR), Pescara, Italy
[16]COR Molise, Oncology Unit, Cardarelli Hospital, Campobasso, Italy
[17]Section Occupational Medicine, Interdisciplinary Department of Medicine, COR Puglia, University of Bari Aldo Moro, Bari, Italy
[18]COR Basilicata, Epidemiologic Regional Center, Basilicata Region, Potenza, Italy
[19]COR Calabria, Public Health Unit, Regione Calabria, Crotone, Italy
[20]Public Health Agency Ragusa (ASP), COR Mesoteliomi della Sicilia, Ragusa, Italy
[21]COR Sardegna, Sardegna Region, Cagliari, Italy

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Contributors Conceptualisation, AM; Methodology, AB and AM; Software, DDM; Validation, AB and DDM; Formal analysis, AM, AB, AS, MB and DDM; Investigation and Data curation, CM, DCo, CGi, EM, CGe, RRG, SE, SM, VCo, VCa, CN, LMa, LMi, SP, AA, IG, GM, IC, LA, TS, FC, DCa, LV, ML, FT, GC and MM; Writing—Original Draft Preparation, AM; Writing—Review and Editing, AB, CM, DCo and MB, Guarantor, AM.

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Patient consent for publication Not applicable.

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ORCID iDs
Alessandro Marinaccio http://orcid.org/0000-0001-9068-2137
Carolina Mensi http://orcid.org/0000-0002-9075-3684
Dario Consonni http://orcid.org/0000-0002-8935-3843
Luigi Vimercati http://orcid.org/0000-0002-4072-2871
Alberto Scarselli http://orcid.org/0000-0001-7931-0375
Alessandra Binazzi http://orcid.org/0000-0002-0435-600X

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