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RESEARCH ARTICLE

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Asbestos exposure and asbestosis mortality in Italian cement-asbestos cohorts: Dose-response relationship and the role of competing death causes

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Abstract

Objectives: In Italy, asbestos was used intensively until its ban in 1992, which was extended for asbestos cement factories until 1994. The aim of this study was to evaluate the dose–response between asbestos exposure and asbestosis mortality across a pool of Italian occupational cohorts, taking into account the presence of competing risks.

Methods: Cohorts were followed for vital status and the cause of death was ascertained by a linkage with mortality registers. Cause-specific (CS) Cox-regression models were used to evaluate the dose-exposure relationship between asbestosis mortality and the time-dependent cumulative exposure index (CEI) to asbestos. Fine and Gray regression models were computed to assess the effect of competing risks of death.

Results: The cohort included 12,963 asbestos cement workers. During the follow-up period (1960–2012), of a total of 6961 deaths, we observed 416 deaths attributed to asbestosis, 879 to lung cancer, 400 to primary pleural cancer, 135 to peritoneal cancer, and 1825 to diseases of the circulatory system. The CS model showed a strong association between CEI and asbestosis mortality. Dose–response models estimated an increasing trend in mortality even below a CEI of 25 ff/mL-years. Lung cancer and circulatory diseases were the main competing causes of death.

Conclusions: Asbestos exposure among Italian asbestos-cement workers has led to a very high number of deaths from asbestosis and asbestos-related diseases. The increasing risk trend associated with excess deaths, even at low exposure levels, suggests that the proposed limit values would not have been adequate to prevent disability and mortality from asbestosis.

KEYWORDS

asbestos, international health regulations, occupational health, risk assessment

1 | INTRODUCTION

Inhalation and subsequent deposition of asbestos fibers within the lung parenchyma, particularly for fibers that reach the interalveolar septa, results in a diffuse interstitial lung fibrosis, commonly referred to as asbestosis.[1] In its early stages, the disease is usually asymptomatic, but its progression leads to disability, respiratory failure and eventually death.[2–5] Asbestosis was the first respiratory disorder linked with exposure to asbestos. The first reports of chronic lung fibrosis in asbestos-exposed workers were presented in the UK at the end of the 19th century,[6] followed by similar observations in other countries.[7] Starting in UK in the 1930s the disease was recognized and compensated as occupational regulations and legislation aimed at avoiding disability and death were introduced in Western countries.[8,9]

From a clinical perspective, asbestosis is characterized by the formation in the lungs of asbestos bodies (asbestos fibers covered with a hyaline substance containing iron) which results from the frustrated phagocytosis of the longest fibers. Asbestos bodies and fibers can be detected in the lung parenchyma, sputum and bronchoalveolar lavage fluid.[10] The detection of asbestos fibers is not pathognomonic of the disease.[1] Rather interstitial fibrosis of the lungs with a certain radiographic appearance and distribution, and a history of asbestos exposure, is necessary to the diagnosis.[11,12] The diagnosis of asbestosis typically relies on radiological exams, in particular the standard chest X-rays, which is interpreted in accordance with the International Labor Organization,[13] and more recently, High-Resolution Computerized Tomography interpreted in accordance with the International Classification of High-resolution Computed Tomography for Occupational and Environmental Respiratory Diseases guidelines.[14] Tests to evaluate clinical severity encompass spirometry and carbon monoxide diffusion tests, which typically demonstrate a reduction in lung volumes and impairment of the diffusion capacity with severity corresponding to that of radiographic images.[15]

Histological presence of interstitial fibrosis detectable at lung surgery or at autopsy can be found in the lungs of workers exposed to asbestos who display no symptoms, leading to the definition of "minimal asbestosis".[16] The clinical worsening of asbestosis is continuous, even after exposure to asbestos has ceased.

The severity of asbestosis and the presence of comorbidities greatly influence survival rates: Keskitalo et al.[17] observed a median survival of 171 months (about 14 years) for patients categorized under GAP (Gender, Age, and Physiology)[18] stage 1 (less severe asbestosis), and 21 months (less than 2 years) for those categorized under GAP stage 3 (worse asbestosis).

Mortality trends for asbestosis in the UK showed an increase up to the year 2006[19]; the same overall increase was observed in the United States, but a sharp decline was predicted from 2020 onwards, in line with the decline in asbestos use that has already occurred[20]; subsequent observations supported the temporal decline in asbestosis mortality.[21] Despite the prohibition in Italy of any new use of

asbestos in 1994, deaths from asbestosis continue to occur: from 2010 to 2016, there were 405 deaths—361 among men, 44 among women—from asbestosis, corresponding to a rate of 0.19 (95% confidence interval [CI]: 0.17–0.22) and 0.01 (95% CI: 0.01–0.02) per 100,000 person-years (PY), respectively. These rates have remained stable during the follow up period of this study.[22]

A number of occupational cohorts have been studied to assess the risk of incidence and mortality from asbestosis. The Environmental Protection Agency of the USA revised in 1986 the health effects of airborne asbestos[23] reviewing a number of occupational cohorts. The study of Berry et al.[24] was considered influential: it reported an association between exposure indices and asbestosis incidence, concluding that there was a near-linear relationship with cumulative exposure, but the study was limited by a high degree of uncertainty in the estimates of asbestosis prevalence at low exposures.

Subsequent cohort analyses considering chrysotile textile workers showed a strong exposure-response relationship between chrysotile exposure and asbestosis mortality.[25,26] However, also in these studies the risk of asbestosis at low exposure levels remains unclear. A study on British asbestos workers who underwent periodic medical examinations found that the incidence of the disease was influenced not only by exposure duration, but also by factors such as birth cohort, age, year at initial exposure, latency, and job type.[27] In the general population, the specific occupation is considered a reliable predictor of asbestosis, as activities exposing to high intensities are associated with a higher likelihood of developing asbestosis.[28]

To the best of our knowledge, there have been no studies on the effect of competing causes of death for the asbestosis mortality. This aspect bears a relevant significance because subjects suffering from asbestosis are prone to respiratory infections and cardiovascular diseases as well. Additionally, these patients face an increased risk of other diseases associated with asbestos exposure, which include several types of cancer, particularly pleural and peritoneal mesothelioma, and lung cancer.[29] As a mark of occupational asbestos exposure, occupational cohorts with a diagnosis of asbestosis showed an increase in mortality, with strong excess for malignant neoplasms,[30] and an augmented incidences for lung cancer, mesothelioma, breast cancer, and endometrial carcinoma.[31] Furthermore, exposure to asbestos increased the risk of death from nonmalignant causes, particularly cardiovascular disease.[32]

An additional factor in assessing the potential impact of competing risk is represented by the presence of differences in time period (latency) between the first exposure and a diagnosis of an asbestos-related disease: for example, the incidence of lung cancer among asbestos workers peaks within about 20–40 years after the first exposure, whereas the incidence of new pleural and peritoneal mesotheliomas reach its highest point later (40–50 years).[33]

In the present study, we used data from a large cohort of asbestos-cement (AC) workers,[33–35] the aim of the current study is to assess the relationship between cumulative asbestos exposure and the risk of death from asbestosis, taking into account competing causes of death: lung cancer, pleural, peritoneal mesothelioma, and diseases of the circulatory system. To evaluate and interpret the results, we considered as a reference value the cumulative exposure threshold limit value (TLV) of 25 fibers/mL-years because of its importance in previous assessments and evaluations.[2]

2 | METHODS

2.1 | Historical considerations on the use of cumulative exposure index (CEI)

In Italy, asbestosis has been included in the list of compensable occupational diseases since the 1940s.[36] The legislation in force required that exposure at work should be prevented using the best available technology, without defining a standard, that is, an exposure level that should not be exceeded. TLVs were introduced in Italy in 1991 in line with European legislation. However, the TLV proposed by the American Conference of Governmental Industrial Hygienists (ACGH) have largely been used as a reference when measuring asbestos fibers in ambient air (that has taken place more frequently only since the 1980s). As a result, the data available to characterize the intensity of asbestos exposure for the factories and workers studied are rather scarce. For this reason the exposure assessment for the subjects of the cohort was based on estimates, as reported in the methods section.

2.1.1 | AC factories

The study concerns the follow up of the workers of 21 Italian AC factories,[33] for a total of 13,076 subjects. In summary, information regarding vital status was obtained from either the local death registries or from the civil registry offices at the individual's place of residence. The length of the follow-up varied between cohorts: the workers of four factories were followed until December 31, 2010, while for the remaining 17 cohorts the follow-up closed on December 31st, 2012 (see Supporting Information S1: Tables 1). Causes of death were provided by the Registries of Causes of Death for deaths after 1985, run by Local Health Authorities, and for earlier years by the Registrar's Office of the municipality in which the death occurred. We started the follow-up from the January 1, 1960 dropping those subjects lost to follow-up or who died before that date ($n = 113$). Expected deaths (used to compute Standardized Mortality Ratios [SMRs]) were based on regional mortality rates by cause, sex, and year provided by the National Institute of Statistics (ISTAT), available since 1970. Accordingly, SMR analyses were restricted to PY and events occurring after January 1, 1970; subjects lost to follow-up or who died before that date were excluded ($n = 385$). The underlying cause of death was coded in compliance with the International Code of Diseases at the date of death (ICD 8th, 9th, and 10th revisions). The cause of death analyzed are asbestosis, lung cancer, primary pleural tumor and pleural mesothelioma, peritoneal tumour and peritoneal mesothelioma, asbestosis, diseases of the circulatory system, and other causes of death.

2.1.2 | Exposure assessment

Due to the scarcity of data available to characterize the intensity of asbestos exposure for the factories and workers studied, as in previous studies[33,35] a cumulative average exposure index (CEI) was derived for each worker by hygienist estimates, and calculated as the sum of the Average Exposure Index (AEI), considering the contribution of all periods of work (pw) as follows

$$CEI = \sum_{pw} AEI_{pw},$$

where AEI was computed for each factory and year as the weighted average of direct and indirect exposures, weighted by the size of the workforce

$$AEI_{pw} = (E_{dpw} \cdot w_{dpw} + E_{ipw} \cdot w_{ipw}),$$

where E_{dpw} and E_{ipw} are the direct and indirect exposure levels (in fibers/milliliters, ff/mL), respectively; w_{dpw} and w_{ipw} are the time variable weighs for those exposures. Concentrations and the amount of direct and indirect exposures varied across time periods and CEI is a proxy of the cumulative amount of asbestos exposure for each individual.

2.1.3 | Statistical analyses

We analyzed categorical variables using frequency tables. To test for differences, we utilized exact Fisher's test (due to the presence of cells with counts lower than five). SMRs were calculated as the ratio between observed and expected deaths, the latter computed using an 5 years age-period indirect standardization and regional mortality rates. Byar's 95% CI were computed. To assess the role of asbestos exposure on asbestosis mortality, we used a cause-specific (CS) time-dependent Cox regression model with a temporal window, that started from the date of assumption or the January 1, 1960 if the subject was hired before. As exposure index we included the CEI variable in both continuous and categorical variable as follows: ≤6.25, 6.25–12.5, 12.5–25, 25–50, 50–100, >100 fibers/milliliters–years (ff/mL-years). In addition the model was adjusted by 5-year age-classes (≤45, 45–50,..., 85–90, >90), age at first employment (AFE; ≤20, 20–29, 30–39, 40–49, >50), and year of first employment (YFE; ≤1950, 1950–60, 1960–70, 1970–80, >1980). Due to the extended follow-up period and a time-varying cumulative exposure, the time-dependent variable was obtained by splitting the follow-up period by 5 years, thus obtaining a time-dependent data set for all the variables of interest (197,741 5-year periods). The baseline mortality function was stratified by gender (Schoenfeld's test p Value less than 5% in Cox models for age covariate). Risks were expressed as Hazard Ratios (HR), calculated by exponentiating regression coefficients, and their relative 95% CI. In addition, dose–response mortality was examined using the CEI in continuous form, using a flexible approach based on a penalized B-spline base function with nodes equally spaced across the exposure range. The number of B-splines bases was selected by minimizing the Bayesian Information Criterion (BIC) value. The model was designed to assess the risk within the cohort and to provide insight into its variation with respect to a fixed reference exposure level of 25 ff/mL-years (for 25 ff/mL-years the HR is fixed to 1). The influence of competing causes of death (lung cancer, pleural and peritoneal mesothelioma, and circulatory system diseases) was tested through a Fine and Gray regression model using the sub-distribution (SD) proportional hazards function. A sensitivity analysis including a single competing disease at a time assessed their contribution on the dose–response estimates for asbestosis mortality. Statistical significance was set at 5%. All analyses were performed using the R statistical software (version 4.3) with the R package *survival* to estimate both Cox and Fine and Gray regression models.

3 | RESULTS

Of the 12,963 workers, we recorded a total of 6196 deaths. Deaths included 6% from asbestosis, 12.5% from lung cancer, 5.7% from pleural mesothelioma, 1.9% from peritoneal mesothelioma, and 26.4% from diseases of circulatory system. Half of the study population worked in three large cement-asbestos factories, Eternit in Casale Monferrato, Eternit in Bagnoli and Fibronit in Broni (Supporting Information S1: Table 1). The distribution of deaths differed by sex (Table 1 and 2; $p < 0.001$). Workers who died from pleural and peritoneal mesothelioma started work at an earlier age ($p < 0.001$). Deaths from lung cancer and asbestosis occurred mostly in workers born before 1929 ($p < 0.001$). Peritoneal mesothelioma and asbestosis were less common in workers with less than 10 years' experience (19% and 11% respectively; $p < 0.001$). Time Since First Exposure (TSFE) influenced death patterns, with asbestosis becoming the leading cause in higher TSFE (Supporting Information S1: Figure 1). Median survival from initial exposure was 44 years for asbestosis, longer than for lung cancer (35.8 years), cardiovascular disease (38.1 years) and pleural mesothelioma (40.6 years), and slightly shorter than for peritoneal mesothelioma (45.7 years; Supporting Information S1: Figure 2). In the study population, the median CEI was 22 ff/mL-years (Supporting Information S1: Table 2; range: 0.01-267.3 ff/mL-years), with very high exposures among asbestosis deaths (41% > 100 ff/mL-years; Supporting Information S1: Table 3). Among women, no asbestosis deaths were recorded in the lowest CEI category (≤6.25 ff/mL-years), but the SMR increased in each subsequent category. As shown in Table 3, HRs for all models increased in all age groups, with a peak in the [80–85] years age group, followed by a modest decrease. Higher AFE values were associated with HRs less than 1 compared to the reference category ≤ 20 years.

There are similarities and differences in the risk estimates between the model without competing causes of death (CS model) and the model with competing causes of death (SD model). More severe exposures, as estimated by the CEI, showed a statistically significant increased risk, especially for the CS model. In this model,

TABLE 1 Main characteristics of the asbestos-cement cohorts, overall and by cause of death.

	Overall N = 12,963[a]	LC N = 879[a]	Asbestosis N = 416[a]	Pleural M. N = 400[a]	Perit. M. N = 135[a]	CD N = 1835[a]	Other N = 3296[a]	p Value[b]
Gender								<0.001
Males	10,617 (82%)	839 (95%)	365 (88%)	309 (77%)	103 (76%)	1,520 (83%)	2,753 (84%)	
Females	2346 (18%)	40 (4.6%)	51 (12%)	91 (23%)	32 (24%)	315 (17%)	543 (16%)	
AFE								<0.001
≤20	2571 (20%)	99 (11%)	63 (15%)	101 (25%)	56 (41%)	180 (9.8%)	400 (12%)	
(20–30)	5134 (40%)	296 (34%)	156 (38%)	164 (41%)	49 (36%)	501 (27%)	1,031 (31%)	
(30–40)	3178 (25%)	290 (33%)	139 (33%)	98 (25%)	25 (19%)	573 (31%)	1,049 (32%)	
>40	2080 (16%)	194 (22%)	58 (14%)	37 (9.3%)	5 (3.7%)	581 (32%)	816 (25%)	
YFE								<0.001
≤1950	1631 (13%)	135 (15%)	172 (41%)	71 (18%)	44 (33%)	427 (23%)	664 (20%)	
(1950–1960)	3133 (24%)	300 (34%)	136 (33%)	126 (32%)	56 (41%)	575 (31%)	992 (30%)	
(1960–1970)	4453 (34%)	332 (38%)	97 (23%)	153 (38%)	30 (22%)	613 (33%)	1171 (36%)	
(1970–1980)	2088 (16%)	84 (9.6%)	10 (2.4%)	38 (9.5%)	5 (3.7%)	168 (9.2%)	319 (9.7%)	
>1980	1658 (13%)	28 (3.2%)	1 (0.2%)	12 (3.0%)	0 (0%)	52 (2.8%)	150 (4.6%)	
Birth cohort								<0.001
≤1920	2252 (17%)	209 (24%)	178 (43%)	46 (12%)	20 (15%)	743 (40%)	1004 (30%)	
(1920–1930)	3,038 (23%)	327 (37%)	174 (42%)	137 (34%)	44 (33%)	655 (36%)	1109 (34%)	
(1930–1940)	3510 (27%)	277 (32%)	54 (13%)	131 (33%)	59 (44%)	338 (18%)	830 (25%)	
(1940–1950)	1947 (15%)	55 (6.3%)	10 (2.4%)	68 (17%)	11 (8.1%)	66 (3.6%)	239 (7.3%)	
>1950	2216 (17%)	11 (1.3%)	0 (0%)	18 (4.5%)	1 (0.7%)	33 (1.8%)	114 (3.5%)	
Duration of work								<0.001
≤10	6943 (54%)	333 (38%)	44 (11%)	125 (31%)	26 (19%)	791 (43%)	1516 (46%)	
(10–20]	2888 (22%)	244 (28%)	130 (31%)	95 (24%)	37 (27%)	492 (27%)	861 (26%)	
(20–30]	2291 (18%)	225 (26%)	154 (37%)	129 (32%)	45 (33%)	381 (21%)	693 (21%)	
>30	841 (6.5%)	77 (8.8%)	88 (21%)	51 (13%)	27 (20%)	171 (9.3%)	226 (6.9%)	

Abbreviations: AFE, age at first exposure; CD, circulatory system diseases; LC, lung cancer, Other, other causes of death; Perit. M., peritoneal mesothelioma; Pleural M., pleural mesothelioma; YFE, year at first exposure.

[a]*n* (%);

[b]Fisher's Exact Test for Count Data with simulated *p* Value (based on 2000 replicates.

TABLE 2 Deaths due to asbestosis[a], crude death rates (x100,000), expected deaths, and SMR with 95% CI by cumulative exposure index (CEI) class (ff/mL-years).

	Males				Females			
CEI class	Deaths (*n*)	Crude death rates (x100,000)	Exp. deaths (*n*)	SMR (95% CI)	Deaths (*n*)	Crude death rates (x100,000)	Exp. deaths	SMR (95% CI)
≤6.25	9	7.36	0.10	91.8 (42.0–174)	0	-	-	-
(6.25–12.5)	4	13.7	0.04	107 (29.1–274)	2	24.2	<0.01	1693 (205–6116)
(12.5–25)	8	31.3	0.04	200 (86.5–395)	2	18.6	<0.01	1152 (140–4163)
(25–50)	43	86.1	0.09	501 (362–675)	4	30.7	<0.01	1789 (487–4581)
(50–100)	149	234	0.14	1089 (921–1278)	18	119	<0.01	6272 (3717- 9913)
>100	135	708	0.05	2805 (2352–3320)	25	264	<0.01	12,354 (7995–18,237)

Abbreviations: CI, confidence interval; ff/mL-years, fibers/milliliters–years; PY, person-years; SMR, standardized Mortality Ratios.

[a]analysis restricted to follow-up after January 1, 1970 (388,914 PY, 399 deaths for asbestosis).

TABLE 3 HR and 95% CI for asbestosis mortality using cause-specific (CS) Cox regression models and sub-distribution (SD) Fine and Gray model.[a]

Predictor	CS-Cox Model			SD-Fine and Gray Model		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age group						
≤45	0.02	0.01–0.04	<0.001	0.01	0.00, 0.03	<0.001
(45, 50)	0.10	0.06–0.19	<0.001	0.09	0.05, 0.16	<0.001
(50, 55)	0.17	0.11–0.29	<0.001	0.15	0.10, 0.25	<0.001
(55, 60)	0.34	0.23–0.51	<0.001	0.32	0.21, 0.47	<0.001
(60, 65)	0.55	0.38–0.79	0.001	0.54	0.38, 0.77	<0.001
(65, 70)	1.00	–		1.00		
(70, 75)	1.88	1.36–2.58	<0.001	2.00	1.45, 2.75	<0.001
(75, 80)	3.48	2.48–4.89	<0.001	3.81	2.73, 5.32	<0.001
(80, 85)	5.57	3.66–8.48	<0.001	6.38	4.24, 9.64	<0.001
>85	4.07	1.82–9.12	<0.001	5.16	2.29, 11.7	<0.001
AFE				–	–	
≤20	1.00	–				
(20, 30)	0.89	0.65–1.21	0.4	0.84	0.61, 1.14	0.3
(30, 40)	0.75	0.54–1.06	0.10	0.58	0.42, 0.80	0.001
>40	0.60	0.38–0.96	0.033	0.31	0.20, 0.48	<0.001
CEI category						
≤6.25	1.00	–		1.00	–	
(6.25–12.5)	1.72	0.61–4.85	0.3	1.61	0.57, 4.50	0.4
(12.5–25)	2.42	0.98–5.97	0.055	2.03	0.83, 5.01	0.12
(25–50)	5.75	2.80–11.8	<0.001	4.76	2.33, 9.73	<0.001
(50–100)	13.0	6.59–25.8	<0.001	9.45	4.83, 18.5	<0.001
>100	21.1	10.2–43.7	<0.001	9.36	4.73, 18.5	<0.001
CEI continuous (+10 ff/mL-years)	1.17	1.14–1.20	<0.001	1.08	1.06–1.10	<0.001
CEI continuous restricted to ≤ 100 ff/mL-years (+10 ff/mL-years)	1.32	1.25–1.39	<0.001	1.26	1.21–1.31	<0.001

Note: CEI evaluated in categorical and continuous form.

Abbreviations: AFE, age at first employment; CI, confidence interval; CEI, cumulative exposure index; ff/mL-years, fibers/milliliters–years; PY, person-years; SMR, standardized Mortality Ratios.

[a]as competing causes of death we considered lung cancer, pleural mesothelioma, peritoneal mesothelioma, and diseases of the circulatory system.

the value of the HR relative to the reference (≤6.25 ff/mL-years) was greater than 1 in all CEI classes and was statistically significant from the [25–50] ff/mL-years category onwards, reaching extremely high HRs. For the CEI category 12.5–25, a greater than twofold increase in risk for asbestosis mortality was observed in the CS model along with a borderline statistical significance. For the SD model, the increasing trend in risk stopped from the [50–100] ff/mL-years category. Considering the models with CEI in continuous form, for each 10 ff/mL-year increase there was a 17% (95% CI: 14–20%) and 8% (95% CI: 6–10%) increase in risk for the CS and SD models, respectively.

Restricting the analysis to 5-year periods with a CEI between 0 and 100 ff/mL-years, we found a stronger dose–response relationship with an overall increase in HR of 32% and 26% for each 10 ff/mL-year increase for the CS and SD models, respectively. In the SD model, there was a decrease in HR values when considering the inclusion of one competing disease at a time, which was greater with the inclusion of circulatory diseases and lung cancer (Table 4).

In the CS model, the number of penalized B-splines was set to 8. A strong association between asbestosis mortality and CEI was observed for the whole range of exposures (Figure 1). Taking as

TABLE 4 HR and 95% CI for asbestosis mortality by sub-distribution (SD) Fine and Gray model by including only one competing cause at a time.

	Competing cause of death included										
	LC			Pleural M.			Perit. M.			CD		
Characteristic	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
CEI category												
≤6.25	–	–		–	–		–	–		–	–	
(6.25–12.5)	1.66	0.59, 4.65	0.3	1.70	0.61, 4.76	0.3	1.72	0.61, 4.81	0.3	1.66	0.59, 4.65	0.3
(12.5–25)	2.26	0.92, 5.58	0.076	2.36	0.96, 5.81	0.062	2.39	0.97, 5.90	0.058	2.16	0.88, 5.32	0.094
(25-50)	5.29	2.59, 10.8	<0.001	5.52	2.70, 11.3	<0.001	5.66	2.77, 11.6	<0.001	5.17	2.53, 10.6	<0.001
(50–100)	11.4	5.84, 22.3	<0.001	12.3	6.28, 24.0	<0.001	12.7	6.49, 24.9	<0.001	10.8	5.55, 21.2	<0.001
>100	15.9	7.94, 31.7	<0.001	18.3	9.12, 36.9	<0.001	19.8	9.79, 39.9	<0.001	12.4	6.23, 24.7	<0.001
CEI continuous (+10 ff/mL-years)	1.13	1.11, 1.16	<0.001	1.15	1.12, 1.17	<0.001	1.16	1.13, 1.19	<0.001	1.10	1.08, 1.12	<0.001

Note: CEI evaluated in categorical and continuous form.

Abbreviations: CI, confidence interval; CD, diseases of the Circulatory System; CEI, cumulative exposure index; HR, hazard ratio; ff/mL-years, fibers/milliliters–years; LC, lung cancer; Perit. M., peritoneal mesothelioma; Pleural M., Pleural Mesothelioma.

FIGURE 1 Asbestosis mortality in cohorts from Italian cement asbestos factories. Adjusted* HRs (black) and 95% CI (red) estimated by CS (top) and SD (bottom) regression model by CEI (ff/mL-years). In blue the CEI values for asbestosis deaths. *adjusted by age (reference category (65-70] years), and AFE (reference category ≤ 20 years). The HR is fixed to 1 for a CEI of 25 ff/mL-years. CI, confidence interval; CD, diseases of the Circulatory System; CEI, cumulative exposure index; HR, hazard ratio; ff/mL-years, fibers/milliliters–years; LC, lung cancer.

reference the age group [65–70] years, the lowest AFE category (≤20 years) and a CEI of 25 ff/mL-years, the adjusted HR showed HRs above 10 for higher CEIs (>175 ff/mL-years). For the SD model, we selected a total of 4 penalized spline bases. The HR showed a similar trend to the CS model up to 50 ff/mL-years, a peak HR of about 4 at 80 ff/mL-years and a flattening at higher exposure levels.

4 | DISCUSSION

The study presents an analysis of the relationship between asbestos exposure and risk of death from asbestosis, taking into account the influence of known competing causes of death due to asbestos exposure, namely lung cancer, pleural and peritoneal mesothelioma, and diseases of the circulatory system. The Cox regression models, which examined cumulative exposure in both a categorical and continuous form, showed an increasing trend in asbestosis mortality over the whole range of cumulative exposures to asbestos. The results of the Fine and Gray regression model showed an initial increase in risk similar to that found by Cox regression, followed by a peak at 80 ff/mL-years and then a levelling off.

Studies analyzing the incidence of asbestosis have reported a clear association with asbestos exposure in occupationally exposed cohorts.[37] In the past, several studies have attempted to identify

appropriate TLVs for occupational exposure to asbestos to prevent the development of asbestosis and to prevent severe disability and death: Berry et al.[24] estimated a prevalence of asbestosis of 2% to 24% associated with exposure of 2 ff/mL over 30–50 years, corresponding to a cumulative exposure of 60–100 ff/mL-years; Huang et al.[38] estimated that a prevalence of asbestosis of about 2% would affect workers over a 35-year working life if exposed to 1 ff/mL, proposed as the maximum permissible asbestos concentration, corresponding to a cumulative exposure of 35 ff/mL-years.

The 2014 revision of the Helsinki Criteria[2] stated that "A cumulative exposure of 25 fiber-years is estimated to increase the risk of lung cancer twofold, clinical cases of asbestosis may occur at comparable cumulative exposure." However, this so-called threshold derived from preceding epidemiological studies does not appear to be as stringent as the one the US Occupational Safety and Health Administration (OHSA) in 1994 set as a limit for occupational asbestos concentrations of up to 0.1 ff/mL, which corresponds to a cumulative exposure of 3 ff/mL-years, assuming a working life of 30 years.[39]

Although our analysis was limited to an internal comparison of mortality rates between different exposure categories, and thus the resulting internal validity implies that the results are dependent on the distribution of exposure levels across the cohort pool, we found an increasing trend similar to previous studies.[40] Interestingly, we found an increasing trend in the initial cumulative exposure segment of 0–25 ff/mL-years associated with high SMRs within this exposure window, suggesting a dose–response relationship between asbestos exposure and the risk of death from asbestosis even at relatively low exposures. Undoubtedly, the mortality of asbestosis is much lower than its incidence, since the severity of disease progression and disability vary depending on the intensity of exposure and individual variability. Considering cohorts of workers compensated for asbestosis, out of 631 Italian female workers only 38 (6%) deceased for asbestosis,[30] while among 1391 Polish workers, 62 (4.5%) died of respiratory system diseases (including asbestosis).[41]

In this study we did not take into account the commercial type of asbestos (amphiboles—amosite and crocidolite—vs. chrysotile) using a weighting potency factor for mesothelioma and lung cancer risk as done in our previous work,[33–35] since the incidence and progression of asbestosis is primarily associated with the intensity and duration of exposure to asbestos, rather than the type of fiber.[42]

Survival analysis for competing risks help to understand the natural history of asbestos-related disease, complementing the picture painted by the traditional CS approach. The Fine and Gray sub-distribution hazard model is generally recommended when the focus is on forecasting incidence to predict prognosis,[43] but our application was aimed at assessing the influence of competing diseases on asbestosis mortality. Indeed, the stronger the dose–response relationship between asbestos exposure and competing events, the greater the likelihood that competing events would become censoring events.[44] Lower risk estimates were found in the SD regression models in this study, because the CEI was associated with an increased CS HR for the competing deaths considered.[44] We showed that the main competing cause of death that most influenced asbestosis mortality was diseases of the circulatory system, followed by lung cancer. This is mainly due to the fact that deaths due to diseases of the circulatory system represented a higher proportion than the other competing causes considered. Moreover, from a pathophysiological point of view, certain diseases of the circulatory system may be a consequence of the impairment of the respiratory system caused by fibrosis of the lungs. Principal among these is cor pulmonale—right-sided heart failure.[32,45,46] In the case of lung cancer and, in particular, mesothelioma, exposure to asbestos increases the risk of developing these diseases even in the absence of underlying asbestosis.

A limitation of this study was that the exposure index used did not adequately capture individual differences among cohort members in terms of the task and activity performed, due to the aggregation of different exposures at the factory level. More detailed exposure information could support more in-depth studies. Fiber measurements were generally carried out using light microscopy; the increasing use of electronic microscopy may help to improve the quality of future risk assessments, particularly where asbestos use is not yet banned, by incorporating detailed fiber characteristics into the analysis. Furthermore, for at least three decades after the Second World War, Italian legislation introduced compensation for asbestosis in manufacturing sectors such as asbestos cement, aimed at supporting laid-off workers during periods of production crisis. Consequently, when these workers died at an advanced age, asbestosis could be attributed as the cause of death, even when it manifested itself as cardio-respiratory failure. However, the potential overestimation of asbestosis-related deaths may be offset by a concurrent underestimation due to the limitations of older generation diagnostic tools, which were less able to detect pathology before it became clearly visible.

In summary, this study successfully compiled a significant number of subjects who were employed in various asbestos cement companies, providing a representative sample of this production sector in Italy. It encompasses major factories owned by multinational corporations that commenced operations in the post-war period, as well as smaller companies that emerged in the 1960s. A consistent number of asbestosis deaths was observed over the extended follow-up period of the cohort studied. Our results suggest that even below the level of 25 ff/mL-years, workers were not adequately protected by the safety legislation in force in Italy and that this may have important consequences in countries where asbestos is still used. In addition to deaths due to asbestosis, a large number of additional competitive deaths related to asbestos exposure were observed. The mortality profile allowed us to investigate the dose–response relationship of asbestosis mortality. The presence of a long follow-up and a high level of completeness in the follow-up allowed a satisfactory level of assessment. The results suggest an increasing trend in risk, even at low levels of exposure, and highlight the inadequacy of the proposed TLVs for the prevention of disability and mortality in exposed workers.

AUTHOR CONTRIBUTIONS

Conceptualization: Paolo Girardi, Sara Rigoni, Daniela Ferrante, Francesco Barone-Adesi, and Corrado Magnani. *Methodology*: Paolo

Girardi, Sara Rigoni, Daniela Ferrante, Stefano Silvestri, Alessia Angelini, Francesco Barone-Adesi, and Corrado Magnani. *Software*: Paolo Girardi and Sara Rigoni. *Validation*: Paolo Girardi, Sara Rigoni, Daniela Ferrante, Francesco Barone-Adesi, and Corrado Magnani. *Formal analysis*: Paolo Girardi, Sara Rigoni, Daniela Ferrante, Francesco Barone-Adesi, and Corrado Magnani. *Investigation*: Paolo Girardi, Sara Rigoni, Daniela Ferrante, and Corrado Magnani. *Resources*: Paolo Girardi, Daniela Ferrante, and Corrado Magnani. *Data Curation*: Paolo Girardi, Sara Rigoni, Daniela Ferrante, Stefano Silvestri, Alessia Angelini, and Corrado Magnani. *Writing—original draft preparation*: Paolo Girardi, Sara Rigoni, and Corrado Magnani. *Writing—review and editing*: all the authors. *Visualization*: All the authors. *Supervision*: Paolo Girardi and Corrado Magnani. *Project administration*: Daniela Ferrante and Corrado Magnani. *Funding acquisition*: Daniela Ferrante, Alessandro Marinaccio, and Corrado Magnani.

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CONFLICT OF INTEREST STATEMENT

The following authors reported that they served as expert witness in court trials on asbestos related diseases: S. S., A. A., E. O., F. B.- A., E. M., and C. M. The remaining authors declare that there are no conflicts of interest.

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

The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND INFORMED CONSENT

The main study was approved by the University of Eastern Piedmont's Ethical Review Board (authorization CE 112/13, July 12th, 2013), while the principal investigators (PI) of each cohort submitted the individual studies to the corresponding local boards.

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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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