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RESEARCH ARTICLE

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Cause specific mortality in an Italian pool of asbestos workers cohorts

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Abstract

Background: Asbestos is a known human carcinogen and is causally associated with malignant mesothelioma, lung, larynx and ovarian cancers.

Methods: Cancer risk was studied among a pool of formerly asbestos-exposed workers in Italy. Fifty-two Italian asbestos cohorts (asbestos-cement, rolling-stock, shipbuilding, and other) were pooled and their mortality follow-up was updated to 2018. Standardized mortality ratios (SMRs) were computed for major causes of death considering duration of exposure and time since first exposure (TSFE), using reference rates by region, age and calendar period.

For affiliations refer to page 12.

Daniela Ferrante is study coordinator.

†Deceased August 10, 2022.

Results: The study included 63,502 subjects (57,156 men and 6346 women): 40% who were alive, 58% who died (cause known for 92%), and 2% lost to follow-up. Mortality was increased for all causes (SMR: men = 1.04, 95% confidence interval [CI] 1.03–1.05; women = 1.15, 95% CI 1.11–1.18), all malignancies (SMR: men = 1.21, 95% CI 1.18–1.23; women = 1.29, 95% CI 1.22–1.37), pleural and peritoneal malignancies (men: SMR = 10.46, 95% CI 9.86–11.09 and 4.29, 95% CI 3.66–5.00; women: SMR = 27.13, 95% CI 23.29–31.42 and 7.51, 95% CI 5.52–9.98), lung (SMR: men = 1.28, 95% CI 1.24–1.32; women = 1.26, 95% CI 1.02–1.53), and ovarian cancer (SMR = 1.42, 95% CI 1.08–1.84). Pleural cancer mortality increased during the first 40 years of TSFE (latency), reaching a plateau thereafter.

Conclusions: Analyses by time-dependent variables showed that the risk for pleural neoplasms increased with latency and no longer increases at long TSFE, consistent with with asbestos clearance from the lungs. Peritoneal neoplasm risk increased over all observation time.

KEYWORDS

asbestos, exposure, occupational cancer, peritoneum, pleura

1 | INTRODUCTION

Worldwide consumption of asbestos has changed dramatically over the past century. The consumption of asbestos greatly increased from the 1920s until its peak in the 1980s. Worldwide consumption rates continued to drop until the late 1990s when they stabilized at roughly 2 million metric tons per year, approximately half of what it was during peak consumption in the 1980s.[1]

Asbestos was used in the manufacture of products including textiles, building materials, insulation and brake linings. At a global scale, the highest level of asbestos consumption occurred in 1977, when approximately 4.7 million tons were used. Then, asbestos health risks triggered country-wide bans and stringent regulations, which resulted in a worldwide asbestos consumption decline until the late 1990s, when it leveled at two million tons, a consumption level that has been maintained since then with some minor fluctuations.[2]

In 2006, the World Health Organization[3] called for the elimination of asbestos-related diseases taking the position that the most efficient way to eliminate them is to cease using all types of asbestos. The 2014 update of this statement, which was attached to the WHO document "Chrysotile Asbestos" published in response to the continuing widespread production and use of chrysotile, emphasized that all forms of asbestos, including chrysotile, are causally associated with an increased risk of cancer of the lung, larynx and ovary, mesothelioma and asbestosis.[4,5] These observations are in line with the evaluation by the International Agency for Research on Cancer on carcinogenicity of asbestos fibers.[6] Positive associations have also been observed between asbestos and cancer of the pharynx, stomach and colorectum.[6] Asbestos also causes non malignant disesases of the respiratory apparatus, including in particular asbestosis and pleural plaques.[7,8]

As in 2022, all forms of asbestos have been banned in 69 countries,[9] including all European Union member countries. Nonetheless, these countries make up about one-third of the 194 WHO member countries.

The estimated global production of asbestos in 2022 was 1.3 million tons; the top four producing countries were Russia (700,000 tons), Kazakhstan (230,000 tons), China (130,000 tons), and Brazil (190,000 tons).[10]

Rates of asbestos-related diseases are expected to decrease in Western high income countries as the results of bans.[11] In a recent article by Walker-Bone et al.[12] Australian mesothelioma age-standardized incidence rates and mortality rates peaked in the early 2000s and then declined. A substantial decrease in the trends of mesothelioma was observed, especially among high income countries, probably attributable to the total ban on the use of asbestos in some countries.[13] Meanwhile, an increase of mesothelioma burden is expected in middle-low income countries in the next few years, considering the current and recent use of asbestos.[14]

WHO estimated at the turn of this century that about 125 million people in the world were exposed to asbestos at the workplace and at least 107,000 people die each year from asbestos-related lung cancer, mesothelioma and asbestosis resulting from occupational exposures.[5] The Global Burden of Disease Study 2019 estimated globally (considering 204 countries and territories) 34,511 incident cases, 29,251 deaths and 668,104 disability-adjusted life years (DALYs) of mesothelioma due to occupational asbestos exposure in 2019.[15]

Italy was one of the major producers and users of asbestos, and is among the countries mostly affected by asbestos-related diseases. Mesothelioma mortality rate increased constantly over time in both genders. In the period 1970–1974, it was 1.09 (per 100,000 person-years) in males and 0.58 (per 100,000 person-years) in females; in 1980–1984, 1.57 in males and 0.72 in females; in 1990–1994, 2.18 in

males and 0.91 in females and in 2000–2004, 3.14 in males and 1.16 in females.[16] In the 2010–2016 period, in Italy, 10,607 subjects (7660 men and 2947 women) died from malignant mesothelioma, corresponding to rates of 3.84 (95% confidence interval [CI] 3.76–3.93) in males and 1.11 (95% CI 1.07–1.15) in females. The annual average was 1094 male and 421 female deaths. The major source of asbestos exposure is in work settings, but the health effects of nonoccupational exposure are also recognized.[17] The study by Marinaccio et al.[18] based on the Italian Register of Mesothelioma (ReNaM) provided an estimation of 10% (1232 cases) for malignant mesothelioma cases due to nonoccupational asbestos exposure based on more than 15,845 detected cases, of which 12,065 individually interviewed. The familial exposure was the most frequent and residence near asbestos cement plants was largely predominant in the environmentally exposed patients. The analysis of the occurrence of pleural and peritoneal neoplasms, as well as of lung cancer and other asbestos-related diseases, by cumulative exposure and time-dependent variables was one of the major purposes that led to the construction of the Italian pooled cohort study of asbestos workers.[19,20] This report describes the pooled cohort in its updated composition and in its second follow-up. It provides the main results on cause-specific mortality and its association with time-dependent variables.

2 | MATERIAL AND METHODS

The study included 51 cohorts of asbestos workers and the cohort of wives of the Eternit plant workers in Casale Monferrato, in part already included in previous papers[19,20] and in part added during the second follow-up of the project. This second follow-up included nine new cohorts: the asbestos-cement cohorts Eternit in Siracusa and Sacelit in San Filippo del Mela, two shipyards cohorts of Genoa and Monfalcone, a cohort of rolling-stock maintenance and repair in Bologna, a cohort of rolling-stock maintenance, repair and construction in Santhià, the cohort of chrysotile miners in Balangero, the cohort of rock salt workers, Saline, in Volterra and a cohort of workers engaged in production of friction materials in Cigliano [Supporting Information: Table S1].

The total number of workers included were 67,135. The data were anonymized at the local study level; variables collected in a database by the study coordinator included in particular: sex, date of birth, vital status and date of follow-up, cause of death for decedents and dates of start and end of each period of employment, as well as the details of the factory and the cohort.

Quality control led to the exclusion of 3500 records (5.2% of the initial 67,135) because of incomplete working periods, conflicting dates or inconsistent hiring or retirement age, first employment after the asbestos ban (1992). Because of follow-up incompleteness, the cohorts of Eternit in Bagnoli and Fibronit in Broni were limited to the workers employed on January, 1, 1950, or hired thereafter ($n = 1939$ and $n = 2012$ respectively). Workers employed in different cohorts were identified according to initials, sex and birth date, with enquiries to the study coordinators, and were annotated, for a total of 132 workers (131 included in two cohorts and 1 in three cohorts). The work histories of workers employed in different cohorts identified according to sex and birth date were merged in the pooled analyses.

The study was submitted to the University of Eastern Piedmont Ethics Committee (most recent Authorization CE 164/21, July 28, 2021) and to the competent Ethics committees of each participating institution.

The vital status was assessed by the Registrar's Offices of the town of residence and the causes of death for decedents were provided by the Local Health Authorities. The underlying cause of death was coded according to the International Classification of Disease, 8th, 9th, and 10th Revisions, according to the date of death.[19] The date of follow-up varied depending on the most recent available update of files and it was at least 2018 for all cohorts except for Monfalcone cohort updated at 2012. In particular, 11 cohorts were followed up until 2021, 12 cohorts until 2020, 8 cohorts until 2019 and 20 cohorts until 2018.

The analyses included 63,502 subjects (57,156 males and 6346 females). The workers of Monfalcone cohort were considered only in the analysis for all causes and pleural cancers mortality and for time since first exposure (TSFE) analysis.

Statistical analyses for the present report were based on the person-years and standardized mortality ratios (SMRs; i.e., the ratio of observed to expected deaths using indirect standardization) method.[21] Workers in the cohort contributed until their most recent date of observation. Duration of exposure was computed by summing up the duration of all employment periods in the cohort and for the cohort of "Eternit" workers' wives in Casale Monferrato it was computed from the husband's period of employment. Latency (TSFE) was computed from the date of first employment.

Reference rates were age-, period-, sex-, region- and cause-specific. Mortality rates of the regions where the cohorts were located were used even if the subjects moved to another region during the follow-up. The set of rates was prepared by the National Institute of Health, using mortality and population figures provided by the Italian National Institute of Statistics - ISTAT (Rome, Italy) and available from 1970. Correspondingly, analyses were restricted to person-years and events occurring after January 1, 1970.

Statistical significance was set at 5%. Confidence intervals for SMRs were computed according to the Poisson distribution of observed deaths[21] at the 95% confidence value (95% CI).

Analyses were carried out using OCMAP plus and SAS 9.4.

3 | RESULTS

Table 1 presents the distribution of cohort members by sex, industrial activity, vital status at follow-up, year at first employment in the cohort.

The main industrial activities were asbestos-cement (14,818 workers), rolling stock (carriages and engines) construction and maintenance (20,927) and shipyards (14,550).

The vital status was assessed for 98% of the workers (55,871 men and 6207 women): 25,126 were alive, 36,952 deceased and 1424 lost to follow-up or moved abroad. The cause of death was known for 92% of the deceased subjects and 96% escluding Monfalcone cohort (about half of the unknown causes was

TABLE 1 Description of the cohort overall and by sex.

	Men		Women		Total	
	n	%	*n*	%	*n*	%
Industrial activity						
Rolling stock construction and maintenance	20,462	35.8	465	7.3	20,927	33.0
Asbestos-cement	11,962	20.9	2856	45.1	14,818	23.3
Shipyards	14,408	25.2	142	2.2	14,550	22.9
Harbour	3730	6.5	2	0.03	3732	5.9
Glassworks	2975	5.2	761	12.0	3736	5.9
Miners	1216	2.1	1	0.02	1217	1.9
Ship furniture	1192	2.1	20	0.3	1212	1.9
Asphalt rolls	335	0.6	72	1.1	407	0.6
Friction materials	243	0.4	128	2.0	371	0.6
Insulation	214	0.4	1	0.02	215	0.3
Industrial ovens	209	0.4	15	0.2	224	0.4
Rock salt workers	188	0.3	107	1.7	295	0.5
Wives of asbestos-cement workers	-	-	1776	28.0	1776	2.8
Wks in multiple activities	22	0.04	-	-	22	0.04
Status at follow-up						
Alive	22,813	39.9	2313	36.5	25,126	39.6
Deceased[a,b]	33,058	57.8	3894	61.3	36,952	58.2
Emigrated[a]	231	0.4	41	0.6	272	0.4
Lost to follow-up	1054	1.8	98	1.5	1152	1.8
Year of first employment						
≤1949	10,621	18.6	1732	27.3	12,353	19.4
1950–1959	7974	14.0	1843	29.0	9817	15.5
1960–1969	14,501	25.3	1298	20.4	15,799	24.9
1970–1979	18,385	32.2	985	15.5	19,370	30.5
1980–1989	5153	9.0	449	7.1	5602	8.8
1990–1992	522	0.9	39	0.6	561	0.9
Total	57,156	100	6346	100	63,502	100.0

[a]Before 1970: 2083 deaths (1929 men and 154 women), 44 emigrated (35 men and 9 women), 319 lost to follow-up (281 men and 38 women);
[b]3038 causes of death unknown (2821 men and 217 women, 8% of decedents).

attributable to Monfalcone cohort, for which the specific causes of death were not available).

34.9% of the subjects were initially employed before 1960.

The total person-years were 1,923,875 (analyses on mortality from all causes and pleural cancers included additional 192,528 py due to Monfalcone cohort).

Table 2 presents the SMRs by cause of death and sex. Mortality was significantly increased in both sexes for all causes, all malignant neoplasms, respiratory tract cancers, lung cancers, pleural and peritoneal malignancies, bladder cancers, respiratory diseases, and asbestosis. Among women, the observed number of ovarian cancers was significantly higher than expected. In men only, an excess was observed for malignant neoplasms of unspecified site. The number of deaths from asbestosis was in great excess in both sexes, and similar figures were observed for the general category of pneumoconioses (including asbestosis). Mortality was significantly lower than expected in men for cardiovascular diseases, neurological disorders and accidents and violence. The SMR for all causes was 1.08 (95% CI 1.07–1.09) in men and 1.15 (CI 95% 1.11–1.19) in women and for pleural cancer 11.39 (95% CI 10.71–12.10) in men and 27.45 (CI 95% 23.57–31.80) in women excluding Monfalcone cohort

TABLE 2 Number of observed and expected deaths, standardized mortality ratio (SMR) and 95% confidence interval (95% CI) by sex and cause of death after 1.1.1970 (see text).

	Men				Women			
Causes of death	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All causes	31130	29997.53	1.04**	1.03–1.05	3739	3266.54	1.15**	1.11–1.18
Malignant neoplasm	11300	9378.66	1.21**	1.18–1.23	1093	845.98	1.29**	1.22–1.37
MN lip, oral cavity and pharynx	226	256.92	0.88	0.77–1.00	13	9.41	1.38	0.74–2.36
MN digestive system (incl peritoneum)	3326	3256.31	1.02	0.99–1.06	354	315.38	1.12*	1.01–1.25
MN stomach	776	814.27	0.95	0.89–1.02	59	62.94	0.94	0.71–1.21
MN small intestine	21	18.10	1.16	0.72–1.77	1	1.69	0.59	0.01–3.30
MN colon	650	642.18	1.01	0.94–1.09	79	75.26	1.05	0.83–1.31
MN rectum	279	269.28	1.04	0.92–1.16	29	27.03	1.07	0.72–1.54
MN of liver and intrahepatic bile ducts	569	560.10	1.02	0.93–1.10	37	40.68	0.91	0.64–1.25
MN peritoneum	166	38.68	4.29**	3.66–5.00	47	6.26	7.51**	5.52–9.98
MN respiratory organs	4852	3115.08	1.56**	1.51–1.60	281	89.53	3.14**	2.78–3.53
MN larynx	217	224.26	0.97	0.84–1.10	2	2.13	0.94	0.11–3.38
MN lung	3535	2760.01	1.28**	1.24–1.32	99	78.68	1.26*	1.02–1.53
MN pleura	1119	106.95	10.46**	9.86–11.09	178	6.56	27.13**	23.29-31.42
MN uterus					51	46.60	1.09	0.81–1.44
MN ovary					58	40.81	1.42*	1.08–1.84
MN prostate	591	604.98	0.98	0.90–1.06				
MN bladder	487	401.62	1.21**	1.11–1.32	25	13.88	1.80**	1.17–2.66
MN kidney	232	251.40	0.92	0.81–1.05	10	14.71	0.68	0.33–1.25
Leukemia and lymphoma	683	666.58	1.02	0.95–1.10	62	72.79	0.85	0.65–1.09
MN unspecified site	342	244.19	1.40**	1.26–1.56	29	26.78	1.08	0.72–1.55
Psychiatric diseases	316	334.55	0.94	0.84–1.05	89	76.90	1.16	0.93–1.42
Neurological diseases	546	667.31	0.82**	0.75–0.89	89	110.19	0.81*	0.65–0.99
Cardiovascular diseases	8737	9758.32	0.89**	0.88–0.91	1387	1372.24	1.01	0.96–1.06
Respiratory diseases	2470	1927.86	1.28**	1.23–1.33	244	179.70	1.36**	1.19–1.54
Pneumoconioses	639	76.33	8.37**	7.73–9.05	70	0.37	191.3**	149.2–241.8
Asbestosis	538	3.76	143.0**	131.2–155.7	68	0.18	374.8**	291.0–475.1
Digestive diseases	1423	1460.83	0.97	0.92–1.03	164	148.03	1.11	0.94–1.29
Genitourinary diseases	354	389.17	0.91	0.82–1.01	61	47.68	1.28	0.98–1.64
Accidents and violence	1171	1347.76	0.87**	0.82–0.92	91	108.67	0.84	0.67–1.03
Poorly specified causes	395	220.82	1.79**	1.62–1.97	117	59.81	1.96**	1.62–2.34

Note: *$p < 0.05$; **$p < 0.01$.

Abbreviations: Exp, expected; MN, malignant neoplasm; Obs, observed.

from the analysis. The SMRs by cohort were reported in Supporting Information: Figures S2–S7.

Table 3 presents mortality in relation to TSFE. In men, total mortality was lower than expected in the first 20 years of TSFE, and increased afterwards. A similar trend was observed for total malignant neoplasms. SMR for cardiovascular diseases increased with TSFE but remained always lower than unity. Regarding the causes of death associated with asbestos exposure, the lung cancer SMR was 1.06 in the first 20 years of TSFE, then increased up to 1.38 in the class 30–39 years, without further increasing with longer TSFE. An increase for pleural malignancies was observed: SMRs increased from 3.95 for TSFE < 20 years to 12.58 for TSFE 40–49 and did not

TABLE 3 Number of observed deaths, standardized mortality ratio (SMR) and 95% confidence interval (95% CI) by time since first exposure (years).

TSFE										
Men	**<20**		**20–29**		**30–39**		**40–49**		**50+**	
Causes of death	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**
All causes	2548	0.72** (0.69–0.75)	5151	1.03* (1.00– 1.06)	8009	1.08** (1.06–1.10)	7821	1.12** (1.10–1.15)	7601	1.07** (1.05–1.10)
Malignant neoplasm	853	0.96 (0.89–1.02)	1858	1.20** (1.14–1.25)	3043	1.24** (1.19–1.28)	3163	1.25** (1.21–1.30)	2383	1.22** (1.17–1.27)
MN peritoneum and retroperi-toneum	4	0.72 (0.20–1.84)	17	2.09** (1.22–3.35)	39	3.59** (2.55–4.91)	59	6.89** (5.25–8.89)	47	8.42** (6.19–11.20)
MN respiratory organs	364	1.12* (1.01–1.25)	832	1.48** (1.38–1.58)	1420	1.66** (1.57–1.75)	1351	1.64** (1.55–1.73)	885	1.61** (1.51–1.72)
MN larynx	25	0.78 (0.50–1.15)	52	1.08 (0.81–1.42)	55	0.88 (0.66–1.14)	54	1.07 (0.80–1.40)	31	1.00 (0.68–1.41)
MN lung	295	1.06 (0.94–1.18)	643	1.30** (1.20–1.41)	1045	1.38** (1.29–1.46)	943	1.28** (1.20–1.36)	609	1.24** (1.15–1.35)
MN pleura	36	3.95** (2.77-5.47)	150	8.29** (7.02–9.73)	349	11.73** (10.53–13.03)	347	12.58** (11.29–13.98)	237	10.57** (9.27–12.00)
Respiratory diseases	101	0.95 (0.77–1.15)	264	1.22** (1.08–1.38)	542	1.33** (1.22–1.45)	662	1.28** (1.18–1.38)	901	1.32** (1.24–1.41)
Asbestosis	12	81.67** (42.20–142.66)	44	131.85** (95.80–177.00)	116	152.05** (125.64–182.38)	147	148.20** (125.21–174.19)	219	143.54** (125.16–163.87)
Cardiovascular diseases	641	0.82** (0.76–0.89)	1172	0.84** (0.80–0.89)	2042	0.90** (0.86–0.94)	2325	0.94** (0.90–0.97)	2557	0.91** (0.87–0.94)
Digestive diseases	189	0.79** (0.68–0.91)	292	0.99 (0.88–1.11)	352	0.97 (0.87–1.07)	314	1.02 (0.91–1.14)	276	1.08 (0.96–1.22)
Accidents and violence	321	0.88* (0.79–0.99)	218	0.83** (0.73–0.95)	247	0.90 (0.79–1.01)	189	0.82** (0.71–0.95)	196	0.90 (0.78–1.04)
Women	**<20**		**20-29**		**30-39**		**40-49**		**50+**	
Causes of death	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**
All causes	93	0.78* (0.63–0.96)	266	1.03 (0.91–1.16)	603	1.09* (1.00–1.18)	913	1.16** (1.09–1.24)	1864	1.20** (1.15–1.26)
Malignant neoplasm	44	0.95 (0.69–1.27)	119	1.21* (1.00–1.45)	205	1.14 (0.99–1.31)	290	1.33** (1.18–1.49)	435	1.44** (1.30–1.58)
MN peritoneum and retroperi-toneum	0	–	2	2.19 (0.26–7.92)	4	2.56 (0.80–6.56)	9	5.16** (2.36–9.80)	32	19.78** (13.53–27.92)
MN respiratory organs	5	1.43 (0.46–3.34)	27	2.97** (1.96–4.32)	60	3.17** (2.42–4.08)	83	3.37** (2.69–4.18)	106	3.17** (2.60–3.83)
MN larynx	0	–	0	–	1	2.00 (0.05–11.13)	0	–	1	1.52 (0.04-8.49)

TABLE 3 (Continued)

Women	<20		20-29		30-39		40-49		50+	
Causes of death	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
MN lung	3	1.03 (0.21–3.00)	14	1.78 (0.97–2.99)	19	1.14 (0.69–1.79)	29	1.34 (0.90–1.92)	34	1.15 (0.80–1.60)
MN pleura	2	7.58 (0.92–27.38)	13	20.26** (10.79–34.65)	38	28.29** (20.02–38.82)	54	29.37** (22.06–38.32)	71	28.71** (22.42–36.21)
Respiratory diseases	0	–	3	0.32* (0.07–0.95)	27	1.11 (0.73–1.62)	55	1.33 (1.00–1.73)	159	1.57** (1.33–1.83)
Asbestosis	0	–	0	–	5	184.34** (59.84–430.18)	14	238.04 (154.74–474.90)	49	558.24** (412.99–738.03)
Cardiovascular diseases	23	0.85 (0.54–1.27)	64	0.78* (0.60–0.99)	197	0.93 (0.81–1.07)	337	1.00 (0.90–1.11)	766	1.07 (1.00–1.15)
Digestive diseases	4	0.51 (0.14–1.30)	15	0.98 (0.55–1.61)	36	1.29 (0.90–1.78)	48	1.32 (0.98–1.76)	61	1.00 (0.77–1.29)
Accidents and violence	13	1.39 (0.74–2.37)	9	0.80 (0.37–1.52)	16	0.86 (0.49–1.40)	19	0.79 (0.47–1.23)	34	0.75 (0.52–1.05)

Note: *$p < 0.05$; **$p < 0.01$.

Abbreviations: –, no cases. MN, malignant neoplasm; Obs, observed; TSFE, time since first exposure.

further increase at longer TSFE periods. Peritoneal neoplasms showed a statistically significant increase in SMRs starting from 20 to 29 years of TSFE, with an increasing trend over the entire follow-up period (Figure 1). Deaths from asbestosis showed an increasing trend until 40 years of TSFE. Laryngeal neoplasms did not show a clear pattern with SMRs close to or lower than unity.

In women, overall mortality and total malignant neoplasms showed an increasing trend from 20 years of TSFE onwards. Pleural and peritoneal neoplasms exhibited a trend with TSFE similar to men. The lung cancer did not show a trend but the SMRs were always higher than the unit (Figure 1). The mortality for asbestosis increased after 30 years of TSFE.

Analyses by duration of exposure are presented in Table 4. In men SMRs for pleural and peritoneal malignancies and for asbestosis increased with duration of occupation, while a less evident trend was observed for lung cancer. Among women an increasing trend was observed for deaths from malignant neoplasms, pleural and peritoneal malignancies (Figure 2) and asbestosis.

Table 5 shows the crosstabulation of SMRs by TSFE and duration of exposure, for lung and pleural neoplasm among men. For pleural neoplasm, the trend at increasing TSFE is appreciable in the shortest and longest class of duration. In particular, SMRs declined after TSFE 30–39 years both among workers with exposure shorter than 10 years and among those with ≥30 years. There was not a clear trend for lung cancer.

4 | DISCUSSION

Our study is a pooled analysis of a large multicentre cohort of workers exposed to asbestos in different industries in Italy. Women accounted for 10% of subjects and therefore it is possible to explore the effects of asbestos exposure in both genders. Most of the cohorts were included in the previous update of the follow-up[20] but the inclusion of new cohorts provides more information on industrial sectors of great importance in Italy, such as shipbuilding and railway engine and carriage construction. The additional follow-up period and the inclusion of new cohorts[19,20] add information to evaluate the cause-specific mortality and the trend of mortality accounting for duration of exposure and TSFE.

The analysis was restricted after 1970 because of the lack of the regional reference mortality rates before that period. Causes of death were classified according to the International Classification of Disease. There was no specific code for mesothelioma of peritoneum and pleura in the 8th and 9th ICD revisions and this can lead to an underestimation of cases. We plan to conduct a record linkage with the Mesothelioma Registry to study mesothelioma incidence in the cohort. The pooled cohort included mostly workers employed in asbestos-cement production (23.3%), rolling stock construction and maintenance (33%), and shipyards (22.9%).

The obtained results clearly showed that pleural neoplasms risk increases with TSFE, for both men and women: after longer latency, SMR no longer increases. These findings confirm the previous observation by Barone-Adesi et al.[22,23] suggesting that the risk for

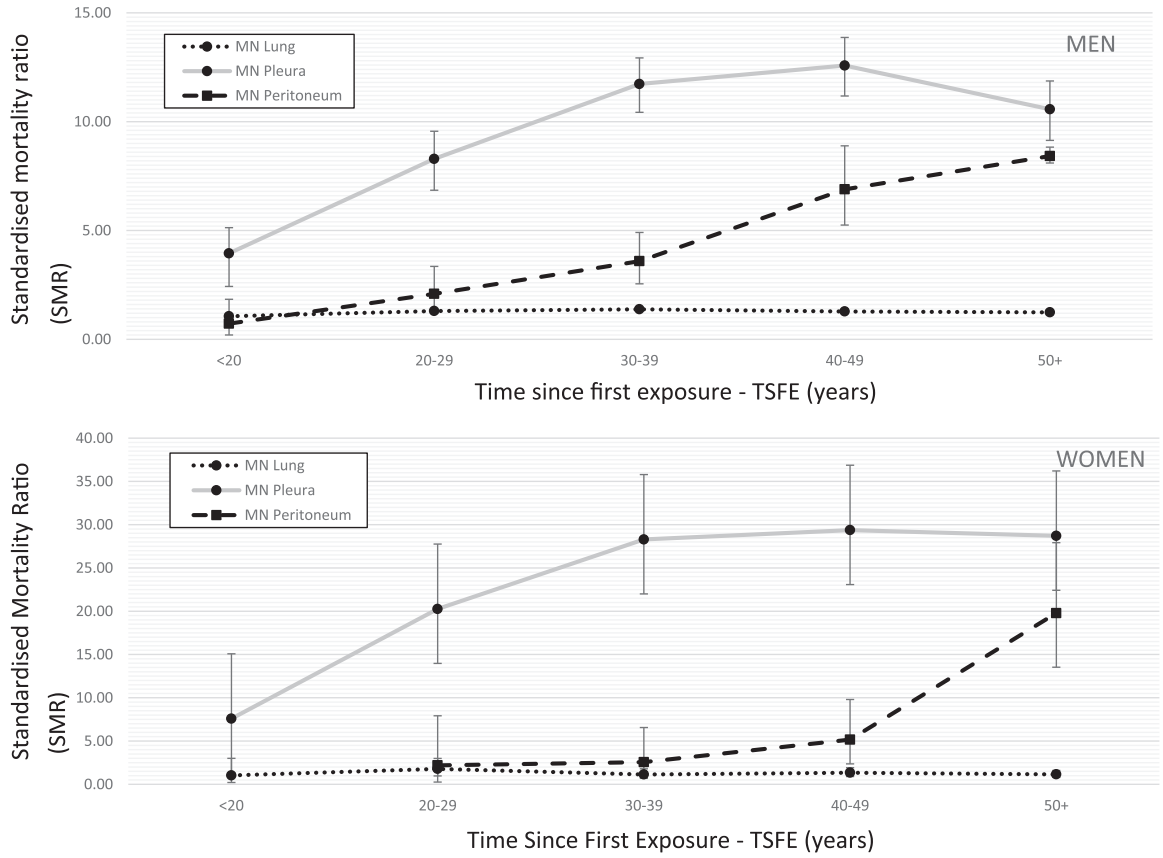

FIGURE 1 Standardized mortality ratio (SMR) for lung, pleural and peritoneal cancer by time since first exposure (years) and sex.

pleural cancer does not increase indefinitely but it reaches a plateau when a sufficiently long time has elapsed since the start of exposure and that this may be related to the clearance of asbestos from the start of exposure, according to Berry's hypothesis.[24,25] Progressive attrition of the subjects with high exposure in the cohort might be responsible for the observed plateau in the highest categories of latency. Contrary to pleural neoplasms, the risk for peritoneal neoplasms increased all over the observation time in men and women. This different behavior could be due to the route followed by the asbestos fibers to translocate to the peritoneum.[22,23]

SMRs increased with duration of exposure for asbestosis and pleural and peritoneal neoplasms in men and women. For lung cancer the trend was less clear. The trend for lung cancer should be evaluated also in consideration of tobacco smoking, given the known interaction effect[26] but the information on individual smoking habits was not known. If the workers' smoking habits differ from those of the reference population whose rates are used, the calculated SMRs can be incorrect. This, however, is not likely to lead to errors in excess of 30 percent.[27,28] Deaths from cardiovascular diseases were fewer than expected, suggesting Healthy Worker Effect (HWE) and suggest the absence of marked differences in smoking habits with the general population. Cardiovascular mortality showed different results in published studies, depending on the prevalence of risk factors and on HWE, but usually few details were reported.[19]

In the present study, no excess risk of laryngeal cancer was found. A meta-analysis reported the association between asbestos exposure and laryngeal cancer risk, and supported the hypothesis that exposure to asbestos was associated with an increase in mortality for laryngeal cancer, especially in male workers.[29] However, given also the better prognosis of laryngeal compared to other asbestos-related cancers, incidence rather than mortality studies might be better suited to assess laryngeal cancer risk. The 5-year survival for laryngeal cancer in Italy for the incidence period 2005–2009 was equal to 69%.[30]

Also for stomach cancer SMR was close to unity and does not support the hypothesis of an association. In a meta-analysis of studies of workers in which a major portion of the cohort was presumed to have been exposed to asbestos reported an increase in the pooled estimate of mortality and incidence in men (meta-SMR = 1.13, 95% CI 1.02–1.26) for stomach cancer in relation to exposure to asbestos.[31]

Regarding the hypothesis of association of asbestos and other digestive system cancer, in a cohort of subjects occupationally exposed to asbestos, a significantly elevated incidence was observed in men for liver cancer, esophageal cancer and for all digestive cancers combined, both including or excluding peritoneal mesothelioma. In the same cohort in women a significant incidence was only found for peritoneal mesothelioma.[32] In a study by Paris et al.[33] an association between occupational exposure to asbestos and colon

TABLE 4 Number of observed deaths, standardized mortality ratio (SMR) and 95% confidence interval (95% CI) by duration of exposure (years).

Duration of exposure								
Men	**<10**		**10–19**		**20–29**		**30+**	
Causes of death	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**
All causes	10,575	1.08** (1.06–1.10)	7360	1.12** (1.10–1.15)	7387	1.07** (1.04–1.09)	4159	1.05** (1.02–1.08)
Malignant neoplasm	3908	1.13** (1.09–1.16)	2796	1.26** (1.21–1.31)	2930	1.22** (1.18–1.27)	1666	1.28** (1.22–1.35)
MN peritoneum and retroperitoneum	47	3.23** (2.37–4.29)	35	3.79** (2.64–5.27)	51	5.28** (3.93–6.94)	33	6.32** (4.35–8.87)
MN respiratory organs	1631	1.42** (1.35–1.49)	1206	1.63** (1.54–1.73)	1293	1.63** (1.54–1.72)	722	1.67** (1.55–1.80)
MN larynx	75	0.95 (0.74–1.18)	49	0.89 (0.66–1.17)	67	1.15 (0.89–1.46)	26	0.82 (0.54–1.20)
MN lung	1209	1.18** (1.12–1.25)	913	1.40** (1.31–1.49)	887	1.26** (1.18–1.34)	526	1.38** (1.26–1.50)
MN pleura	328	9.76** (8.73–10.88)	223	10.17** (8.88–11.60)	328	14.60** (13.06–16.27)	162	12.07** (10.28–14.08)
Respiratory diseases	763	1.19** (1.10–1.27)	645	1.38** (1.27–1.49)	645	1.28** (1.19–1.39)	417	1.33** (1.21–1.46)
Asbestosis	69	58.34** (45.39–73.83)	144	158.48** (133.65–186.58)	206	241.50** (209.64–276.83)	119	145.70** (120.70–174.36)
Cardiovascular diseases	2961	0.89** (0.86–0.93)	2234	0.93** (0.89–0.97)	2281	0.90** (0.87–0.94)	1261	0.83** (0.78–0.87)
Digestive diseases	533	1.00 (0.92–1.09)	356	0.98 (0.88–1.08)	348	0.95 (0.85–1.06)	186	0.93 (0.80–1.08)
Accidents and violence	549	0.92* (0.84–1.00)	259	0.81** (0.71–0.91)	243	0.84** (0.74–0.96)	120	0.84 (0.70–1.01)
Women	**<10**		**10–19**		**20–29**		**30+**	
Causes of death	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**
All causes	1642	1.14** (1.08–1.19)	974	1.12** (1.05–1.19)	811	1.20** (1.12–1.28)	271	1.18** (1.04–1.33)
Malignant neoplasm	457	1.12* (1.02–1.23)	301	1.40** (1.24–1.56)	245	1.42** (1.25–1.61)	90	1.73** (1.39–2.13)
MN peritoneum and retroperitoneum	6	2.09 (0.77–4.54)	19	11.52** (6.94–18.00)	12	9.10** (4.70–15.90)	10	23.92** (11.47–43.99)
MN respiratory organs	117	2.62** (2.17–3.14)	69	3.15** (2.45–3.99)	67	3.72** (2.88–4.72)	28	5.56** (3.69–8.03)
MN larynx	1	0.98 (0.02–5.47)	0	–	1	2.32 (0.06–12.94)	0	–
MN lung	52	1.31 (0.98–1.72)	22	1.15 (0.72–1.74)	16	1.03 (0.59–1.67)	9	2.05 (0.94–3.90)
MN pleura	62	21.21** (16.26–27.20)	47	28.48** (20.93–37.87)	50	32.89** (24.41–43.36)	19	48.61** (29.26–75.91)
Respiratory diseases	96	1.22 (0.98–1.48)	66	1.35* (1.04–1.72)	58	1.50** (1.14–1.94)	24	1.81* (1.16–2.69)
Asbestosis	13	184.19** (98.07–314.96)	23	466.12** (295.48–699.41)	20	405.16** (247.49–625.73)	12	988.06** (510.58–1725.98)

(Continues)

TABLE 4 (Continued)

Women	<10		10–19		20–29		30+	
Causes of death	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
Cardiovascular diseases	621	1.07 (0.99–1.16)	367	0.94 (0.85–1.05)	301	1.02 (0.90–1.14)	98	0.90 (0.73–1.09)
Digestive diseases	77	1.15 (0.91–1.44)	38	0.95 (0.67–1.30)	38	1.23 (0.87–1.68)	11	1.06 (0.53–1.90)
Accidents and violence	35	0.70* (0.49–0.97)	29	0.99 (0.66–1.42)	17	0.78 (0.45–1.25)	10	1.31 (0.63–2.41)

Note: *$p < 0.05$; **$p < 0.01$.

Abbreviations: –, no cases; MN, malignant neoplasm; Obs, observed.

cancer incidence in men was reported. Incidence of colon cancer rather than mortality might be better suited to assess the risk.

The 5-year survival for colon cancer in Italy for the incidence period 2005–2009 was equal to 65% and for stomach cancer equal to 32%.[30]

In our results, mortality was around the unit for stomach, colon, rectum and liver cancers and diseases of the digestive tract, while for peritoneal mesothelioma it was in excess in both sexes.

A statistically significant increase of ovarian cancer mortality (58 observed vs 40.8 expected, SMR = 1.42, $p < 0.05$) was found in our study. This result supports the association between asbestos exposure and ovarian cancer reported in a meta-analysis by Camargo et al.[34] that estimated a meta-analytical SMR of 1.77 (95% CI 1.37–2.28) over 18 studies.

We observed a statistically significant increase in bladder cancer for both men (SMR = 1.21; $p < 0.01$) and women (SMR = 1.80; $p < 0.01$) as in our previous paper.[19,20] The role of tobacco smoking and exposure to other occupational carcinogens, as possible confounders, cannot be evaluated on an individual basis because of lack of information. A meta-analysis by Franco et al.[35] reported that workers with occupational asbestos exposure had a bladder cancer incidence and mortality rate similar to the general population.

The cohort showed a large increase in mortality from asbestosis: 606 deaths were observed while 3.94 were expected. Considering these subjects, more than half of the workers were younger than 30 years of age at date of first employment (58.6%) and the year of first employment was before 1950 for the 39.9% of the workers.

Our study has some limitations. First, there was no specific code for mesothelioma of peritoneum and pleura in the 8th and 9th ICD revisions and this can lead to a misdiagnosis of mesothelioma. Second, the confounding effect of smoking cannot be assessed because of the lack of information on individual smoking habits. Third, the exposure could not be assessed on an individual basis, because of the lack of individual data on jobs and work activities of cohort members in almost all cohorts. Finally, there are some differences in the follow up time between the cohorts. The cohort of Monfalcone was included as it is a very important shipbuilding area despite the shorter follow-up time compared to the others. Future studies might apply cohort-specific average exposures estimated by calendar year for all workers in each cohort.[20,23,36,37]

We are reporting on one of the largest cohort studies of asbestos exposed workers worldwide. Our results, apart from increased mortality from asbestosis and neoplasms of the lung, pleura and peritoneum, also showed excess deaths from ovarian neoplasms. Our findings indicated an increase of mortality for pleural neoplasm with TSFE reaching a plateau after 40 years since the first exposure. This trend has been observed in previous studies.[22,36] Further analyses from this pooled cohort are warranted and will include analyses by industrial activity and cumulative exposure.

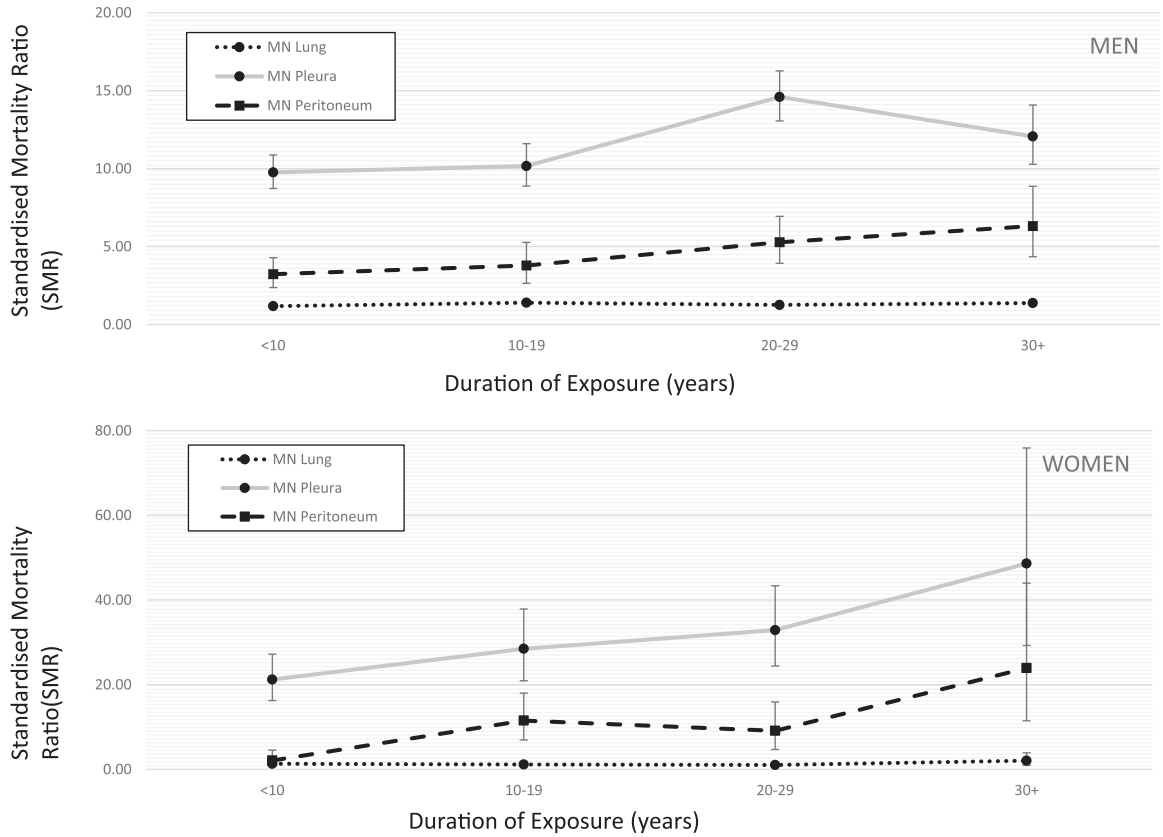

FIGURE 2 Standardized mortality ratio (SMR) for lung, pleural and peritoneal cancer by duration of exposure (years) and sex.

TABLE 5 Number of observed deaths, standardized mortality ratio (SMR) by duration of exposure and time since first exposure (years), for pleural and lung cancer among men.

	Duration of exposure (years)							
TS of death	0–9		10–19		20–29		30+	
TSFE (years)	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
Pleural neoplasm								
0–19	14	3.70**	20	9.38**				
20–29	47	8.65**	41	9.76**	30	11.33**		
30–39	111	13.33**	67	9.20**	97	15.89**	30	20.13**
40–49	106	11.45**	63	10.54**	129	14.67**	49	13.80**
50+	50	7.36**	32	13.78**	72	14.62**	83	9.91**
Lung neoplasm								
0–19	189	1.06	106	1.05				
20–29	260	1.27**	232	1.43**	151	1.19*		
30–39	331	1.28**	295	1.47**	326	1.44**	93	1.25*
40–49	290	1.24**	192	1.44**	286	1.20**	175	1.31**
50+	139	0.95	88	1.60**	124	1.09	258	1.47**

Note: *$p < 0.05$; **$p < 0.01$.

Abbreviations: Obs, observed; TSFE, time since first exposure.

AUTHOR CONTRIBUTIONS

Daniela Ferrante, Corrado Magnani and Alessandro Marinaccio designed the study. All the authors contributed to acquisition and interpretation of data. Daniela Ferrante performed the analysis and drafted the work. All the authors contributed to revise critically the work, provided final approval for publication and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The following authors reported that they served as expert witness for the public prosecutor in court trials on asbestos related diseases: Alessia Angelini, Fabio Barbone, Massimo Bovenzi, Corrado Magnani, Enrico Oddone, Stefano Silvestri. Stefano Mattioli served as consultant for the court, the public prosecutor and the defense in court trials concerning asbestos-related diseases.

DISCLOSURE BY AJIM EDITOR OF RECORD

John Meyer declares that he has no conflict of interest in the review and publication decision regarding this article.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS APPROVAL AND INFORMED CONSENT

The study was submitted to the University of Eastern Piedmont Ethics Committee (Authorization CE 164/21, July 28, 2021) and to the competent Ethics committees of each participating institution.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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