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Original articles and reviews

Italian pool of asbestos workers cohorts: asbestos related mortality by industrial sector and cumulative exposure

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Abstract
Objective. Italy has been a large user of asbestos and asbestos containing materials until the 1992 ban. We present a pooled cohort study on long-term mortality in exposed workers.
Methods. Pool of 43 Italian asbestos cohorts (asbestos cement, rolling stock, shipbuilding, glasswork, harbors, insulation and other industries). SMRs were computed by industrial sector for the 1970-2010 period, for the major causes, using reference rates by age, sex, region and calendar period.
Results. The study included 51 801 subjects (5741 women): 55.9% alive, 42.6% died (cause known for 95%) and 1.5% lost to follow-up. Asbestos exposure was estimated at the plant and period levels. Asbestos related mortality was significantly increased. All industrial sectors showed increased mortality from pleural malignancies, and most also

Key words
- asbestos
- glassworks
- rolling stock
- shipyards
- mesothelioma

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from peritoneal and lung cancer and asbestosis, with exposure related trend. Increased mortality was also observed for ovarian cancer and for bladder cancer.

Discussion. The study confirmed the increased risk for cancer of the lung, ovary, pleura and peritoneum but not of the larynx and the digestive tract. A large increase in mortality from asbestosis was observed.

INTRODUCTION

Italy has been an important producer and user of asbestos and asbestos containing products. The consumption of asbestos was estimated nationwide in 132 358 tons in 1970, gradually increasing to the 1980 peak of 180 528 tons, and declining afterwards [1]. The largest use of asbestos was in asbestos-cement production, followed by fire proofing and thermal insulation in shipbuilding and railway carriages. EU Directives on permissible occupational exposure levels and on the limitation of asbestos use in some applications and products had been gradually enforced (Council Directive 83/477/EEC of 19 September 1983). The use of asbestos definitely ceased following a law-enforced ban on production, import, export, and trading (Law 257/1992) that become fully effective in 1994. However, asbestos in place is only being gradually removed [2] and over 70 000 exposed were estimated as for the period 2000-2003, in the construction and in the asbestos removal sectors [3, 4].

The burden of asbestos related deaths include malignant mesothelioma, cancers of the lung, the larynx and of the ovary, and asbestosis. Limited evidence of carcinogenicity also exist for pharynx, stomach and colon and rectum neoplasms [5].

Current production worldwide is reduced to about 1.1 million tons, and is limited to chrysotile [6]. Its use is concentrated in emerging economy countries, where information on work conditions, number of exposed workers and frequency of asbestos related diseases are limited [7, 8].

The present study is part of a large project aiming at the evaluation of the occurrence of asbestos related deaths in the main industrial sectors interested by the use of asbestos in Italy. The study has multiple aims: to evaluate the burden of asbestos related diseases, to assess the occurrence of cancers with limited evidence of association with asbestos, and to investigate the role of time-related factors in disease occurrence. The study design consisted in the updating and pooling a large number of Italian cohort studies. It started as part of the "Asbestos Project" coordinated by the Italian National Institute of Health (ISS) [9], as prompted by the conclusions of the 2nd Governmental Asbestos Conference [10] and was later extended as a part of the Asbestos Special Program of the Italian Workers' Compensation Authority (INAIL).

A first report described the pooled cohort, providing overall results on cause-specific mortality and mortality time trends using external references [11]. A second report described the methodology and results of the estimation of asbestos exposure in the cohorts under study and presented results on exposure levels and mortality by cumulative exposure in the asbestos-cement sector [12]. The present study investigated systematically mortality by industrial sector and cumulative exposure.

MATERIAL AND METHODS

The pooled cohort study aimed at the inclusion of all Italian cohorts of workers in asbestos using factories. The candidate list was formed after a literature review also including unpublished reports and the personal experience of participants. Eligible cohorts were identified, principal investigators invited, and when accepted they were invited to share the protocol and to submit it to the ethical committee of competence. Cohort data were then updated and pooled. Participation was restricted to cohorts with at least one follow-up investigation completed in the past and, once updated, an observation period longer than 40 years. The final pool included 43 cohorts, including a cohort of women with domestic exposure and a cohort of Italian crocidolite miners in Australia. *Supplementary Table 1* (available online) lists the cohorts with information on location, use of asbestos, number of workers, and references to previous studies.

The study was submitted to the University of Eastern Piedmont Ethical Review Board (Authorization CE 112/13, July 12th, 2013) and to the corresponding Boards of participating institutions. Only anonymized data were pooled, nominal data remaining at the local study level.

The initial size included 54 436 subjects but quality control led to the exclusion of 2453 records (4.5%), from all industrial sectors. Causes were: conflicting dates, incomplete working periods, hiring or retirement age out of normal range (n = 737); first employment after the asbestos ban, (fixed on 1.1.1993 – midterm between law approval and enforcement) (n = 594). Two cohorts, from the asbestos cement factories of Eternit-Bagnoli and of Fibronit-Broni, were limited to the workers hired after 1.1.1950 (n = 1122) to ensure completeness of follow-up.

Workers employed in different cohorts were identified, for a total of 178 workers of which 4 with 3 employment records each. Their work histories were merged in the pooled analyses, for a total of 51 801 individual records, and were left separate in the analyses of individual cohorts. The few (n. 47) workers employed in different sectors were excluded from the sector-specific analyses.

For each factory and time period, the study investigators had provided all available information, in particular estimates of the proportion of workers directly and indirectly exposed to asbestos, the percentage of working time in tasks with asbestos exposure and the minimum and maximum levels of asbestos concentration for direct and indirect exposures. Two expert industrial hygienists

(AA and SS) collected and evaluated for each plant and year of activity the information available on the work process, the plant layout, the use of asbestos in total and by asbestos type, and the measurements of asbestos fibres, as well as the information provided by investigators. Data sources included published and unpublished reports. Company reports, exposure surveys, judicial examinations, and narrative reports from workers [13] were used. Company-specific data were checked against the evidence from other factories with similar activity included in our pooled study and from literature data to identify inconsistencies (*i.e.* differences not explained by plant-specific characteristics) and to fill gaps in the data (*e.g.* estimating asbestos concentration).

The experts estimated for each plant and year the proportion of exposed workers, the percentage of time in asbestos exposing tasks and the minimum and maximum concentrations of asbestos airborne fibres (f/ml, from data measured in optical microscopy), for direct and indirect exposure separately.

As the cohort information did not include tasks and jobs of individual workers, only plant and period-specific estimates were generated. An Average Exposure Index (AEI) was computed for each plant and year and it was applied to all members of the corresponding cohort. It summarized in one value the range of concentration for each plant and period. The geometric mean between minimum and maximum levels, adjusted for the average proportion of time in tasks with asbestos exposure, was first calculated separately for direct and indirect exposures. The AEI value for each plant and year was obtained as the weighted average of direct and indirect exposures, weights being the respective proportional size of the workforce, as in the following formula:

$$AEI_{py} = (E_{dpy} * w_{dpy} + E_{ipy} * w_{ipy})$$

where E = exposure geometric mean, w = proportional size of the workforce and d = direct, i= indirect exposure, p = plant, and y = year

From the AEI a Cumulative Average Exposure Index (CEI) was computed for the occupational history of each worker summing the contribution of all periods of activity:

$$CEI = \sum_{py} AEI_{py}$$

A fibre-type-weighted-AEI was computed taking into account the proportion of chrysotile (CH_{py}), amosite (A_{py}), and crocidolite (CR_{py}) used in each plant and year. The weights were the MM potency factors estimated by Hodgson and Darnton for chrysotile, amosite and crocidolite (respective 1:14:71) [14]. The fibre-type-weighted-AEI corresponds to the chrysotile equivalent asbestos concentration in fibres per ml. It was computed as:

$$\textit{fibre-type-weighted } AEI_{py} = AEI_{py} * (1 * CH_{py} + 14 * A_{py} + 71 * CR_{py})$$

A fibre-type-weighted-Cumulative Exposure Index (fibre-type-weighted-CEI) was computed for each worker summing the fibre-type-weighted AEI over the entire period of activity.

$$\textit{fibre-type-weighted-CEI} = \sum_{py} \textit{fibre-type-weighted-}AEI_{py}$$

Sensitivity analyses were conducted using factors derived by other authors [15-17]. The same weights were used also in the analyses for other Asbestos Related Diseases (ARDs).

The AEI dimension was a concentration (fibres/ml) and the dimension of the fibre-type-weighted-AEI was the equivalent concentration of chrysotile asbestos fibres (fibres of chrysotile/ml). CEI and fibre-type-weighted-CEI had the dimension of concentration times years (f/ml × year), the latter being the equivalent concentration of chrysotile asbestos fibres times years. *Supplementary Table 2* (available online) presents the exposure indices by sector and period of activity.

Follow-up, and ascertainment of the causes of death, were carried out by each research unit, using agreed procedures already tested in previous studies [18]. The Registrar's Offices of the town of residence provided the information on vital status. The causes of death were provided by the Local Health Authority Registries of Causes of Death for deaths after 1985 and by the Registrar Office of the municipality of death for earlier years. The underlying cause of death was coded according to the ICD, 8th, 9th, and 10th Revisions, according to the date of death. The date of follow-up depended on the available update of files but it was required to be at least 31/12/2010. Limited to the regions where files of residents and of causes of death are kept at the regional level (Tuscany for both, Veneto and Emilia-Romagna for causes of death), similar procedures were applied to the regional files. Each research unit forwarded to the study coordination the anonymous database for each cohort, with sex, date of birth, vital status and date of follow-up, cause of death for decedents and dates of start and finish of each period of employment.

Statistical analyses were based on person-years (p-y) and standardized mortality ratios (SMRs; *i.e.* the ratio of observed to expected deaths using indirect standardization) [19]. Subjects contributed person-years up to their most recent date of observation. Duration of exposure was computed by summing up the duration of all employment periods in the cohort. TSFE (latency) was computed from the date of first employment. Cumulative exposure was computed as described before. Numerical variables were analyzed in classes; tertiles or other percentiles were defined on the basis of the cumulative distribution by industrial sector. Duration of exposure was calculated by summing up all the work periods since the date of first employment. TSFE was calculated from the date of first employment until the most recent date of observation.

Reference rates were age-, period-, sex-, region- and cause-specific. Regional mortality rates were used, according to the region of location of each plant. The set of rates was prepared by the ISS, using mortality and population figures provided by the National Institute of Statistics (ISTAT) for years from 1970 on [20]. Present analyses were therefore limited to p-y and events occurring after January 1st 1970.

We computed SMRs for the major causes of death. SMRs were stratified by gender, industrial sector, and a priori defined classes of calendar time and cumulative exposure. Present report is focused on mortality by industrial sector and cumulative exposure. We included the causes of death associated with asbestos following IARC evaluation, namely: pleural and peritoneal malignant neoplasm or MM, cancers of lung, larynx and ovary and asbestosis, and those with limited evidence of association [5]. Respiratory and cardiovascular diseases were included, as relevant for the evaluation of the Healthy Worker Effect (HWE) [19]. The list of causes was decided a priori.

Throughout the paper the number of observed and expected cases are abbreviated as Obs and Exp. SMRs are computed in percent, as (Obs/Exp) × 100. For consistency, SMRs from other studies were reported in the discussion using the percent scale. Statistical significance was set at 5%. Confidence intervals were computed according to the Poisson distribution of observed deaths, at the 95% confidence value (95% CI) [19]. Data were prepared using MS Access and SAS 9.2. Analyses were carried out using OCMAP plus, STATA 11 and SAS 9.2.

RESULTS

Table 1 provides some descriptive information of the pooled cohort under study. It included 51 801 persons (89% men and 11% women). The industrial activities were: asbestos-cement (13 076 workers); rolling stock construction and maintenance (23 810 in total; 12 789 in private plants and 11 021 in the Italian Railways, of which 2626 in the Major Maintenance Workshops - OGR), shipyards (5120) and ship furnishing (1170), glassworks (3727), dockyards (1939), insulation (205), asphalt rolls (413) and ovens construction (217). The cohort also included a cohort of Italian miners in Wittenoom and a cohort of asbestos-cement workers' wives, with domestic exposure, that were not included in the analyses by industrial sector. To avoid possible confusion a limited number (47) of workers active in different sectors were not included in any of the analyses by in-

Table 1
Italian pool of asbestos workers cohorts. Description of the cohort

		Men		Women		Total		
		n	%	n	%	n	%	p-y[a]
Industrial activity	Asbestos-cement	10 714	23.3	2362	41.1	13 076	25.2	388 915
	Rolling stock constr. maint.	23 099	50.1	711	12.4	23,810	46.0	755 034
	Shipyards	5099	11.1	21	0.4	5,120	9.9	172 583
	Glassworks	2966	6.4	761	13.2	3727	7.2	105 446
	Insulation	205	0.4	-	-	205	0.4	6482
	Ship furniture	1150	2.5	20	0.3	1170	2.3	36 957
	Dockyards and harbours	1,938	4.2	1	0.02	1939	3.7	62 102
	Asphalt rolls production	341	0.7	72	1.2	413	0.8	14 429
	Industrial ovens const.	202	0.4	15	0.3	217	0.4	7107
	Crocidolite miners	299	0.6	1	0.02	300	0.6	9314
	Domestic exposure	-	-	1777	30.9	1777	3.4	55 658
	Wks in multiple sectors	47	0.1	-	-	47	0.1	1626
Status at follow-up	alive	25 977	56.4	3010	52.4	28 987	55.9	-
	deceased [b, c]	19 394	42.1	2651	46.2	22 045	42.6	-
	emigrated [c]	172	0.4	31	0.5	203	0.4	-
	Lost to follow-up	517	1.1	49	0.9	566	1.1	-
Year of first exposure	<= 1949	6649	14.4	1514	26.4	8163	15.7	169 669
	1950-1959	6647	14.4	1517	26.4	8164	15.8	247 211
	1960-1969	13 896	30.2	1295	22.6	15 191	29.3	538 718
	1970-1979	13 033	28.3	839	14.6	13 872	26.8	488 420
	1980-1989	5461	11.9	553	9.6	6014	11.6	163 752
	1990-1992	374	0.8	23	0.4	397	0.8	7883
Total		46 060	100	5741	100	51 801	100.0	1 615 653

[a] *p-y computed from 1970;*
[b] *1092 causes of death unknown* (960 men and 132 women, in both sexes 5% of decedents);
[c] *Before 1970: 1172 deaths (1024 men and 148 women), 32 emigrated (25 men and 7 women), 230 lost to follow-up (211 men and 19 women)*

dustrial sector. The number of workers in the insulation, asphalt rolls and ovens construction sectors is small, but it was decided to include these sectors given the relevance of the exposure and the absence of larger Italian cohorts. Follow-up was known for 98.5% of workers (98.5% for men and 98.6% for women), the remaining being lost or untraced after abroad migration. Overall 42.6% of cohort members were dead: 42.1% among men and 46.2% among women. The cause of death was known for 95.0% of decedents, with the same percentage in both sexes.

Supplementary Table 2 (available online) presents the distribution of the exposure indices in the plants included in the pooled cohort study, summarized by industrial sector and period. For the asbestos cement sector, more details can be found in the specific analyses presented by Luberto *et al.* [12]: the highest exposure in this sector was observed before 1974, and declined sharply after 1980. The decennium 1970-1979 was a period of transition, with high exposures at the beginning and a reduction in the last quinquennium, as observed in particular with consideration of the range and of the median values of the different industrial sectors.

SMR analyses were limited to subjects contributing person-years after 1/1/1970, excluding therefore 1172 decedents (1024 men and 148 women), 32 emigrated (25 men and 7 women) and 230 lost to follow-up (211 men and 19 women) before 1970.

Table 2 presents mortality by cause of death in the pooled cohort, with observed and expected deaths, and SMRs with 95% CI, by gender. Total mortality was increased in both genders, with 1183 excess deaths, corresponding to a 6% increase in mortality. Causes that showed a statistically significant increase in mortality in both sexes were: all cancers, respiratory tract cancers, lung cancers, pleural and peritoneal malignancies, bladder cancers, respiratory diseases, and asbestosis. Women also showed an increase for ovarian cancers and men for malignant neoplasms of unspecified site. The number of deaths from asbestosis was in great excess in both genders; an excess was also shown for the "other pneumoconiosis" category, with 89 deaths observed (*vs* 49.16 expected) in men and 2 (*vs* 0.14) in women. Mortality did not show a statistically significant increase for laryngeal cancer, cancers of the digestive tract or pharyngeal cancer. A statistically significant reduction in mortality was observed for neurological, cardiovascular, digestive and genitourinary diseases in men. Deaths from unspecified causes represented 1.5% of total deaths.

Class (tertiles) limits for CEI and for fibre-type-weighted-CEI by industrial sector are presented in the *Supplementary Table 3* (available online).

Supplementary Table 4 (also available online) (nine panels numbered from 4.1 to 4.9) presents the summary report of mortality by cause by industrial sector in men. Some of the sectors, in particular asbestos cement, ship furniture, glassworks, dockyards, insulation and industrial ovens, showed an increase in total mortality. Workers in the railway rolling stock construction and maintenance, on the contrary showed a statistically significant reduction in total mortality.

Malignant neoplasms of the pleura and peritoneum were of special interest, as they closely estimate the occurrence of mesothelioma. An increase in the SMRs for pleural neoplasms, with exposure response trends was observed for the asbestos cement, railway rolling stock, shipyards, ship furniture, glasswork. Increased SMRs were also observed in the Insulation and Industrial Ovens sectors, accompanied by a statistically significant increased SMR in the highest exposure tertile, and in Dockyards, where an overall statistically significant increase was present but not an increasing trend. However, among Dockyard workers, the contrast in exposure was rather small *(Supplementary Table 3)* (available online).

A statistically significant increase in mortality for lung cancer was observed in most industrial sectors, in particular in asbestos cement. Railway rolling stock workers showed an increasing trend (statistically significant) and a statistically significant increase in the SMR for the highest tertile. Glassworks also showed a statistically significant trend for lung cancer and an increased SMR in the highest category. Shipyards showed a statistically significant SMR in the highest category. The Insulation sector also showed a suggestion for an increasing trend in SMRs for lung cancer.

No industrial sector showed an increase in mortality for laryngeal cancer, confirming the overall results presented in *Table 2*, that did not show an increase in mortality for this neoplasm in this pooled cohort.

Mortality from asbestosis was significantly increased in the sectors of asbestos cement, railway rolling stock and ship furniture, while uncertain results were observed for the shipyard, industrial ovens and insulation industrial sectors, and no cases were observed in the remaining sectors.

These occupational cohorts also showed some increases in mortality from diseases associated to other specific occupational risk factors. Shipyard workers showed an excess (5 cases *vs* 2.95 expected; SMR: 169, 95% CI 55-396) of deaths from pneumoconiosis not due to asbestos exposure and a similar excess was also observed for the ship furniture (11 *vs* 1.68, SMR: 655, 95% CI 327-1172) and the glassworks (25 *vs* 8.64, SMR: 289, 95% CI 187-427) sectors.

Workers in the ship furniture and in the insulation sectors presented an increase of deaths from malignant neoplasm of the nose and paranasal sinuses: 3 observed *vs* 0.20 expected deaths (SMR: 1528, 95% CI 315-4466) and 3 observed *vs* 0.03 expected deaths (SMR:10179, 95% CI 2099- 29 747), respectively.

Dockyard workers also showed a statistically significant increase in mortality from bladder cancer (17 obs *vs* 9.09 exp; SMR:187, 95% CI 109-299), that is not a priori associated to asbestos exposure but it is likely associated to some exposures collinear with it, as the excess increased over the tertiles of cumulative asbestos exposure.

Analyses for women are limited to the industrial sectors where female occupation was large enough to have meaningful results, namely the asbestos cement and the glasswork sectors, and are presented in the *Supplementary Table 5* (available online) (two panels).

In both sectors, women showed a statistically signifi-

Table 2
Italian pool of asbestos workers cohorts. Observed (OBS) and expected (EXP) deaths, by gender and cause of death

	Men					Women				
Causes of death	**OBS**	**EXP**	**SMR**	**95% CI**		**OBS**	**EXP**	**SMR**	**95% CI**	
All causes	18370	17551.8	105**	103	106	2503	2138.0	117**	112	122
Malignant neoplasm (MN)	7361	6293.7	117**	114	120	818	612.7	133**	124	143
MN lip, oral cavity and pharynx	149	191.5	78**	66	91	9	6.6	137	62	259
MN digestive organs (incl peritoneum)	2198	2194.5	100	96	104	262	226.9	116*	102	130
MN stomach	523	575.2	91*	83	99	44	47.9	92	67	123
MN small intestine	14	10.8	130	71	218	1	1.2	84	2	468
MN colon	408	413.2	99	89	109	62	52.8	117	90	150
MN rectum	173	180.4	96	82	111	22	20.3	108	68	164
MN of liver and intrahepatic bile ducts	378	380.4	99	90	110	25	28.9	87	56	128
MN peritoneum	136	28.5	477**	400	564	35	5.2	675**	470	939
MN respiratory organs	3207	2155.3	149**	144	154	217	62.6	347**	302	396
MN larynx	141	162.9	87	73	102	2	1.6	124	15	448
MN lung	2415	1918.6	126**	121	131	78	54.6	143**	113	178
MN pleura	611	46.0	1328**	1224	1437	134	4.7	2844**	2383	3369
MN uterus						34	35.7	95	66	133
MN ovary						43	31.1	138*	100	187
MN prostate	352	361.4	97	87	108					
MN bladder	291	249.2	117*	104	131	19	9.5	199**	120	311
MN kidney	157	160.7	98	83	114	6	10.2	59	22	129
Leukemia and lymphoma	446	434.2	103	93	113	47	50.7	93	68	123
MN unspecified site	220	158.3	139**	121	159	19	18.1	105	63	164
Psychiatric diseases	143	161.0	89	75	105	51	34.6	147*	110	194
Neurological diseases	275	361.2	76**	67	86	45	63.3	71*	52	95
Cardiovascular diseases	5452	6209.0	88**	85	90	909	912.2	100	93	106
Respiratory diseases	1413	1113.4	127**	120	134	154	108.7	142**	120	166
Digestive diseases	932	1034.5	90**	84	96	118	104.3	113	94	136
Genitourinary diseases	184	219.0	84*	72	97	31	27.8	112	76	158
Asbestosis	366	1.22	30072**	27070	33317	51	0.13	38961**	29009	51227
Other Pneumoconioses	89	49.16	181**	145	224	2	0.1	143**	153	5160
Accidents and violence	851	1004	85**	79	91	76	78.6	97	76	121
Poorly specified causes	230	120.9	190**	166	216	75	32.93	228**	179	286

*p < 0.05; **p < 0.01; (-) no cases

cant increase in overall mortality. In the asbestos cement sector mortality was significantly increased for peritoneal and pleural malignancies, lung cancer, and asbestosis. Mortality was also increased for ovarian cancer but not reaching statistical significance.

In the glasswork sector, only pleural neoplasm showed a statistically significant increase, based on 3 deaths and with a trend for cumulative exposure. Ovarian cancers were also more than expected. In this sector "all cancer" mortality showed a reduction, in particular for gastrointestinal cancers, while an increase was observed for the deaths from diseases of the digestive tract. It is interesting to note that no similar variations were observed for men.

DISCUSSION

Asbestos exposure has been an important source of risk for Italian workers, because of the large use of asbestos and asbestos containing materials. The Italian Registry of Malignant Mesothelioma (ReNaM) has documented the large number of cases of malignant mesothelioma that occur each year in Italy, for a total of 27 356 reported cases in the period 1993 to 2015 [21]. Besides the analysis of the occurrence of malignant mesothelioma it is relevant also to investigate the occurrence of other diseases in the subjects who have been occupationally exposed to asbestos, as the assessment of the global burden of asbestos related diseases is important for epidemiological surveillance and compensation purposes.

A large project under this perspective was launched in 2013, after the recommendations issued by the Second Italian Governmental Conference on Asbestos and Asbestos related Diseases [10], including a large number of cohorts in different industrial sectors. The project already produced results on the cause specific mortality in the total cohort [11], on mortality in the large and homogeneous sector of the asbestos cement production [12] and on the variation of pleural cancer mortality by latency [22]. This report is a first systematic presentation of the results of mortality analyses by cumulative exposure and industrial sectors, including all industrial sectors in the cohort.

The pooled study included a large number of subjects (over 50 000) active in different industrial sectors, forming 43 different cohorts. This large number of different study groups, followed up and investigated by different research groups makes unlikely the occurrence of systematic errors affecting the entire project and is therefore an element of strength of the project. Other characteristics include the very long follow-up, more than 40 years, and the significant number of women, that made possible gender-specific analyses.

The follow-up results are satisfactory: only 1.3% of subjects were lost or emigrated and had to be classified as "unknown" status. The cause of death was known for over 95% of decedents in both sexes. Causes of death were classified according to standard classifications. SMR analyses were based on regional mortality rates, for increasing comparability with reference rates. Analyses were limited to period from 1970 onwards to increase comparability with reference mortality rates, that were available only from then [20].

The study was based on mortality data, that are the only information homogeneously available for the population and period of interest for the study. There was no specific code for MM of peritoneum and pleura in the 8th and 9th ICD revisions, and ICD 10th revision is in use from 2003 in Italy. We classified in the categories of pleural malignant neoplasm the following codes: ICD8: 1630, ICD9: 1630-1639, ICD10: C38.4, C45.0, C45.9. The codes according to which we classified the cause of death as peritoneal malignant neoplasm were: ICD8 and ICD9: 1580-1589, ICD10: C48, C45.1. More information on the codes used for each cause of death were provided by Ferrante *et al.* [11]. The use of mortality data might cause random misclassification between MM and other cancers, in particular metastasis or lung cancer. Kopylev *et al*. [23] explored in a meta-analysis the sensitivity of death certificates vs MM diagnosis and observed an underestimation of MM incidence from mortality data. Other studies not included in that review came to the same conclusion: 74.5% of pleural MM cases were identified from mortality records in Italy [24] and 87% in Southern England [25]. Similar results were observed by Conti *et al.*, who compared mortality and incidence for peritoneal MM in Italy [26]. Some reports on mortality in cohorts included in our pooled study [18, 27, 28] conducted a record linkage with the Italian ReNaM data observing that SMRs did not over-estimate MM SIRs. Loomis *et al* [29] came to a similar conclusion after a review conducted mainly on US data. They also analysed individual data in their record and came to the conclusion that under-ascertainment of pleural mesothelioma also occurred after the adoption of ICD 10th classification.

The information available in our cohort did not include individual data on jobs and work activities. Asbestos exposure therefore could not be quantitatively assessed within each factory/cohort at the job or department level. Instead it had to be carried out at the factory/cohort level only. Exposure assessment was based on an average index (AEI) representing the plant and period average exposure, obtained by combining two distinct exposure estimates, for workers with direct and indirect asbestos exposure respectively. The individual cumulative exposure index (CEI) of cohort members was then calculated by applying the plant- and period-specific AEI to the duration and timing of employment of each worker. AEI and CEI were weighted for the proportion of the different fibre types used in each plant and period and their estimated carcinogenic potency factor for pleural MM [14]. More recent estimates of fibre type potency [16], were used in sensitivity analyses [12], and no relevant difference was observed. In this analysis we applied the same estimates of exposure intensity to men and women, as available historical data on airborne asbestos fibre concentrations in the factories included in the pooled cohort are not gender-specific.

Our findings for the asbestos cement sector are similar to results observed in comparable studies presented in the international literature [12, 30]. The asbestos cement sector has been analysed in a specific project, whose report can be accessed for more details [12]. In both sexes mortality was increased for "all causes" and "all malignant neoplasm (MN)", and for all asbestos related diseases, namely MN of peritoneum, pleura, lung and ovary, and asbestosis, with an exposure response trend. The large size of the cohort enabled analyses focused on the effect at long latency, not presented here, showing a flattening of the increasing trend after 40 years of latency, for pleural but not for peritoneal malignancies [22]. Further analyses of asbestosis and of risk in women are under progress.

Glass making is more frequent in a few regions, in particular Veneto, Tuscany, and also Emilia-Romagna [31]. Our cohort included two large plants with industrial production of flat glass and glass containers. The use of asbestos is associated to the handling and production of melting glass, in ovens insulation, in guide holes to convey glass drops to molds, and for personal protection devices. Other carcinogens are present in the glass making factories environment, including in particular silica, polynuclear aromatic hydrocarbons (PAHs) and for some special productions also arsenic or other metals [32] making the interpretation of results more complex. The pooled cohort did not include art glass, that instead was the focus of most published studies [33, 34]. Our cohort was very large, more than any of the cohort studies included in the metanalysis by Lehnert *et al* [35], and included a large number of women, therefore had more power to estimate the risk for rare cancers. We observed a statistically significant excess of pleural malignancies, with an SMR of 377 in men and 700 in women, with an increasing trend with cumulative exposure in both sexes, statistically significant in men. Only Plato *et al.,* had reported on the occurrence of mesothelioma, observing a non statistically significant SIR of 147 based on 3 cases in the Swedish surveillance of occupational diseases related to asbestos [36]. We observed an excess of deaths from pneumoconiosis but no cases of asbestosis, suggesting that silica was an important exposure.

The industrial sector of rolling stock construction and maintenance in Italy has been investigated with the study of individual cohorts and with the report of mesothelioma cases in railway and rolling stock workers [37-39]. Massive asbestos exposure in the Italian rolling stock construction and maintenance started in 1956 and lasted until 1986, corresponding to the decision of the Italian National Railways first to introduce asbestos lagging for fire prevention and later to systematically remove it because of the observation of increasing number of mesothelioma cases. Asbestos insulation was sprayed, also by external firms; crocidolite was used for the new carriages until 1970, while chrysotile and amosite were used afterward. The firms building new cars also carried on maintenance activities on existing cars, and these activities included asbestos removal or replacement. The current pool includes the studies considered in the comprehensive review by Merler *et al.,* [37] and the studies published afterwards, as well as some unpublished cohorts. It also included a cohort of maintenance workers in the local train depots. The pool of this industrial sector showed a healthy worker effect, with lower than expected total and cardiovascular mortality. Mortality from pleural and peritoneal cancer was increased, with a sharp exposure response relation, in particular for pleural cancer. A few cases of asbestosis were observed, all in the second and third tertiles of cumulative exposure. These results are consistent with the observations from the international literature [40], although in the comparison it is important to take into consideration the structural differences in the railway system of the different countries, and in particular the extension of the use of steam vs electrical engines.

We could include two shipyard workers cohorts and one cohort from a related plant involved in the interior furnishing of vessels. Other shipyards are active in Italy and have been investigated, but could not participate in the present call for this pooled study. In particular, the Genoa shipyard was analysed and published recently, providing a detailed analysis of risk by job [41]. Overall, they observed a statistically significant increase for cancers of the larynx, lung, and pleura, as well as for asbestosis and for liver cirrhosis. The shipyards included in the present study were mainly active in the construction and repair, and therefore may not be comparable to shipbreaking shipyards [42]. In our study, main result was related to the increased risk for lung cancer and pleural malignancies, both with the observation of an exposure response trend. The cohort of ship furniture workers was characterized by a different pattern, as it showed a statistically significant increase for both pleural malignancies (with exposure response trend) and sinonasal cancers, suggesting that workers were exposed also to wood dust [5]. This cohort also showed a statistically significant increase in mortality from pneumoconiosis (14 cases), only partially explained by asbestosis (3 cases). The excess for pneumoconiosis (not asbestosis) suggests the presence of other risk factors and calls for further investigations of this occupational activity.

The sectors of "dockyards", "insulation", "industrial oven production", "asphalt rolls" are represented by a single cohort each, none of which can be assumed as representative of its sector.

Dockyard workers showed a large excess of pleural cancer, with no clear trend with asbestos cumulative exposure and a statistically significant excess of lung and bladder cancer, suggesting the presence of exposure to other carcinogens. The lack of exposure response trend can depend on the small variation of exposure but it is also possible that our estimation of intensity of asbestos exposure did not catch appropriately the characteristics of exposure in that environment. The possible confounding effect of smoking cannot be ruled out but it must be noticed that there is no increase in mortality for cardiovascular diseases. A large increase in mesothelioma occurrence has been observed in the cohort of the British Naval Dockyard [43]. An Italian pool of five dockyards, not included in the present study, also showed a statistically significant increase in lung cancer deaths but did not provide information on mesothelioma [44].

The cohort of insulators is very small and represents only a tiny fraction of workers in this sector. Nevertheless results correspond to the expectation showing an excess of all asbestos related diseases [45], even if with broad confidence intervals due to the small cohort size.

The production of industrial ovens is peculiar as, despite only a fraction of the workers had been considered to be actually exposed due to handling asbestos panels [46] a statistically significant excess of mesothelioma was observed, with an exposure-response relation.

The small cohort of asphalt rolls workers was recently investigated by Zanardi *et al.,* [47] and the present study provided similar information, with no increase of asbestos related diseases. A statistically significant excess was observed for "lip, oral cavity and pharynx", increasing by tertiles of cumulative asbestos exposure. The asbestos sampled at the factory was chrysotile only, although Zanardi *et al.,* [47] did not exclude the possible occurrence of amphibole contamination.

Despite the interest in providing through this pooled study a broad description of the industrial sectors mostly involved by the use of asbestos, their representation in the pool is not homogeneous. The sector of asbestos cement is very well represented, with all the largest firms included and a large number of medium and small ones [48]. On the other side, the representation of the other industrial sectors is more limited, with examples rather than a representative description. Nevertheless, our results do highlight a generalised, increased risk of asbestos related diseases and call for an extension of this pioneering effort to the largest possible number of cohorts of asbestos exposed workers. Some industrial sectors were not represented altogether, such as the textile and the friction material sectors or the cohort of Balangero chrysotile miners [49]. Other industrial sectors in which only a limited proportion of workers have been interested by asbestos exposure, most often maintenance workers, cannot be evaluated appropriately through a cohort study design, unless the jobs or department assignments of all workers are known.

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Authors contribution

CM (study coordinator), PI the study, overview of the study and critical revision of the article; SS overview and analysis of exposure information, estimation of cumulative exposure and critical revision of the article; AA overview and analysis of exposure information, estimation of cumulative exposure and critical revision of the article; AR, TC, ST data management, data analysis and critical revision of the article; DA data analysis and critical revision of the article; EC, EM, VP, LM, GG, VB, PG, LB, ER, FL, OS, CS, SM, EO, PP, AP, FC, SM, AB, MM design of the study, conduct of the study and critical revision of the article; FB-A planning and overview of data analysis and critical revision of the article; DM design of the study, evaluation of exposure information and critical revision of the article; RP design of the study, overview of mortality data analyses and critical revision of the article; AM design of the study, incidence data collection coordination, and critical revision of the article; SM design of the study and critical revision of the article; DF design of the study, design and conduct of data analysis and drafting of the article; MNB, CB, BC, SC, MG, FG, PL, LM, FM, PM, CP, FR, CS, AS, MV, SV, AMN, LB contributed to the conduct of the study and to data collection.

Conflict of interest statement

The authors declare that they have no competing interests. No authors declared financial conflict of interest.

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