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Original research

Peritoneal mesothelioma and asbestos exposure: a population-based case–control study in Italy, 2000–2021

Dario Consonni ,[1] Enrica Migliore,[2] Manuela Gangemi,[2] Domenica Cavone,[3] Luigi Vimercati ,[3] Sara Piro,[4] Lucia Giovannetti,[4] Valentina Zabeo,[5] Vera Comiati,[5] Stefania Curti ,[6] Stefano Mattioli ,[7] Maria Teresa Landi,[8] Carmela Gioscia,[9] Silvia Eccher,[10] Stefano Murano,[11] Flavia D'Agostin,[12] Carlo Genova,[13,14] Riccardo Perduri,[15] Iolanda Grappasonni,[16] Fabrizio Stracci,[17] Ilaria Cozzi,[18] Tommaso Staniscia,[19] Franco Calista,[20] Italo Francesco Angelillo,[21] Rocco Galasso ,[22] Federico Tallarigo,[23] Giuseppe Cascone,[24] Massimo Melis,[25] Susan Peters ,[26] Hans Kromhout ,[26] Alessandra Binazzi ,[27] Alessandro Marinaccio ,[27] Carolina Mensi ,[1] ReNaM Working Group

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For numbered affiliations see end of article.

Correspondence to
Dr Dario Consonni;
dario.consonni@unimi.it

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ABSTRACT

Objectives Using a case–control design, we examined the association between occupational asbestos exposure and risk of peritoneal mesothelioma in the general population in Italy.

Methods From the National Mesothelioma Registry, we selected cases (2000–2021) with lifetime occupational history. Controls were 3045 from three case–control studies (region-sex-age-matched, performed in six regions), one in 2002–2004 (2116 population controls) and two in 2012–2016 (718 population and 211 hospital controls). For all subjects, exposure assignment was based on a quantitative job-exposure matrix (SYN-JEM). Qualitative expert-based evaluation was available for all cases, but only in 2012–2016 for 929 controls. We estimated ORs and 90% CIs using logistic regression models adjusted for residence, gender, period and age.

Results In complete analyses (1591 cases, all years/regions), the OR for ever exposure was 3.66 (CI 3.21 to 4.18, 45.4% cases and 27.8% controls exposed). Among the exposed, median cumulative exposure (fibres/mL-years) was 1.4 (max 20.0) in cases and 1.1 (max 10.9) in controls. The OR was 1.55 (1.48 to 1.62) per $\log_{10}$-transformed cumulative exposure. In analyses restricted to 290 cases (same years/regions of controls), ORs were 3.35 (2.57 to 4.37, 43.8% cases exposed) for ever exposure and 1.52 (1.39 to 1.65) for cumulative exposure. ORs for ever asbestos exposure using expert-based evaluation were particularly high, 4.32 (3.50 to 5.34, 53.9% cases and 26.4% controls exposed) in complete analyses (778 cases) and 6.35 (4.58 to 8.81, 57.1% cases exposed) in restricted analyses (245 cases), but are known to be more prone to bias.

Conclusions Peritoneal mesothelioma showed clear associations with asbestos exposure using different exposure assessment methods.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cohort studies in highly exposed workers showed that peritoneal mesothelioma is strongly associated with asbestos exposure. However, this disease has mainly been studied in industrial cohorts and has rarely been investigated in community-based studies.

WHAT THIS STUDY ADDS

⇒ Using existing datasets, we performed a nationwide population-based case–control study based on data of a high-quality of the National Mesothelioma Registry covering 22 years.

⇒ We provided strong evidence of the association between peritoneal mesothelioma and several indices of asbestos exposure, including expert-based evaluation and cumulative exposure assessed with a job-exposure matrix.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results may be of relevance for compensation of individuals affected by peritoneal mesothelioma, independently of the industrial sectors in which they were exposed.

⇒ Epidemiological surveillance and epidemiological studies are crucial for identifying all sources of asbestos exposure, enhancing the awareness of mesothelioma aetiology and supporting prevention policies and effectiveness of insurance systems.

INTRODUCTION

Peritoneal mesothelioma (PM) is a rare cancer. In Europe, the crude incidence rate of PM in the period 1995–2002 was 0.12 per 100 000 person-years,[1] and it represents a small minority of all

mesotheliomas. In Italy in the period 1993–2021 out of 37 003 mesothelioma cases, there were 2381 PM (6.4%), with incidence rates (per 100 000) in 2019 of 0.24 (men) and 0.15 (women).[2]

The main recognised risk factor, as for any mesothelioma, is asbestos (all forms).[3] Compared with pleural mesothelioma, PM shows some differences, including a lower male/female ratio,[4–7] a less strong association with asbestos exposure[8 9] and less definite temporal trends.[4 5 9] Some cohort studies suggest continuous increasing PM risk with time since first exposure, while a plateauing was found for pleural mesothelioma.[7 10 11] Many occupational cohort studies have shown excesses of PM among asbestos-exposed workers.[8 12] Conversely, this association has been rarely investigated in the general population using a case–control design.[13–17]

Italy has been a great consumer of all types of asbestos (4.5 million tons) from 1933 until the ban in 1992 and is among the countries with the highest mesothelioma burden.[18–20] A National Mesothelioma Registry (Registro Nazionale Mesoteliomi, ReNaM) has been established (law 308/2002) at the National Institute for Insurance against Accidents at Work (INAIL, Rome), to monitor mesothelioma occurrence. In Italy, it has been shown that only half of mesothelioma patients filed compensation claims; the proportion of claims filed by the minority of workers exposed in industries involving direct use of asbestos was 63.9%, while in the large majority (about 80%, employed in other industries), the proportions of claims were below 50%.[21] However, we previously showed that mesothelioma risk is increased in many industries/occupations at any level of asbestos exposure.[17 22–24]

Aim of the present study is to analyse PM risk in a population-based study in order to cover all types of industries and occupations: we performed a 'control-initiated case–control study',[25] that is, we exploited the availability of datasets of controls from three Italian studies (one unpublished),[22 26] to implement a nationwide case–control study on PM risk within the National Mesothelioma Registry (ReNaM).

METHODS

Cases

ReNaM is organised as a network of regional centres (Centri Operativi Regionali, COR).[2] Each COR collects information on newly diagnosed mesothelioma cases. Confirmed cases are classified as 'definite' (histological diagnosis, possibly with immunohistochemical confirmation), 'probable' (usually, cytology plus imaging) or 'possible' (positive imaging). Completeness of reporting (compulsory by law) is periodically verified using various sources, including hospital admission databases.

Cases or their next-of-kin are interviewed by trained personnel using a standardised ReNaM questionnaire covering life-time job history (including industry, occupation and details about tasks or indirect exposure within each jobs) and sources of extraoccupational asbestos exposure. Industries and occupations are coded using Italian classifications ATECO-91 and CIP-91, respectively. Asbestos exposure is evaluated by experts and classified as occupational (definite, probable or possible) or extraoccupational exposure (attributed to cases non-occupationally exposed only), which includes: (a) paraoccupational or familial (eg, from contaminated clothes of a family member); (b) environmental (residence near industries using asbestos) and (c) domestic or home-related (eg, ironing on asbestos boards, small repair works in the house).

Data of the regional centres are transmitted to ReNaM, which performs data editing and use them to produce periodical reports. For this work, we extracted all PM cases first diagnosed in the period 2000–2021.

Controls

The first set of controls comes from the Environment And Genetics in Lung cancer Etiology (EAGLE) population-based case–control study.[26] Controls (frequency matched to cases by area of residence, gender and age) had been randomly sampled in 2002–2004 among residents aged 35–79 years in five Lombardy (North-West Italy) provinces. Participation rate (participants/eligible) was 72.4%. Subjects underwent a computer-assisted personal interview on lifetime occupational history (years of start/stop, industries, occupations).[26]

The second set of controls was taken from the Multicentre Italian Study on the Etiology of Mesothelioma (MISEM) population-based case–control study on pleural mesothelioma.[22] It was performed in five regions in North-West (Lombardy, Piedmont), North-East (Veneto), Centre (Tuscany) and South (Apulia). Controls (frequency matched to cases by province of residence, gender and age) had been randomly sampled from residents aged 20–89 years and interviewed in 2012–2014 using ReNaM questionnaire. Participation rate was 48.1%.

The third set of controls was taken from the hospital-based Cholangiocarcinoma Aetiology: Role of Asbestos (CARA) study performed in Emilia-Romagna (North-East) in the period 2014–2016 (unpublished). Hospital controls aged 22–92 years were interviewed with a questionnaire including occupational sections taken from the ReNaM questionnaire.

Since CARA controls were few and were enrolled in a period overlapping with MISEM, in statistical analyses CARA and MISEM controls were pooled together to cover years 2012–2016.

The regions in which controls were sampled cover 31 million residents (52% of the Italian population) and were highly industrialised (online supplemental figure 1).

Coding of industries and occupations

In the EAGLE, MISEM and CARA studies, occupations had been coded following the International Standard Industrial Classification of All Economic Activities (ISIC-71) and the International Standard Classification of Occupations (ISCO-68). For cases, we used a recently published crows-walk to translate Italian occupation codes (CIP-91) into ISCO-68 codes[27]; we translated a few ATECO-91 codes into ISIC-71 codes.

Exposure to asbestos

Asbestos exposure was evaluated using two methods, one based on a quantitative job-exposure matrix (JEM), the other based on expert evaluation of information collected through interviews with ReNaM questionnaire.

The quantitative JEM (called SYN-JEM) had been developed based on more than 100 000 personal occupational asbestos measurements from Europe and Canada and has been used in several studies within the SYNERGY project, a pooled analysis of case–control studies on the joint effects of occupational carcinogens in the development of lung cancer.[28–30] Calculation of exposure at the individual level requires the availability of all ISCO-68 codes (with start/end dates for each job) and a few ISCI-71 codes.[30] For EAGLE and MISEM controls, asbestos exposure estimates (yearly intensity of exposure in fibres per mL, ff/mL) based on SYN-JEM were already available because they had been used in previous studies.[17 22] For PM cases and CARA controls, the exposure assignment through the SYN-JEM was

Table 1 Characteristics of controls and peritoneal mesothelioma cases included in complete and restricted analyses, Italy, 2000–2021

	Controls		Cases Complete analysis*		Cases Restricted analysis*	
	N	%	N	%	N	%
All	3045		1591		290	100
Men	2210	100	965	100	161	100
Age, mean (SD)	66.1	(9.0)	67.2	(11.7)	68.5	11.7
Min–max	22–92		18–91		31–89	
Interview						
Subject	2174	98.4	479	49.6	89	55.3
Next-of-kin	36	1.6	486	50.4	72	44.7
Blue-collar job						
Never	790	35.8	192	19.9	27	16.8
Ever	1420	64.2	733	76.0	123	76.4
Missing	0	0.0	40	4.1	11	6.8
Asbestos exposure†						
Never	1448	65.5	345	35.8	56	34.8
Ever	762	34.5	580	60.1	94	58.4
Missing	0	0.0	40	4.1	11	6.8
Diagnosis						
Definite			852	88.3	139	86.3
Probable			85	8.8	17	10.6
Possible			28	2.9	5	3.1
Morphology (ICD-O-3)						
Unspecified (90503)			161	16.7	22	13.7
Sarcomatoid (90513)			34	3.5	2	1.2
Epithelioid (90523)			659	68.3	115	71.4
Biphasic (90533)			70	7.3	12	7.5
Not available			41	4.2	10	6.2
Women	835	100	626	100	129	100
Age, mean (SD)	65.0	(11.7)	66.6	(13.0)	68.3	(12.7)
Min–max	24–98		18–97		25–91	
Interview						
Subject	824	98.7	285	45.5	60	46.5
Next-of-kin	11	1.3	341	54.5	69	53.5
Blue-collar job						
Never	496	59.4	239	38.2	36	27.9
Ever	339	40.6	316	50.5	74	57.4
Missing	0	0.0	71	11.3	19	14.7
Asbestos exposure						
Never	751	89.9	413	66.0	77	59.7
Ever	84	10.1	142	22.7	33	25.6
Missing	0	0.0	71	11.3	19	14.7
Diagnosis						
Definite			541	86.4	112	86.8
Probable			67	10.7	13	10.1
Possible			18	2.9	4	3.1
Morphology (ICD-O-3 codes)						
Unspecified (90503)			118	18.9	26	20.2
Sarcomatoid (90513)			29	4.6	4	3.1
Epithelioid (90523)			388	62.0	82	63.6
Biphasic (90533)			74	11.8	11	8.5
Not available			17	2.7	6	4.6

*Complete analysis is based on cases diagnosed in all years, any region of residence; restricted analysis is based on cases diagnosed in the same years (2002–2004 and 2012–2016) and in the same six regions as controls.
†From the job-exposure-matrix (SYN-JEM).
ICD-O-3, International Classification of Diseases for Oncology, Third Edition.

performed for this work by one of the authors (HK). We calculated individual lifetime cumulative exposure to asbestos (ff/mL-years) and other exposure metrics for all cases and controls.

The qualitative expert-based evaluation of both occupational and extraoccupational asbestos exposure was available for all cases and for MISEM/CARA controls only.

Statistical analysis

Among all cases and controls, we performed analyses for several indices of asbestos exposure according to SYN-JEM: ever versus never; duration of exposure (categorical and continuous in 10 years); time since first exposure (categorical); and cumulative exposure, either categorical (non-exposed and two categories based on the median calculated among exposed cases) or analysed as a continuous variable (untransformed and $\log_{10}$-transformed).

Among cases diagnosed in 2011–2021 and MISEM/CARA controls, we analysed expert-based assessment of occupational (definite, probable, possible) and non-occupational (para-occupational, environmental, home-related asbestos exposure).

We employed two approaches to analyse both exposure evaluations: (1) 'complete analyses', in order to fully exploit the sample size of the ReNaM dataset (at the cost of incomplete spatiotemporal case–control overlap); (2) 'restricted analyses', in which we included only cases diagnosed in the same years (2002–2004 for EAGLE controls and/or 2012–2016 for MISEM/CARA controls) and living in the same six regions of controls; this analysis is theoretically preferable because cases and controls came from approximately the same population over time. We quantified the bias in estimating ORs and OR excess (ie, OR – 1) in complete versus restricted analyses.

Given the rarity of disease, we combined men and women and fitted unconditional logistic regression models to calculate ORs adjusted for the following covariates: area of residence (North-West, North-East, Centre and South Italy, complete analyses) or region of residence (restricted analyses); gender; period (2000–2010 or 2002–2004 vs 2011–2021 or 2012–2016); and age (<50, 50–54, 55–59, 60–64, 65–69, 70–74 and 75+ years). We calculated OR and 90% CIs to avoid a reductive interpretation of CIs as significance tests.[31]

We present analyses stratified by gender in the supplementary materials. Additionally, for ever-exposure to asbestos, we calculated separately by gender the population attributable fraction (PAF) with the Miettinen's formula $PAF=P_{EC}(OR-1)/OR$ (where OR is adjusted and P_{EC} is the proportion of exposed cases) and 90% CI with a formula valid in both large strata and sparse data.[32]

Since socioeconomic status and education might have affected differential study participation of cases and controls,[33] we performed sensitivity analyses including only blue-collar workers (a proxy for those variables), defined on the basis of ISCO-68 codes.[34]

Finally, sensitivity analyses were performed for ever and cumulative exposure based on SYN-JEM by using separately each set of controls; in these analyses, we considered years 2012–2014 for MISEM controls and 2014–2016 for CARA controls.

In a subset of data in which both SYN-JEM and expert-based ReNaM evaluations of occupational exposure were available (all cases and MISEM/CARA controls), we assessed their agreement by calculating Cohen's kappa. One potential difficulty with kappa is that it depends on the marginal totals (which affect expected agreement and thus comparison of different kappas). Therefore, to compare agreement across case/control status and sex, we calculated the 'raked' kappa (a standardised form proposed to overcome this limitation), by taking uniform margins.[35] Differences between kappa and raked kappa indicate the extent of disagreement due to marginal heterogeneity. Statistical analyses were performed with Stata V.19 (StataCorp. 2025).

RESULTS

The ReNaM dataset contained 2121 PM records. We excluded 530 (25.0%) individuals not interviewed or with non-informative interview, leaving 1591 cases (965 men and 626 women) for complete analysis and 290 (161 men and 129 women) for restricted analysis. Controls were 3045 (2210 men and 835 women), 2116 from the EAGLE study, 718 from the MISEM study and 211 from the CARA study (online supplemental table 1). Most controls (2834/3045, 93.1%) were sampled from the general population (EAGLE and MISEM studies). In Lombardy during 2002–2004, there were 45 PM cases (22.7% of all cases in restricted analyses), while in the period 2012–2016 in the six regions, there were 245 cases (69.8% of all cases in restricted analyses) (online supplemental table 2).

Characteristics of cases and controls

Most controls were personally interviewed, while among 1591 cases, the proportion of interview administered to patients was 49.6% in men and 45.5% in women (table 1). Controls who ever worked in blue-collar job were 64.2% (men) and 40.6% (women), while for cases the proportions were 76.0% (men) and 50.5% (women). In men, asbestos exposure (ever) as estimated with the SYN-JEM was 34.5% in controls and 60.1% among cases; in women, the proportions were lower (10.1% for controls and 22.7% for cases). In both genders, most cases had a definite mesothelioma diagnosis and the most frequent histological type was epithelioid. Distribution of the variables above

Table 2 Occupational duration (years) and cumulative exposure (fibres/mL-years) to asbestos from the job-exposure matrix (SYN-JEM) among exposed controls and peritoneal mesothelioma cases included in complete and restricted analyses, Italy, 2000–2021.

Occupational asbestos exposure	N	Min	25th percentile	Median	Mean	75th percentile	Max	SD
Duration of exposure								
Controls	830	1	5	15	18.7	31	63	14.9
Cases, complete analysis	721	1	7	19	20.4	33	67	14.9
Cases, restricted analysis	127	1	7	18	21.0	34	63	15.0
Cumulative exposure								
Controls	830	<0.1	0.4	1.1	1.6	2.4	10.9	1.5
Cases, complete analysis	721	<0.1	0.4	1.4	2.3	3.1	20.0	2.9
Cases, restricted analysis	127	<0.1	0.6	1.7	2.5	3.4	16.8	2.9

*Complete analysis is based on cases diagnosed in all years, any region of residence; restricted analysis is based on cases diagnosed in the same years (2002–2004 and 2012–2016) and in the same six regions as controls.

among cases included in complete and restricted analyses was similar, except for a higher proportion of ever employed in blue-collar jobs among women in the restricted analysis (57.4%).

Peritoneal mesothelioma ORs based on asbestos exposure metrics derived from SYN-JEM

Among study subjects ever exposed to asbestos, duration of exposure and cumulative exposures were higher in cases than in controls (table 2). Most individuals had been exposed for 40 year or less; a small percentage (151, 2.7%, 147 men) had longer durations. Among women, duration of exposure was longer among controls, while cumulative exposure was higher in cases in both genders (online supplemental table 3).

In complete analyses with men and women combined (table 3), we found elevated ORs for each category of duration and cumulative exposure, with positive trends. OR did not increase 60 years after first exposure. We found positive associations for both quantitative duration and cumulative exposure: OR was 1.45 per fibre/mL-years and 1.55 per log10(fibres/mL-years). In restricted analyses, the ORs for categorical variables were slightly/moderately lower, but CIs were overlapping with those of complete analysis. The ORs for quantitative metrics were quite similar. For ever exposure to asbestos, the bias in complete analysis compared with restricted analysis was small (bias in OR: (3.66 – 3.35)/3.35×100=9.3%; bias in OR excess: (2.66 – 2.35)/2.35×100=13.2%). For $\log_{10}$-transformed cumulative exposure, the biases were smaller, respectively (1.55 – 1.52)/1.52×100=2.0% and (0.55 – 0.52)/0.52×100=5.8%.

In men, we found ORs of 3.35 for ever asbestos exposure, based on 60.1% cases exposed in complete analysis (PAF=0.42, CI 0.39 to 0.47) and 2.71 based on 58.4% cases exposed in restricted analysis (PAF=0.37, CI 0.25 to 0.47) (online supplemental table 4). Positive associations were found for all exposure variables. In women, ORs for ever exposure to asbestos

Table 3 Peritoneal mesothelioma odds ratios (OR) and 90% CIs for occupational asbestos exposure from the job-exposure matrix (SYN-JEM), both genders combined, in complete and restricted analyses, Italy, 2000–2021

Occupational asbestos exposure	Controls	Cases Complete analysis*			Cases Restricted analysis*		
	N (%)	N (%)	OR†	90% CI	N (%)	OR†	90% CI
Total 2000–2021	3045 (100)	1591 (100)			290 (100)		
Never exposed	2199 (72.2)	758 (47.6)	1.00	Reference	133 (45.9)	1.00	Reference
Categorical variables							
Ever exposed	846 (27.8)	722 (45.4)	3.66	3.21 to 4.18	127 (43.8)	3.35	2.57 to 4.37
Missing	0 (0.0)	111 (4.1)			30 (10.3)		
Duration							
<10 years	328 (10.8)	233 (14.6)	2.96	2.46 to 3.56	36 (12.4)	2.28	1.57 to 3.33
10–19 years	143 (4.7)	145 (9.1)	4.34	3.43 to 5.48	31 (10.7)	4.98	3.27 to 7.58
20–29 years	125 (4.1)	111 (7.0)	3.50	2.72 to 4.51	15 (5.2)	2.83	1.67 to 4.69
30+years	234 (7.7)	232 (14.6)	4.54	3.73 to 5.52	45 (15.5)	4.21	2.91 to 6.08
Missing	16 (0.5)	112 (7.0)			30 (10.3)		
P-trend			<0.001			<0.001	
P-trend (exposed only)			0.005			0.06	
Cumulative							
<0.5953 ff/mL-years	298 (9.8)	219 (13.8)	2.77	2.28 to 3.36	31 (10.7)	2.08	1.40 to 3.09
<2.1459 ff/mL-years	284 (9.3)	233 (14.6)	3.60	2.98 to 4.35	43 (14.8)	3.66	2.55 to 5.26
2.1459+ff/mL-years	248 (8.1)	269 (16.9)	4.94	4.11 to 5.94	53 (18.3)	4.67	3.29 to 6.63
Missing	16 (0.5)	112 (7.0)			30 (10.3)		
P-trend			<0.001			<0.001	
P-trend (exposed only)			<0.001			0.003	
TSFE							
<40 years	252 (8.3)	171 (10.8)	2.94	2.37 to 3.64	24 (8.3)	2.78	1.78 to 4.33
40–49 years	285 (9.4)	221 (13.9)	3.74	3.08 to 4.54	36 (12.4)	3.58	2.41 to 5.31
50–59 years	223 (7.3)	228 (14.3)	4.43	3.62 to 5.43	42 (14.5)	3.57	2.42 to 5.24
60+ years	75 (2.5)	101 (6.4)	3.94	2.90 to 5.35	25 (8.6)	3.67	2.23 to 6.05
Missing	11 (0.4)	112 (7.0)			30 (10.3)		
P-trend			<0.001			<0.001	
P-trend (exposed only)			0.02			0.74	
Quantitative variables							
Duration (10 years)	3029 (99.5)	1479 (93.0)	1.46	1.39 to 1.53	260 (89.7)	1.42	1.30 to 1.54
Cumulative	3029 (99.5)	1479 (93.0)	1.45	1.39 to 1.52	260 (89.7)	1.40	1.30 to 1.51
(fibres/mL-years)							
Cumulative	3029 (99.5)	1479 (93.0)	1.55	1.48 to 1.62	260 (89.7)	1.52	1.39 to 1.65
$\log_{10}$(fibres/mL-years)							

*Complete analysis is based on cases diagnosed in all years, any region of residence; restricted analysis is based on cases diagnosed in the same years (2002–2004 and 2012–2016) and in the same six regions as controls.
†Estimated with unconditional logistic regression models adjusted for area of residence (North-West, North-East, Centre and South Italy, complete analysis) or region of residence (restricted analysis), gender, period and age category.
TSFE, time since first exposure.

were 4.56 based on 22.7% cases exposed in complete analysis (PAF=0.18, CI 0.15 to 0.21) and 5.10 based on 25.6% cases exposed in restricted analysis (PAF=0.21, CI 0.13 to 0.27) (online supplemental table 5). Positive associations were found for all exposure variables.

In the complete analysis, the spline relationship between $\log_{10}$-transformed cumulative exposure and PM risk was fairly linearly increasing at low exposures (<0.75 ff/mL-years, approximately), flat between 0.75 and 1.5 ff/mL-years, and again linearly increasing and steeper at higher exposures (1.5+ ff/mL-years, approximately) (figure 1, left panel). In restricted analysis, the slopes at low and high exposures were lower but still clearly positive, with a slope change at 1.5 ff/mL-years, approximately (figure 1, right panel).

In analyses among blue-collar workers of both genders (1759 controls, 1049 cases in complete analyses and 197 cases in restricted analyses), ORs were in general lower than among all subjects but still showed strong associations between PM risk and all exposure metrics (online supplemental table 6).

In analyses with each set of controls separately, always positive exposure-disease associations were seen, although when using CARA control estimates were very imprecise (online supplemental table 7).

Peritoneal mesothelioma ORs based on ReNaM expert-based asbestos exposure assessment

In a subset of cases and controls of both genders, ORs for occupational exposure were 4.32 (53.9% of cases exposed) in complete analyses and 6.35 (57.1% of cases exposed) in restricted analyses (table 4). ORs were higher for definite occupational exposure, followed by probable and possible. We found evidence of a positive association for paraoccupational exposure in restricted analyses.

In men, we found ORs of 3.95 for ever asbestos exposure (66.9% cases exposed) in complete analyses 2011–2021 (PAF=0.50, CI 043 to 0.56) and 5.77 (71.2% cases exposed) in restricted analyses 2012–2016 (PAF=0.59, CI 0.48 to 0.67) (online supplemental table 8). In women, the ORs were 5.02 (33.6% cases exposed) in complete analysis (PAF=0.27, CI 0.21 to 0.32) and 9.37 (38.7% cases exposed) in restricted analysis (PAF=0.35, CI 0.25 to 0.43). ORs were higher for definite occupational exposure. We found evidence of an elevated OR for paraoccupational exposure in women.

Comparison of SYN-JEM and expert-based evaluation of occupational exposure

Considering subjects evaluated with both approaches (all cases 2000–2021 and MISEM/CARA controls), the overall Cohen's kappa was 0.48 (labelled 'fair to good' according to Fleiss or 'moderate' according to Landis and Koch) (online supplemental table 9). Kappa was higher for cases (0.48) than for controls (0.41); raked kappas were higher, but still differed between cases (0.52) and controls (0.45); the same pattern was observed by gender. Both statistics were higher in men; agreement was particularly low in female controls.

DISCUSSION

We found positive associations between PM and life-time asbestos exposure as estimated by the quantitative JEM. We found strong positive associations with duration of and cumulative exposure, either categorical or continuous. There was some indication that the relative risk flattened after 40–50 years since first exposure. OR estimates were similar in the complete analysis and in the theoretically preferable time-space restricted analyses. Moreover, in subanalyses of expert-based assessment, we

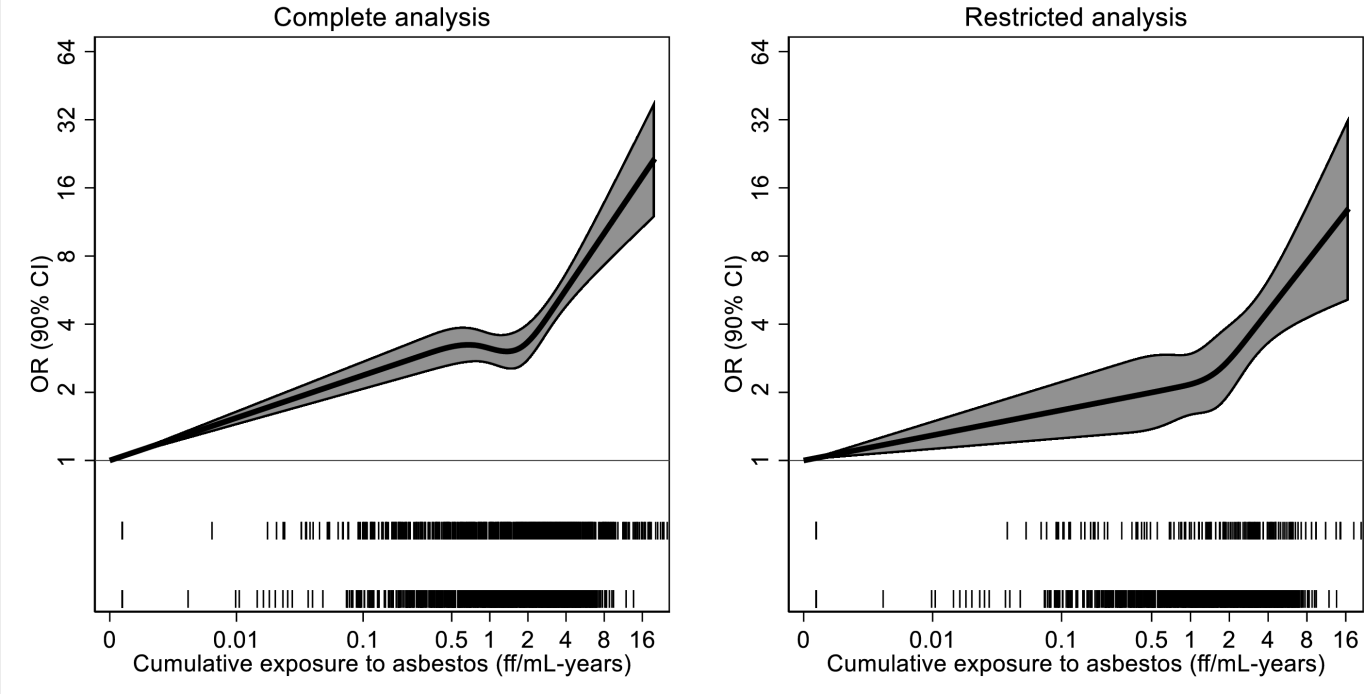

Figure 1 OR and 90% CIs for peritoneal mesothelioma and cumulative asbestos exposure (ff/mL-years, $\log_{10}$-transformed), both genders combined, estimated with restricted cubic splines (knots at 10th, 25th, 50th, 75th and 90th percentiles of cumulative exposure among exposed), Italy, 2000–2021. ORs adjusted for area of residence (North-West, North-East, Centre and South, complete analysis) or region of residence (restricted analysis), gender, period (2000–2010, 2011–2021) and age category. Vertical bars close to the horizontal axis indicate cases (upper bars) and controls (lower bars).

Table 4 Peritoneal mesothelioma OR and 90% CIs for occupational and extra-occupational asbestos exposure, both genders combined, based on expert evaluation of the National Mesothelioma Registry (ReNaM), Italy, 2011–2021

Asbestos exposure	Controls	Cases Complete analysis*			Cases Restricted analysis*		
	N (%)	N (%)	OR†	90% CI	N (%)	OR†	90% CI
Total 2011–2021	929 (100)	778 (100)			245 (100)		
Never exposed	481 (51.8)	274 (35.2)	1.00	Reference	80 (32.6)	1.00	Reference
Occupational	245 (26.4)	419 (53.9)	4.32	3.50 to 5.34	140 (57.1)	6.35	4.58 to 8.81
Extra-occupational	203 (21.8)	85 (10.9)	0.83	0.64 to 1.09	25 (10.2)	1.31	0.83 to 2.07
Occupational							
Definite	116 (12.5)	277 (35.6)	6.71	5.21 to 8.64	99 (40.4)	10.9	7.43 to 16.0
Probable	25 (2.7)	38 (4.9)	3.79	2.33 to 6.16	9 (3.7)	3.73	1.70 to 8.19
Possible	104 (11.2)	104 (13.4)	2.18	1.64 to 2.91	32 (13.1)	3.08	1.98 to 4.79
Extra-occupational							
Para-occupational	88 (9.5)	45 (5.8)	1.02	0.72 to 1.46	14 (5.7)	1.80	1.02 to 3.18
Environmental	85 (9.1)	26 (3.3)	0.63	0.42 to 0.95	6 (2.5)	0.79	0.36 to 1.72
Home-related	30 (3.2)	14 (1.8)	0.84	0.46 to 1.52	5 (2.0)	1.65	0.68 to 3.98

*Complete analysis is based on all cases 2011–2021 and any region of residence; restricted analysis is based on cases diagnosed in the same years (2012–2016) and in the same six regions as controls.
†Estimated with unconditional logistic regression models adjusted for area of residence (North-West, North-East, Centre and South Italy, complete analysis) or region of residence (restricted analysis), gender and age category.

found a markedly increased risk of PM in subjects occupationally exposed and for paraoccupational exposure in family members (mostly women) of asbestos exposed workers.

Strengths and limitations

The present study has several strengths. First, it is the first case–control study on PM with a large sample size covering a long period and using general population controls; this allowed us to evaluate PM risk associated with asbestos exposure in all industries and occupations, not only in specific highly exposed industrial cohorts. Second, it was based on a virtually complete series of cases with good-quality diagnosis. Third, this study was highly cost-efficient: we exploited datasets already available and used a crosswalk to obtain standardised international codes.

The main limitation of this study is that population samples (controls) had been recruited over short time periods, 2002–2004 (EAGLE) and 2012–2016 (MISEM and CARA) and in only six regions. As to incomplete time coverage, we have to consider that our focus was on lifetime asbestos exposure: since for most workers exposure ceased in 1992 (due to the asbestos ban), we expect exposure remained rather constant over the study period.[25] As to incomplete geographical coverage, we note that the regions in which controls were sampled cover half of the Italian population and some of the most industrialised areas. A similar approach has been shown to be valid in a nationwide case–control study in France.[36] We showed in three previous studies on PM (in Lombardy), on mesothelioma of tunica vaginalis testis and pericardium, and on pleural mesothelioma in construction, that this study design, although imperfect, is robust to study-base misspecification.[17 23 24] Results in this study were basically confirmed in restricted analyses and the ORs of complete analyses exploiting all 1591 cases were only slightly biased compared with the theoretically preferable time-space restricted analysis on a reduced sample size (290 cases). Results from sensitivity analyses using each set of controls separately were consistent with results of the main analyses.

Another limitation is that study participation might have differed between cases and controls. However, the positive associations, although attenuated, were confirmed in analyses that included only blue-collar workers.

Comparison with published research

Many occupational cohort studies have shown excesses of PM among asbestos-exposed workers.[8 12] Moreover, strong correlation has been found between proportions of PM and pleural mesothelioma deaths, particularly among highly exposed subjects (insulators, asbestos-cement workers and asbestosis patients).[8] Recent cohort studies showed continuously increasing relative risks by latency for PM, while an attenuation of the increase was found for pleural mesothelioma.[7 10 11]

Possibly due to its rarity, PM has been infrequently investigated in general populations. We are aware of four population-based studies specifically focused on PM and performed outside Italy, all showing positive associations (we reviewed them in detail in our previous study on PM in Lombardy).[17] Three were small studies, the first which examined a case series in London,[15] the second a small hospital-based study in the USA,[16] and the third a registry-based study in the USA.[14] The fourth was a large study based on deceased cases and controls in 24 US states.[13] In Italy, we previously found clear positive associations in a study based on incident PM cases (2000–2015) from the Lombardy Mesothelioma Registry and EAGLE/MISEM population controls resident in Lombardy.[17]

Comparison of SYN-JEM and expert-based evaluation of occupational exposure

The SYN-JEM has two main advantages. First, job histories are translated into specific exposure histories in a systematic and unbiased way (ie, the same tool is used for all subjects, cases and controls). Second, it is very efficient and can thus be used with large datasets. These characteristics make SYN-JEM particularly suited for epidemiological studies.[37 38] Non-differential coding errors and the differential use of crosswalk for cases' job histories might have led to attenuation of the ORs. Applying a JEM results in Berkson-type error, because the same average exposure estimate is assigned to all workers with the same job code in a given year, irrespective of the true individual value. However, Berkson-type error results in no or little bias of risk estimates but comes with less precision, that in a large study as ours is not a problem.[39 40]

Expert-based evaluation is based on detailed information beyond industry and job, including specific tasks (type, estimated intensity and frequency) and indirect exposure (from activities carried out by other workers in the same work environment): for this reason, it is instrumental for individual assessment of cases and the associated medicolegal implications, most importantly compensation of occupationally exposed individuals.

Although in this study, expert evaluation was based on interviews collected using the same ReNaM questionnaire for cases and controls, this was not made in a blinded way. OR estimates for occupational exposure when using expert-based estimates were higher than when exposure assignment was made using the SYN-JEM. Moreover, the agreement between SYN-JEM and expert-based evaluations was higher in cases than in controls. Taken together, these results could indicate some degree of differential misclassification when using expert-based evaluation, that is, a higher proportion of cases than controls were classified as occupationally exposed, due to a combination of recall, reporting, interviewer or assessor biases.

CONCLUSIONS

In this first nationwide population-based case–control study on PM, we found clear associations between PM risk and several quantitative indices of occupational asbestos exposure, in industrial settings and of short duration not usually evaluated in industrial cohort studies of highly exposed workers. Moreover, we found higher elevated risks when using expert-based assessment. The present results showed convincing associations for PM and indicate that also subjects with PM should be eligible for compensation independently of the sectors and occupations in which they had been exposed. Epidemiological surveillance and epidemiological studies are crucial for identifying all sources of asbestos exposure, enhancing the awareness of mesothelioma aetiology and supporting the prevention policies and the effectiveness of insurance systems.

Author affiliations
[1]Occupational Health Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[2]COR Piemonte, Cancer Epidemiology Unit, University of Turin, Turin, Italy
[3]COR Puglia, Section of Occupational Medicine "B. Ramazzini", Department of Interdisciplinary Medicine, University of Bari Aldo Moro, Bari, Italy
[4]COR Toscana, Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy
[5]COR Veneto, Azienda Zero, Padua, Italy
[6]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[7]Department of Environmental and Prevention Sciences, University of Ferrara, Ferrara, Italy
[8]Division of Cancer Epidemiology and Genetics, National Cancer Institute Division of Cancer Epidemiology and Genetics, Bethesda, Maryland, USA
[9]COR Valle d'Aosta, Local Health Authority of Valle d'Aosta, Aosta, Italy
[10]COR Province of Trento, Provincial Unit of Health, Hygiene and Occupational Medicine, Trento, Italy
[11]COR Province of Bolzano, Alto Adige Health Local Unit, Bolzano, Italy
[12]COR Friuli-Venezia Giulia, University of Trieste - Trieste General Hospitals, Clinical Unit of Occupational Medicine, Trieste, Italy
[13]Dipartimento di Medicina Interna e Specialità Mediche, Università degli Studi di Genova, Genoa, Italy
[14]UO Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[15]COR Emilia-Romagna, AUSL-IRCCS Reggio Emilia, Reggio Emilia, Italy
[16]COR Marche, University of Camerino, School of Medicinal and Health Products Sciences, Camerino, Italy
[17]COR Umbria, Servizio Prevenzione, Sanità Veterinaria e Sicurezza Alimentare - Regione Umbria, Perugia, Italy
[18]COR Lazio, Department of Epidemiology, Lazio Regional Health Service, ASL Roma 1, Rome, Italy
[19]COR Abruzzo, Abruzzo Regional Health Agency (ASR), Pescara, Italy
[20]COR Molise, Regione Molise Cancer Registry, Campobasso, Italy
[21]COR Campania, Department of Experimental Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy
[22]COR Basilicata, IRCCS CROB, Rionero in Vulture, Italy
[23]COR Calabria, Public Health Unit, Crotone, Italy
[24]COR Sicilia, Cancer Registry ASP Ragusa and Sicily Regional Epidemiological Observatory, Ragusa, Italy
[25]COR Sardegna, Regional Epidemiological Center, Cagliari, Italy
[26]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands
[27]Occupational and Environmental Medicine, Epidemiology and Hygiene Department, Italian Workers' Compensation Authority (INAIL), Rome, Italy

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ORCID iDs
Dario Consonni https://orcid.org/0000-0002-8935-3843
Luigi Vimercati https://orcid.org/0000-0002-4072-2871
Stefania Curti https://orcid.org/0000-0003-4343-8873
Stefano Mattioli https://orcid.org/0000-0002-9639-7430
Rocco Galasso https://orcid.org/0000-0003-4831-6437
Susan Peters https://orcid.org/0000-0001-5662-1971
Hans Kromhout https://orcid.org/0000-0002-4233-1890
Alessandra Binazzi https://orcid.org/0000-0002-0435-600X
Alessandro Marinaccio https://orcid.org/0000-0001-9068-2137
Carolina Mensi https://orcid.org/0000-0002-9075-3684

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