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The proportion of mesothelioma attributable to living in industrial areas in Italy can be ranked on a priori evidence on asbestos risk in each industrial sector. The health impact of asbestos exposure concerns not only industrial sites with direct use of asbestos in the past, but also a wide range of working and living environments with asbestos "in place".

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Key terms: asbestos; attributable risk; contaminated site industry; environmental exposure; epidemiological monitoring; Italy; mesothelioma; occupational exposure

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Proportion of mesothelioma attributable to living in industrially contaminated areas in Italy

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Objectives The aim of this study was to estimate the attributable proportion (AP) of mesothelioma resulting from living in or close to major Italian industrially contaminated areas.

Methods For populations living close to 39 sites of "national priority for remediation", incident mesothelioma cases were extracted from the Italian National Mesothelioma Registry (ReNaM) in the period 2000−2011. Each site was classified in one of seven asbestos risk groups (RG) on the basis of the type of industrial plants. RG were ranked by the *a priori* evidence on asbestos risk. The AP for each RG was calculated as the meta-analytic estimate of AP of sites of the same group by gender and age class (0–64, 65–74, ≥75 years). The sex ratio (men/women) was computed for each RG.

Results Among men, the AP by age class had the same gradient in each RG, with the highest values in the age class 0–64 years and the lowest in the ≥75 class; in the age class 0–64 years, the AP was positive in each RG, >90% in the presence of asbestos cement factories and harbors with shipyards. Among women, the overall AP decreased by RG, with negative values in the last two ranked RG; the AP by age class was variable without a definite gradient. The sex ratio was close to one only in the RG "only asbestos-cement factories"; the highest value (9.6) was observed in the age class 0–64 years in the RG "harbors with shipyard".

Conclusions The integration of a geographic- and case-based approach provides valuable insights into occupational and environmental determinants of mesothelioma risk in industrially contaminated sites.

Key terms asbestos; attributable risk; contaminated site industry; environmental exposure; epidemiological monitoring; occupational exposure.

Current and past asbestos use worldwide and its impact on human health (non-malignant and malignant diseases) − even after decades from the first occupational or environmental exposure − still make studies on the matter useful and relevant. The aim remains to discover unknown sources of exposure and plan, if needed, epidemiologic or sanitary surveillance programmes or clean-up activities. National disease registries are extremely useful to conduct scientific studies on this subject as they provide researchers with plenty of data at the individual level, which make it possible to evaluate, inter alia, whether the exposure has been occupational or environmental (non-occupational).

A meta-analysis explored the relation between non-occupational exposure to asbestos and pleural malignant mesothelioma (MM) risk: the authors confirmed the increased risk of MM due to environmental exposure and found a different level of risk, dependent on fiber type (1). Non-occupational exposure includes domestic/household and residential/neighborhood exposure. The former is due to installation, degradation, removal or repair of asbestos-containing products, exposure to fibers taken home by workers, or use of asbestos-containing tools and products at home. The latter encompasses the presence of industrial emissions, natural presence of fibers, and damaged building materials containing asbestos.

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In Sweden, an asbestos ban took place in 1982, and the total number of new cases of pleural MM has been stable since 1995 in both genders. Järvholm & Burdorf used birth cohorts to study the efficacy of the ban (2). Identifying cases through the Swedish Cancer Registry, they measured the effect by comparing pleural MM incidence in birth cohorts which began working before and after the decrease in the use of asbestos. The authors found that men and women born 1955–1979 had a decreased risk of MM compared to men and women born 1940–1949 [risk ratio (RR) 0.16, 95% confidence interval (CI) 0.11–0.25; and RR 0.47, 95% CI 0.23–0.97 respectively], highlighting the efficacy of the ban.

Using a national registry, MM incidence during 2009–2013 in Germany was explored. A total of 7547 malignant mesotheliomas were reported, mainly pleural (90%) (3). Regional clusters were present in former shipyards and steel industry areas. The authors demonstrated decreasing incidence trends 20 years after the asbestos ban.

In Italy, more than 50 contaminated sites have been defined to be of national interest for reclamation activities (NPCS). Since 2006, the National Health Institute has been coordinating the SENTIERI Project, an epidemiological study of residents in NPCS looking at health outcomes and publishing reports on local mortality, hospital discharges, and cancer incidence (4–6). Because of the large use of asbestos until the national ban in 1992 (3 748 550 tons of raw asbestos produced up to 1992) (7), the 2016 report focused on mesothelioma incidence (8) and was conducted in cooperation with the National Register of Malignant Mesotheliomas (ReNaM). The registry ensures high-quality information on exposure to asbestos for each case identified by regional operating centre, which collect occupational and residential histories as well as lifestyles habits.

The present study estimated the attributable proportion (AP) of mesothelioma resulting from living in or close to major Italian industrially contaminated areas.

Methods

The observed MM cases were extracted from the ReNaM archives in the period of diagnosis 2000–2011, as described in a previous publication (9).

The proportion of MM attributable to industrially contaminated sites was assessed for the populations residing in 39 NPCS (as identified by national decrees highlighting contamination sources and the affected municipalities targeted for reclamation activities). In the NPCS, numerous and different sources of contamination, possibly leading to human exposures, are present; they include chemical industry, petrochemicals and refineries, steel plants, power plants, mines or quarries, harbor areas, asbestos or other mineral fibers, landfills and incinerators.

In the present study, the presence of asbestos risk in each NPCS was defined combining both the information on sources of contamination available in national and local environmental remediation programs and the documentation on studies of asbestos exposure available for each area in the SENTIERI reports (8). Each NPCS was then classified in one of seven risk groups (RG) on the basis of the type of contamination sources in its area, graded from the most to the least risky for asbestos exposure. This grading was completed based on the a priori knowledge of asbestos risk available in the scientific literature and mainly on the information about occupational sectors available in the ReNaM epidemiological surveillance on MM incident cases (7). Finally, the NPCS were classified and ranked considering the presence of the following polluting sources: RG1: only asbestos cement factories; RG2: including asbestos cement factories; RG3: mines of asbestos or other mineral fibers; RG4: harbors with shipyards; RG5: illegal dumping sites including presence of asbestos-containing waste; RG6: petrochemicals/refineries or steel plants; and RG7: chemical plants or landfills without explicit mention of asbestos or harbors without shipyard. RG2 included NPCS with more than one source of contamination including an asbestos cement factory active prior to the asbestos ban in 1992. In the presence of more than one contamination source, usually the potential exposure from each source affects only a portion of the total population residing in the NPCS. In case an NPCS had more than one source of asbestos exposure, it was ranked considering the highest a priori risky source. The RG "mines of asbestos or other mineral fibers" included two NPCS, one with a quarry of chrysotile asbestos, the other with a quarry of material used in construction industry and contaminated by fluoro-edenite, an asbestiform fiber (10). Since the two NPCS had very different contamination sources, a combined meta-analytic estimate was not computed.

For each NPCS, observed and expected cases were computed by gender. The expected cases were estimated on the basis of gender- and age-specific rates of MM in four geographical macro areas (northeast, northwest, centre, south islands). These macro areas were taken as reference, since the pattern of mesothelioma risk in Italy in not homogeneous, with the highest risk in the north and lowest in the south, reflecting the different industrial development across Italy (11). Expected cases in the NPCS were computed having as reference the mesothelioma figures of the geographical macro area they were included in so that the expected figures reflected the specific background of mesothelioma risk (9).

For each RG, the AP, intended as the proportion of cases attributable to the specific context of exposures of RG versus the general context of the geographical macro area of reference, was calculated by gender and age class (0–64, 65–74, ≥75 years). The sex ratio (cases in men/cases in women) of RG by age class was computed as an average of sex ratio of NPCS belonging to the same RG, weighted for the number of cases observed in each NPCS. Exposure to asbestos of cases by RG was assessed using information available in ReNaM (7). Following ReNaM procedure, information on asbestos exposure were obtained for each case through detailed interview of patients or their next of kin and classified in the following categories according to the ReNaM classification: (i) occupational exposure; (ii) familial exposure (when patients had lived with a cohabitant who had been occupationally exposed); (iii) environmental exposure (for a MM subject without any work-related exposure residing near industries that used asbestos as raw material or asbestos-containing material or used to be in places polluted by asbestos); (iv) other non-occupational exposure (indirect use of asbestos containing products at home or during leisure time); (v) unlikely or unknown exposure (for subjects with good quality information available that excluded any asbestos exposure or with incomplete information available that did not allow one to assign an exposure category).

The AP were computed following a number of steps. First, the ratio between observed and expected cases [standardized incidence ratio (SIR)] was calculated for each NPCS. The meta-analytic SIR estimates of NPCS belonging to the same RG were then computed with their 90% CI using the STATA 10 software and applying the random-effects model and estimating heterogeneity through the statistics I^2. The meta-analytic estimates of the SIR and their CI were finally converted in meta-analytic estimates of AP considering that the AP can be expressed with the following algebra: (1-1/SIR) × 100.

Results

The number of MM cases in the 39 NPCS in the study period was 2683 (1998 men and 685 women). The estimates of AP in each RG by gender and age class and the sex ratio are shown in table 1. The overall AP in men was positive in all RG with the exception of "chemical plants or landfills without explicit mention of asbestos or harbors without shipyard" (the lowest ranked RG). In men, the AP by age class had the same gradient in each RG, with the highest values in the age class 0–64 years and the lowest in ≥75 years. In the age class 0–64, the AP was positive in each RG, and it was nearly 90% in RG1 ("only asbestos cement factories"), RG2 ("including asbestos cement factories"), and RG4 ("harbors with shipyard"). In women, the pattern was different: the overall AP was positive and progressively decreased in RG1−5, while it was negative in RG6 and 7. Furthermore, among women, the AP by age class was variable without a definite gradient.

The men/women ratio of the MM cases was close to 1 only in RG1 ("only asbestos cement factories") while in most of the other RG and age classes it ranged from 3 to 6. The highest value (9.6) was found for the 0–64 age class in RG4 ("harbors with shipyard").

Table 2 shows results on exposure to asbestos by RG, using data from interviews of MM cases. The percentage of interviewed cases was variable by RG, ranging from 95% in RG4 ("harbors with shipyards") to 46% in the RG5 ("illegal landfills with asbestos"). In men, the occupational exposure was prevalent in all RG. Environmental exposures were associated with >15% of the cases only in RG1 ("asbestos cement only"). In women, familiar and environmental exposures had a relevant role: in the RG1 ("asbestos cement only") and RG4 ("harbors with shipyard"), familiar exposures were higher than the occupational ones; environmental exposures were higher than occupational ones in RG1 ("asbestos cement only") and RG2 ("including asbestos cement factories") where asbestos cement was the source of exposure. Exposures classified as unlikely or unknown were prevalent in women in RG4−7.

Discussion

Our findings confirm the relevance of asbestos-related diseases in NPCS and allow for the categorization of industrial contaminated areas, according to different level of asbestos exposure risk. The classification of NPCS in seven asbestos risk groups, based on the a priori evaluation, has been confirmed by the epidemiological analyses. Asbestos cement production appears as the industrial sector with the most important level of exposure in Italian historical context. For the sites of Casale Monferrato (Piedmont, northwestern Italy) and Broni (Lombardy, northwestern Italy), previous papers (12, 13) have demonstrated the extent of occupational risk for mesothelioma and the level of environmental contamination to asbestos.

As a possible source of bias in the present study, it is necessary to consider that the modalities of identifying asbestos exposure were not fully uniform in the ReNaM network, as previously discussed (7). The percentage of interviewed subjects varied between 39.3−95.2% according to risk group and gender. Familial and environmental modalities of exposure were prevalent for MM in women. Recently the proportion of MM cases due to non-occupational circumstances of exposure was

Table 1. Mesothelioma cases in Italian national priority contaminated sites (NPCS) by asbestos risk group, meta attributable proportion (AP) by age class and gender, and sex ratio (men/women) by age class. Incident cases in the period 2000–2011. [SIR=standardized incidence ratio; CI=confidence interval.]

Asbestos risk group (number of NPCS) [a]	Age (years)	Men				Women				Sex ratio (weighted average) [b]
		Cases	Meta SIR	Meta AP	Meta AP 90% CI	Cases	Meta SIR	Meta AP	Meta AP 90% CI	
Asbestos cement only (2)										
	0–64	144	65.17	98	98–99	81	23.38	96	90–98	1.8
	65–74	121	18.21	95	92–96	72	10.82	91	88–92	1.7
	≥75	104	10.07	90	78–94	138	13.31	92	91–93	0.8
	all	369	10.6	91	87–93	291	16.07	94	91–95	1.3
Including asbestos cement (5)										
	0–64	91	12.61	92	90–93	25	2.68	63	40–73	3.8
	65–74	92	5.58	82	76–86	22	2.73	63	-16–78	5.1
	≥75	45	2.14	53	31–65	17	2.06	52	5–68	3.1
	all	228	2.8	64	53–71	64	2.42	59	34–70	4.0
Harbors with shipyards (6)										
	0–64	177	12.57	92	89–94	34	1.22	18	-43–43	9.6
	65–74	269	6.6	85	78–88	52	1.67	40	19–53	6.2
	≥75	304	4.65	78	69–84	73	1.73	43	10–58	4.8
	all	750	3.4	71	60–77	159	1.69	41	27–57	5.0
Illegal landfills with asbestos (2)										
	0–64	124	9.46	89	76–93	32	1.53	35	5–50	4.2
	65–74	103	4.21	76	22–86	12	0.82	-20	-376–31	8.6
	≥75	60	2.24	55	-23–73	12	1.01	1	-122–37	5.1
	all	287	2.43	59	-14–75	56	1.21	17	-18–36	5.3
Petrochemicals and/or refineries and/or steel plants (7)										
	0–64	28	3.06	67	45–77	9	0.79	-25	-355–27	4.3
	65–74	62	2.74	64	47–72	16	0.87	-15	-150–25	5.5
	≥75	42	1.2	17	-61–44	12	0.55	-82	-376–-11	6.2
	all	132	1.43	30	0–46	37	0.70	-42	-104–-9	5.4
Chemical plants and/or landfills without asbestos and/or harbors without shipyards (15)										
	0–64	64	3.89	74	62–80	15	0.86	-16	-163–26	4.9
	65–74	76	1.42	30	-6–48	22	0.75	-33	-150–8	4.6
	≥75	53	0.73	-37	-100–-5	26	0.58	-72	-203–-19	3.1
	all	193	0.87	-15	-59–6	63	0.61	-64	-116–-32	4.5

[a] The risk group number 3 'mines of asbestos or other mineral fibers' included two NPCSs, one with a quarry of chrysotile asbestos, the other with a quarry of material used in construction industry and contaminated by fluoro-edenite, an asbestiform fiber. Since the two NPCSs have very different contamination sources, a combined meta-analytic estimate was not computed.

[b] Sex-ratio of NPCS belonging to the same RG weighted for the number of cases observed in each NPCS.

estimated around 10% of cases in Italy (14).

The meta-analytic estimate of AP enabled us to estimate a single indicator for groups of NPCS homogeneous for the main source of asbestos exposure, but heterogeneous for other characteristics: (i) some NPCS had a variety of exposure sources; (ii) most NPCS included different communities that could have different exposures, depending on the type of asbestos exposure and intensity of cumulative exposure, that were mainly related to the type of polluting sources, industrial plants, and the duration of their activity; and (iii) the proportion of individuals exposed to asbestos could be very different among the NPCS. These factors influenced the meta-analytic AP estimates that had a high intra-group heterogeneity. In men, the I_2 statistics was always >70%, while in women it was very high in RG1 ("asbestos-cement only") and RG2 ("including asbestos-cement factories").

Our findings confirmed the evidence of a specific pattern of exposure for MM female cases, with an unclear age gradient in attributable risk and a consistent percentage of female cases without defined asbestos exposure modalities. The great variety of job and domestic circumstances potentially involved in asbestos exposure induced real difficulties in identifying the cause of the diseases, the time of first exposure and the latency period, and suggested the need to implement the tools to investigate the modalities of exposure in a gender perspective. Epidemiological population-based analyses in France (15), South Korea (16), Italy (17), and recently Denmark (18) have demonstrated and discussed the relevance of the role of non-occupational (environmental, but also familial) exposure to asbestos MM in women. The distribution of gender ratio among RG is strongly related to the characteristics of asbestos exposure among sites and the ratio is significantly lower where RG is typified by activities with a relevant environmental contamination as asbestos cement factories in the Italian experience.

Table 2a. Proportions of interviewed mesothelioma cases (men) by asbestos risk group and asbestos exposure for each asbestos risk group, Italian national priority contaminated sites (NPCS).

Asbestos risk group [a]	Cases	Interviews (%)	Asbestos exposure				
			Occupation (%)	Familial (%)	Environment (%)	Other (%) [b]	Unlikely/ Unknown (%)
Asbestos-cement only	392	324 (82.7)	73.5	7.4	16.4	1.9	0.9
Including asbestos-cement	230	158 (68.7)	84.2		7.6		8.2
Harbors with shipyards	750	714 (95.2)	92.9	0.4	0.8	0.1	5.7
Illegal landfills with asbestos	287	133 (46.3)	88.0	0.8	3.8	2.3	5.3
Petrochemicals and/or refineries and/or steel plants	132	123 (93.2)	90.2		0.8	1.6	7.3
Chemical plants and/or landfills without asbestos and/or harbors without shipyards	193	171 (88.6)	86.0	0.6	1.2		12.3

[a] The risk group "mines of asbestos or other mineral fibers" included two NPCS, one with a quarry of chrysotile asbestos, the other with a quarry of material used in construction industry and contaminated by fluoro-edenite, an asbestiform fiber. Since the two NPCS have very different contamination sources, combined data are not presented.

[b] Proportion of interviewed cases with leisure -time activity exposure.

Table 2b. Proportions of interviewed mesothelioma cases (women) by asbestos risk group and asbestos exposure for each asbestos risk group, Italian national priority contaminated sites (NPCS).

Asbestos risk group [a]	Cases	Interviews (%)	Asbestos exposure				
			Occupation (%)	Familial (%)	Environment (%)	Other (%) [b]	Unlikely/ Unknown (%)
Asbestos-cement only	291	219 (75.3)	20.5	35.2	40.6	1.8	1.8
Including asbestos-cement	65	46 (70.8)	15.2	8.7	45.7		30.4
Harbors with shipyards	160	140 (87.5)	19.3	34.3	8.6	1.4	36.4
Illegal landfills with asbestos	56	22 (39.3)	22.7	22.7	13.6		40.9
Petrochemicals and/or refineries and/or steel plants	37	24 (64.9)	25.0	4.2	8.3	3.1	68.7
Chemical plants and/or landfills without asbestos and/or harbors without shipyards	63	47 (74.6)	27.7	4.3	10.6	2.0	57.1

[a] The risk group "mines of asbestos or other mineral fibers" included two NPCS, one with a quarry of chrysotile asbestos, the other with a quarry of material used in construction industry and contaminated by fluoro-edenite, an asbestiform fiber. Since the two NPCS have very different contamination sources, combined data are not presented.

[b] Proportion of interviewed cases with leisure -time activity exposure.

Asbestos pollution is a real concern in industrially contaminated sites, due to both the occupational exposure and environmental contamination. The non-occupational sources of asbestos exposure are particularly relevant for occurrence of asbestos-related diseases in women. The health impact of asbestos exposure concerns not only industrial sites with direct use of asbestos as raw material in the past, but also a wide range of activities and working and living environments characterized by the "in place" occurrence of this material.

The role of epidemiological surveillance of MM cases, by the means of an incident cases register performing individual analysis of asbestos exposure, is a useful tool to identify the source of contamination, produce epidemiological evidence, and support prevention policies and insurance systems effectiveness in countries where asbestos has been banned and where it is still used.

Conflict of interest

The authors declare no conflict of interest.

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