ORIGINAL ARTICLE

Italian pool of asbestos workers cohorts: mortality trends of asbestos-related neoplasms after long time since first exposure

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ABSTRACT

Objective Asbestos is a known human carcinogen, with evidence for malignant mesothelioma (MM), cancers of lung, ovary, larynx and possibly other organs. MM rates are predicted to increase with a power of time since first exposure (TSFE), but the possible long-term attenuation of the trend is debated. The asbestos ban enforced in Italy in 1992 gives an opportunity to measure long-term cancer risk in formerly exposed workers.

Methods Pool of 43 previously studied Italian asbestos cohorts (asbestos cement, rolling stock, shipbuilding), with mortality follow-up updated to 2010. SMRs were computed for the 1970â€"2010 period, for the major causes, with consideration of duration and TSFE, 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. Mortality was significantly increased for all deaths (SMR: men: 1.05, 95% CI 1.03 to 1.06; women: 1.17, 95% CI to 1.12 to 1.22), all malignancies combined (SMR: men: 1.17, 95% CI to 1.14 to 1.20; women: 1.33, 95% CI 1.24 to 1.43), pleural and peritoneal malignancies (SMR: men: 13.28 and 4.77, 95% CI 12.24 to 14.37 and 4.00 to 5.64; women: 28.44 and 6.75, 95% CI 23.83 to 33.69 and 4.70 to 9.39), lung (SMR: men: 1.26, 95% CI 1.21 to 1.31; women: 1.43, 95% CI 1.13 to 1.78) and ovarian cancer (SMR=1.38, 95% CI 1.00 to 1.87) and asbestosis (SMR: men: 300.7, 95% CI 270.7 to 333.2; women: 389.6, 95% CI 290.1 to 512.3). Pleural cancer rate increased during the first 40 years of TSFE and reached a plateau after.

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. Pleural cancer mortality reached a plateau at long TSFE, coherently with recent reports.

What this paper adds

- Asbestos is a known human carcinogen largely diffused in occupational and environmental setting, nowadays in particular in low-income, middle-income countries.
- We conducted a large cohort study pooling 43 Italian industrial cohorts of asbestos using industries to update mortality analyses in former exposed workers and to study cancer risk after over 40 years of time since first exposure.
- Results in this first report of the project confirm the increased risk for pleural and peritoneal malignancy, lung and ovarian cancer and asbestosis and also suggest an increased risk for bladder cancer, but give little support to the association with other cancers.
- Risk of death for pleural malignancies flattens after long time since first exposure. This result is not compatible with the traditional model which predicts a continuous exponential increase in risk of mesothelioma. These results prompt a revision of the model and have practical implication for prevention, risk apportionment and forecasts of future burden of disease.

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INTRODUCTION

Asbestos is among the most widely diffused occupational carcinogens: 107 000 deaths caused by asbestos exposure were estimated each year worldwide, including lung cancer, malignant mesothelioma (MM) and asbestosis.[1] According to the International Agency for Research on Cancer (IARC), there is sufficient evidence that asbestos fibres cause cancers of the lung and larynx, of the serosae (pleura, peritoneum) and of the ovary. Evidence of carcinogenicity was limited for pharynx, stomach and colon and rectum neoplasms.[2]

The functional relationship between asbestos exposure, time since first exposure (TSFE) and cancer has been studied in asbestos workers cohorts

and is a matter of current discussion, particularly for MM.[3] On the basis of early results, MM incidence was observed to increases as a power of TSFE.[4–6] More recently, Berry suggested that on the long run the increase in incidence may slow down and a negative exponential term should be added in the model to describe a downward curvature.[7] Moreover, differences were shown according to the MM site: a pooled analysis showed that the trend in MM risk slowed down after about 45 years of TSFE for pleural, but not for peritoneal, MM.[8] Epidemiological studies capable of investigating these questions must cover very long periods, at least 40 years after first exposure and have a large size.[8–12] Studies with similar characteristics will be helpful also to investigate the full spectrum of tumours associated to asbestos exposure.

Italy has been a large producer and user of asbestos and asbestos products. The apparent national consumption of asbestos gradually increased to 132 358 tons in 1970, peaked at 180 528 tons in 1980 and declined afterwards.[13] The largest use was in asbestos cement production, followed by fire proofing and thermal insulation in shipbuilding and railway carriages. According to CAREX, the number of Italian workers definitely exposed was 352 691 in 1990–1993, dropping to 76 100 in 2005.[14] The use of asbestos was definitely interrupted in 1994 following a law-enforced ban on production, import, export, use and trading (Law 257/1992). The ban had been preceded by the implementation since 1983 of European Union Directives on permissible occupational exposure levels and the limitation of use in some applications and products (Council Directive 83/477/EEC of 19 September 1983).

Current asbestos production worldwide is about 2 million tons and is limited to chrysotile.[13] Its use is concentrated in emerging economy countries, where information on work conditions, number of exposed workers and frequency of asbestos-related diseases is limited.[15 16]

Our project was designed as a large pool of Italian cohort studies, with multiple aims, including to evaluate the burden of asbestos-related diseases in former asbestos workers, to assess the occurrence of cancers with limited evidence of association and to investigate the role of time-related factors in disease occurrence. It is part of the 'Asbestos Project' coordinated by the Italian National Institute of Health (ISS), as prompted by the conclusions of the second Governmental Asbestos Conference.[17 18]

This first report describes the pooled cohort and provides results on cause-specific mortality, and on mortality for selected causes by duration of employment and TSFE, using external references.

MATERIALS AND METHODS

We aimed at including as many as possible Italian cohorts already investigated in the past with mortality follow-up and providing, once updated, an observation period >40 years. After a literature search including also unpublished reports, eligible cohorts were identified, principal investigators invited, data updated and pooled. Participation required the pooling of individual records for all the workers in the cohorts. Only anonymised data were pooled, nominal data remaining at the local study level.

Online supplementary table 1 lists the 43 cohorts, with information on location, use of asbestos, industrial sector and number of workers and references.

The study was submitted to the University of Eastern Piedmont Ethical Review Board (Authorisation CE 112/13, 12 July 2013) and to the corresponding boards of participating institutions.

Follow-up, including causes of death ascertainment, was carried out by each research unit, using common procedures. The Registrar's Offices of the town of residence were accessed to obtain the information on vital status, according to a procedure tested in Italian cohort studies.[9] The causes of death were provided by the Local Health Authority Registries of Causes of Death for decedents after 1985 and by the Registrar Office of the municipality where death occurred for earlier years. The underlying cause of death was coded according to the International Classification of Disease (ICD), 8th, 9th and 10th revisions, according to the date of death. ICD 10th revision in Italy is used from 2003. Limited to the last two decades and the regions where files of residents and causes of death are kept at the regional level (Tuscany for both, Veneto and Emilia-Romagna for causes of death), information was obtained from the regional data. The date of follow-up varied depending on the most recent available update of files but it was required to be at least 31 December 2010.

After the completion of follow-up, each research unit forwarded to the study coordination the anonymised list of workers in each cohort. The following information was included: sex, date of birth, vital status, date of follow-up (either date of death for decedents or date of most recent observation for alive and lost subjects), cause of death and date of start and finish of each period of employment.

Quality control led to the exclusion of 2453 records (4.5% of the initial 54 436), distributed over all industrial sectors and most cohorts, as follows: incomplete working periods, conflicting dates or impossible hiring or retirement age (n=737); first employment after the asbestos ban, set on 1 January 1993 (n=594); because of follow-up incompleteness, two cohorts (ie, the asbestos cement factories of Eternit-Bagnoli and Fibronit–Broni), were limited to the workers hired after 1 January 1950 (n=1122). Workers employed in different cohorts were identified according to initials, gender and birth date, with enquiries to the study coordinators, and were annotated: 174 workers were included in two cohorts and 4 in 3. Their work histories were merged in the pooled analyses. The total pooled cohort included 51 801 individuals. Online supplementary figure 1 presents a flow chart.

Statistical analyses were based on person-years and SMRs (ratio of observed to expected deaths using indirect standardisation).[19] Workers contributed person-years until their follow-up date. Duration of exposure was computed by summing up all employment periods in the cohort. TSFE (latency) 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. The set of rates was prepared by the National Institute of Health—ISS, using mortality and population figures provided by the National Institute of Statistics—ISTAT for years from 1970 on.[20] Correspondingly, present analyses were restricted to person-years and events after 1 January 1970. Person-years and events occurring earlier were counted for descriptive purposes only.

We computed SMRs for the major causes of death. We included the asbestos-associated causes of death (pleural and peritoneal malignant neoplasm or MM, cancers of lung, larynx and ovary, and asbestosis), and those with limited evidence of association, following IARC evaluation.[2] The causes connected to the healthy worker effect (HWE), in particular respiratory, cardiovascular and gastrointestinal diseases, were also included.[19] The list of causes was decided a priori. Online supplementary table 2 presents the ICD codes.

SMRs were adjusted by age, period, sex and region and the analyses are presented stratified by sex and time-related variables: TSFE, duration, calendar period and period of first exposure. Linear trends were tested.[19] Statistical significance was set at 5%. CIs were computed according to the Poisson distribution of observed deaths, at the 95% CI value.[19] Variation among cohorts was evaluated using graphical methods and the computation of χ^2 test for heterogeneity.[19]

Data were prepared using MS Access and SAS V.9.2. Analyses were carried out using OCMAP plus, STATA V.11 and SAS V.9.2.

RESULTS

The cohort included 51 801 workers (46 060 men and 5741 women). Main industrial activities were asbestos cement (13 076 workers), rolling stock (carriages and engines) construction and maintenance (23 810, of which 11 021 employed by the Italian Railways, including 2626 workers of the 'Special Maintenance Workshops' (OGR) and 12 789 by other private firms), shipyards (5120) and related activities (1170), glassworks (3727), harbour and dockyard workers (1939), different industrial categories (835 workers), a cohort of Italian miners in Wittenoom (300) and a non-occupational cohort of asbestos cement workers' wives (1777). Table 1 presents the distribution of subjects and person-years by industrial activity sector, year and age at first employment in the cohort, TSFE and vital status at follow-up: total number of person-years after 1 January 1970 was 1 430 713 for men and 184 940 for women.

Follow-up was successful for 98.5% of workers (98.5% for men and 98.6% for women), the remaining being lost to follow-up or untraced after migration. Decedents were 22 045 (42.6% overall), 19 394 (42.1%) among men and 2651 (46.2%) among women. The cause of death was known for 95.0% of decedents in both sexes. Workers not contributing person-years after 1970, excluded from present analyses, were 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).

Table 2 presents mortality figures (observed and expected deaths, SMRs with 95% CI) by gender. Mortality was significantly increased in both sexes for all-causes (total excess of 1183 deaths), all-cancers, respiratory tract cancers, lung cancers, pleural and peritoneal malignancies, bladder cancers, respiratory diseases and asbestosis. Excesses were observed in men for malignant neoplasms of unspecified site and in women for ovarian cancers and for psychiatric diseases. The excess observed in women for 'Malignant neoplasms of digestive organs' was due to the inclusion of the neoplasms of peritoneum: excluding this category, observed and expected deaths were 227 and 221.7, respectively (SMR=1.02, 95% CI 0.90 to 1.17). Deaths from asbestosis were in great excess in both genders. Deaths attributed to 'other pneumoconiosis' were 89 (vs 49.16 expected) in men and 2 (vs 0.14) in women; corresponding SMRs were 1.81 (95% CI 1.45 to 2.23) and 14.3 (95% CI 1.53 to 51.60).

Some causes of death showed a statistically significant reduction of SMR. For men, cancers of lip, oral cavity and pharynx, and stomach, neurological, cardiovascular, digestive and genitourinary diseases, and accidents and violence. For women, only deaths from neurological diseases showed a statistically significant reduction. Mortality for laryngeal cancer showed a non-statistically significant reduction (SMR 0.87, 95% CI 0.73 to 1.02) in men, while it was similar to expected in women. In both genders, deaths from unspecified causes represented 1.5% of total deaths. Heterogeneity among cohorts was tested for cancer of lung, pleura and peritoneum by gender. It resulted statistically significant, with the exception of lung cancer in women (figure 1 and online supplementary figures 2–6).

Table 3 presents the SMRs stratified by duration of employment, for the causes selected 'a priori' for evidence of association with asbestos or as indicators of HWE. In men, SMRs for all-deaths showed a significant reduction with duration of employment (from 1.08 for 0–9 years to 0.96 for 30+), while no trends were observed for women. In men, SMRs for pleural and peritoneal malignancies and for asbestosis increased significantly, while no clear trend was observed for lung cancer. Cardiovascular and digestive diseases showed a downward trend, statistically significant for cardiovascular diseases. Women showed more unstable SMRs; however, a significant increasing mortality trend was observed for malignant neoplasms, pleural and peritoneal malignancies and asbestosis, while a significant downward trend was observed for cardiovascular diseases.

Table 3 also presents mortality in relation to TSFE (latency) for the same causes considered for duration. In men, all-cause mortality was lower than expected in the first 20 years of TSFE, and increased afterwards, with a statistically significant trend. A similar trend was observed for total malignant neoplasms, with SMRs increasing from 0.84 to 1.29. SMRs for cardiovascular diseases increased with TSFE but remained always lower than unity. Regarding the causes of death associated with asbestos exposure, SMR for lung cancer was lower than unity until 19 years of TSFE, then increased up to 1.35 in the class 30–39 years, without further increasing with longer TSFE. Pleural malignancies were not observed in the first 10 years (not tabulated); SMRs were 5.05 until 19 years of TSFE, and increased to 14.99 for 30–39 years and did not further increase. Peritoneal neoplasms showed a statistically significant increase in SMRs starting from 20 to 29 years of TSFE, with an increasing trend over the entire observation period. Deaths from asbestosis were first observed after 10–19 years of TSFE, with an increasing trend over the entire observation period. Laryngeal neoplasms showed SMRs close to or lower than unity. In women, similar results were observed, although the HWE was less marked than in men. Mortality from cardiovascular diseases was close to expectation. SMRs for lung cancer were similar to those observed in men but, due to the smaller observed numbers, did not reach statistical significance. Pleural, peritoneal neoplasm and asbestosis also showed trends similar to men, with higher SMRs, reflecting the lower mortality from these diseases in the reference female population. The trend of SMRs for pleural malignancy by gender is also presented graphically in online supplementary figure 7: in both genders, the curve does not show an exponential increase after period 30–39 years of TSFE.

Table 4 shows the cross-tabulation of SMRs by TSFE and duration of employment, for lung, peritoneal and pleural neoplasm, in men and women combined. The SMRs for pleural neoplasm show an attenuation of the increasing trend with TSFE in the classes of TSFE longer than 40, more evident in the shorter classes of duration.

The analysis of the variation of SMRs by TSFE was completed with the exploration of the trend by TSFE and period of first employment, which is presented in online supplementary table 3, confirming the attenuation of the increase in SMRs with TSFE for pleural but not for peritoneal neoplasms in all periods of first employment.

DISCUSSION

Our study is a pooled analysis of cohorts of workers exposed to asbestos in different industries in Italy, including in particular

Table 1 Pooled Italian asbestos cohort study: description of the cohort

		Men		Women		Total		
		n	%	n	%	n	%	Person-years*
Industrial activity	Asbestos-cement	10 714	23.3	2362	41.1	13 076	25.2	388 915
	Rolling stock construction maintenance	23 099	50.1	711	12.4	23 810	46.0	755 034
	Shipyards	5099	11.1	21	0.4	5120	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	1938	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 construction	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
	Works in multiple sectors	47	0.1	–	–	47	0.1	1626
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
Age at first exposure (years)	<20	6304	13.7	1473	25.6	7777	15.0	274 614
	20–29	23 527	51.1	2405	41.9	25 932	50.1	871 259
	30–39	10 259	22.3	1259	21.9	11 518	22.2	328 551
	40–49	4541	9.8	521	9.1	5062	9.8	114 842
	50+	1429	3.1	83	1.4	1512	2.9	26 387
Status at follow-up	Alive	25 977	56.4	3010	52.4	28 987	55.9	–
	Deceased†,‡	19 394	42.1	2651	46.2	22 045	42.6	–
	Emigrated‡	172	0.4	31	0.5	203	0.4	–
	Lost to follow-up	517	1.1	49	0.9	566	1.1	–
	Total	46 060	100	5741	100	51 801	100.0	
		Person-years	**%**	**Person-years**	**%**	**Person-years**	**%**	
Time since first exposure (years)	<10	252 522	17.7	18 298	9.9	270 820	16.8	
	10–9	348 090	24.3	33 075	17.9	381 165	23.6	
	20–29	365 493	25.5	43 396	23.5	408 889	25.3	
	30–39	285 621	20.0	40 809	22.1	326 430	20.2	
	40–9	133 975	9.4	30 465	16.5	164 440	10.2	
	50+	45 012	3.1	18 897	10.2	63 909	4.0	
	Total	1 430 713		184 940		1 615 653		

*Person-years computed from 1970.
†*1092 causes of death unknown* (960 men and 132 women, in both sexes 5% of decedents).
‡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).

asbestos cement, rolling-stock production and maintenance, shipbuilding, dockyard and harbour workers. These industries accounted for a large fraction of asbestos-exposed workers in Italy. The contribution of female workers was substantial, making gender-specific specific analyses possible. Follow-up results were satisfactory as only 1.5% of cohort members were lost to follow-up (including untraced migrants) and causes of death were known for 95%. The decision to restrict our analyses to 1970 onwards depends on the availability of reference mortality rates and not on data quality.[20]

These first analyses were focused on the burden of asbestos-related mortality, including tumour types with limited evidence of association with asbestos, and on mortality by duration of employment and TSFE. ICD revisions 8th to 10th were used during our study period. The use of ICD 10th revision in Italy started in 2003. The sensitivity of death certificates for the identification of MM was explored in the meta-analysis by Kopylev *et al*,[21] which observed an underestimation of MM incidence from mortality data. This observation was supported by other studies not included in that revision: 74.5% of pleural MM cases

Table 2 Pooled Italian asbestos cohort study

	Men					Women				
Causes of death	**Observed**	**Expected**	**SMR**	**95% CI**		**Observed**	**Expected**	**SMR**	**95% CI**	
All causes	18370	17551.8	1.05	1.03	1.06	2503	2138.0	1.17	1.12	1.22
MN	7361	6293.7	1.17	1.14	1.20	818	612.7	1.33	1.24	1.43
MN lip, oral cavity and pharynx	149	191.5	0.78	0.66	0.91	9	6.6	1.37	0.62	2.59
MN digestive organs (including peritoneum)	2198	2194.5	1.00	0.96	1.04	262	226.9	1.16	1.02	1.30
MN stomach	523	575.2	0.91	0.83	0.99	44	47.9	0.92	0.67	1.23
MN small intestine	14	10.8	1.30	0.71	2.18	1	1.2	0.84	0.02	4.68
MN colon	408	413.2	0.99	0.89	1.09	62	52.8	1.17	0.90	1.50
MN rectum	173	180.4	0.96	0.82	1.11	22	20.3	1.08	0.68	1.64
MN of liver and intrahepatic bile ducts	378	380.4	0.99	0.90	1.10	25	28.9	0.87	0.56	1.28
MN peritoneum	136	28.5	4.77	4.00	5.64	35	5.2	6.75	4.70	9.39
MN respiratory organs	3207	2155.3	1.49	1.44	1.54	217	62.6	3.47	3.02	3.96
MN larynx	141	162.9	0.87	0.73	1.02	2	1.6	1.24	0.15	4.48
MN lung	2415	1918.6	1.26	1.21	1.31	78	54.6	1.43	1.13	1.78
MN pleura	611	46.0	13.28	12.24	14.37	134	4.7	28.44	23.83	33.69
MN uterus						34	35.7	0.95	0.66	1.33
MN ovary						43	31.1	1.38	1.00	1.87
MN prostate	352	361.4	0.97	0.87	1.08					
MN bladder	291	249.2	1.17	1.04	1.31	19	9.5	1.99	1.20	3.11
MN kidney	157	160.7	0.98	0.83	1.14	6	10.2	0.59	0.22	1.29
Leukaemia and lymphoma	446	434.2	1.03	0.93	1.13	47	50.7	0.93	0.68	1.23
MN unspecified site	220	158.3	1.39	1.21	1.59	19	18.1	1.05	0.63	1.64
Psychiatric diseases	143	161.0	0.89	0.75	1.05	51	34.6	1.47	1.10	1.94
Neurological diseases	275	361.2	0.76	0.67	0.86	45	63.3	0.71	0.52	0.95
Cardiovascular diseases	5452	6209.0	0.88	0.85	0.90	909	912.2	1.00	0.93	1.06
Respiratory diseases	1413	1113.4	1.27	1.20	1.34	154	108.7	1.42	1.20	1.66
Digestive diseases	932	1034.5	0.90	0.84	0.96	118	104.3	1.13	0.94	1.36
Genitourinary diseases	184	219.0	0.84	0.72	0.97	31	27.8	1.12	0.76	1.58
Asbestosis	366	1.2	300.72	270.70	333.17	51	0.1	389.61	290.09	512.27
Pneumoconioses	455	50.4	9.03	8.22	9.90	53	0.3	193.6	145.0	253.21
Accidents and violence	851	1004.7	0.85	0.79	0.91	76	78.6	0.97	0.76	1.21
Poorly specified causes	230	120.9	1.90	1.66	2.16	75	32.93	2.28	1.79	2.86

Number of observed and expected deaths, SMR and 95% CI by gender and cause of death after 1 January 1970 (see text).
MN, malignant neoplasm.

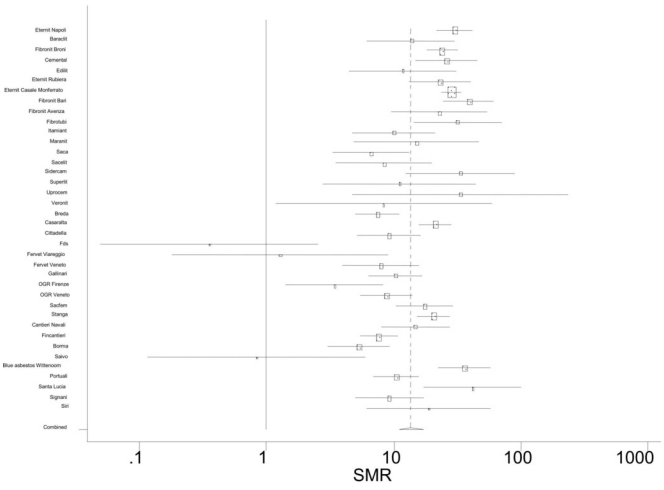

Figure 1 Pooled Italian asbestos cohort study. Forest plot of SMRs for pleural neoplasm in men. Test for heterogeneity: χ^2= 331.05; 41 df: p<0.0001.

could be identified from mortality records in Italy[22] and 87% in southern England.[23] Similar results were provided by descriptive analyses of pleural cancer mortality and MM incidence in Italy.[24 25] On the contrary, a cohort study showed similar figures for pleural neoplasms mortality and pleural MMs incidence.[9] These results support our conclusions of an increased risk for MM. We plan a record linkage with the National Mesothelioma Registry (ReNaM) files to identify incident MM cases and to conduct more precise evaluations.

Inclusion of existing cohorts in this study depended on the respective principal investigator's decision to participate. This pooled study was restricted for practical purposes to cohorts previously submitted to mortality follow-up studies and with observation period >40 years. Not all asbestos using Italian industries were included: most notably the asbestos textile and the brake and clutches lining production are not represented. Epidemiological investigations on mortality of workers in these sectors are limited and the invitation to join this project was not always accepted by the principal investigators. The update of mortality cohort studies of chrysotile miners and millers[26] and of asbestos textile workers[10] has been published in the last years and offers a contribution to the evaluation of our results, even if these cohorts could not be included in the pooled data. Only a small cohort of insulators was included, while another could not be updated.[27] Other categories not represented here include work activities such as roofers, bricklayers, plumbers, electricians and maintenance workers in general, which used asbestos-containing materials and whose asbestos exposure was often not constant. For these and similar categories, no cohort study was ever conducted in Italy. It is clear, however, that these industrial activities, and especially construction, contributed very large numbers of asbestos-exposed workers[14] and are contributing a large proportion of Italian MM cases.[28 29]

In this study, exposure could not be assessed on an individual basis because of the lack of individual data on jobs and work activities. Cohort-specific average exposures are being estimated by calendar year and will be applied to all workers in each cohort for the purpose of analyses of mortality by quantitative exposure.

The cohort showed a large increase in mortality from asbestosis, an indication of the extent of asbestos exposure: 417 deaths were observed while 1.35 were expected, corresponding to an excess of 300 times. In men, 89 additional cases were attributed to other pneumoconiosis, a figure that suggests also exposure to other pneumoconiotic dusts, such as silica—or misclassification of diagnosis. The excess risk is similar for men and women: asbestosis deaths were 2% of deaths in both sexes, suggesting a similarly relevant exposure. Mortality from asbestosis declined among men, but not among women, by calendar period of observation (data not detailed); it declined by period of first employment in both sexes, but remaining well above unity even for workers hired in 1970–1979, suggesting inadequate control of workplace exposures up to the last periods of industrial asbestos use in Italy. In the UK Great Britain Asbestos Survey, deaths from asbestosis were 0.8% of deaths in men from 1970 to 2005, with an SMR of 54.2.[30] Mortality from asbestosis was assessed on the basis of the underlying cause of death; in other cohorts, we observed additional cases reported as concomitant cause, therefore an underestimation is likely also in this study.[9]

Deaths from cardiovascular diseases were fewer than expected in men and close to expected in women; the SMRs in men increased with TSFE, suggesting HWE and excluding 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. Hein *et al*[31] observed an increased risk in white men and no changes in coloured men and in women; Loomis *et al*[32] and Larson *et al*[33] observed an increase in the whole cohort; Finkelstein[34] observed an increase of cardiovascular mortality among workers with asbestosis and a reduction among the others; Pira *et al*[10] did not observe variations from expected in the Balangero cohort miners. Deaths from unspecified causes, although more than expected, represented only 1.5% of total deaths. Heterogeneity among the cohorts was tested for lung, pleural and peritoneal malignancy by sex and resulted statistically significant, as can be expected pooling different industries and working conditions. This result was not unexpected, given previous results from international meta-analyses from asbestos cohort studies.[35]

We observed a statistically significant increase in bladder cancer for both men (SMR=1.17, p<0.05) and women (SMR=1.99, p<0.01). This was an unexpected result that needs further evaluation. Asbestos fibres were detected in urines[36] but bladder cancers are seldom reported in excess in asbestos cohort studies. Preliminary analyses (not given in detail) suggest that the risk was concentrated in the industrial sectors where asbestos exposure is associated to combustion fumes and other agents related to metalworking and painting. These industries have been classified by the IARC in relation to carcinogenic risk and will be considered in the industry-specific reports.[37] The role of tobacco smoking, as possible confounder for lung and bladder cancer, cannot be evaluated on an individual basis because of lack of information; however, the low mortality for cardiovascular diseases does not suggest smoking habits higher than the general population.

SMRs increased with duration of employment for asbestosis and pleural and peritoneal neoplasms in men and women, even if in men asbestosis and pleural cancer SMRs increased only slightly after 10–19 years duration. For lung cancer, no statistically significant trend with duration was observed. Duration of employment may be a modest indicator of exposure severity in this pooled analysis. Even in cohorts with generalised exposure conditions, such as the asbestos cement workers in Casale Monferrato, exposure intensity was known to have varied, for instance, between dry-processing and wet-processing jobs.[9] Duration, therefore, is only one dimension of exposure severity. In very severe exposure conditions, intensity and duration may

Table 3 Pooled Italian asbestos cohort study

	Duration of employment (years)								
	0–9		10–19		20–29		30+		Trend
	n	SMR (95% CI)	n	SMR (95% CI)	n	SMR (95% CI)	n	SMR (95% CI)	p Value
Men									
All causes	6866	1.08 (1.06 to 1.11)	4420	1.06 (1.02 to 1.09)	4735	1.03 (1.00 to 1.06)	2349	0.96 (0.92 to 0.99)	**
MN	2611	1.14 (1.09 to 1.18)	1775	1.22 (1.16 to 1.27)	1956	1.18 (1.13 to 1.24)	1019	1.14 (1.08 to 1.22)	
MN peritoneum	34	3.11 (2.16 to 4.35)	28	4.27 (2.84 to 6.17)	48	6.63 (4.89 to 8.79)	26	6.87 (4.48 to 10.06)	**
MN respiratory organs	1123	1.43 (1.35 to 1.52)	806	1.62 (1.51 to 1.74)	857	1.52 (1.42 to 1.62)	421	1.36 (1.23 to 1.50)	
MN larynx	56	0.97 (0.73 to 1.25)	29	0.74 (0.49 to 1.06)	48	1.11 (0.82 to 1.47)	8	0.36 (0.16 to 0.71)	
MN lung	851	1.22 (1.14 to 1.30)	615	1.40 (1.29 to 1.51)	630	1.25 (1.16 to 1.36)	319	1.15 (1.03 to 1.28)	
MN pleura	201	10.95 (9.49 to 12.58)	147	14.32 (12.10 to 16.83)	174	14.98 (12.84 to 17.38)	89	15.36 (12.34 to 18.90)	**
Respiratory diseases	464	1.25 (1.14 to 1.37)	366	1.34 (1.21 to 1.49)	391	1.30 (1.17 to 1.44)	192	1.13 (0.97 to 1.30)	
Asbestosis	45	96.71 (70.54 to 129.40)	109	404.11 (331.81 to 487.48)	136	435.73 (365.57 to 515.43)	76	447.33 (352.44 to 559.89)	**
Cardiovascular diseases	1950	0.92 (0.88 to 0.96)	1299	0.86 (0.81 to 0.91)	1482	0.89 (0.95 to 0.94)	721	0.79 (0.74 to 0.85)	**
Digestive diseases	364	0.96 (0.87 to 1.07)	224	0.87 (0.76 to 0.99)	235	0.88 (0.78 to 1.01)	109	0.82 (0.68 to 1.00)	
Accidents and violence	427	0.93 (0.84 to 1.02)	186	0.78 (0.67 to 0.90)	162	0.77 (0.65 to 0.89)	76	0.81 (0.64 to 1.02)	*
Women									
All causes	1073	1.16 (1.09 to 1.23)	639	1.15 (1.06 to 1.24)	580	1.21 (1.12 to 1.32)	211	1.17 (1.01 to 1.33)	
MN	323	1.13 (1.01 to 1.26)	222	1.47 (1.28 to 1.67)	195	1.46 (1.26 to 1.68)	78	1.90 (1.50 to 2.38)	**
MN peritoneum	4	1.69 (0.46 to 4.32)	16	12.29 (7.02 to 19.96)	9	7.84 (3.58 to 14.87)	6	16.60 (6.09 to 36.12)	**
MN respiratory organs	86	2.88 (2.30 to 3.56)	54	3.58 (2.69 to 4.67)	52	3.77 (2.81 to 4.94)	25	6.54 (4.23 to 9.66)	**
MN larynx	1	1.32 (0.03 to 7.37)	–		1	2.89 (0.07 to 16.09)	–		
MN lung	42	1.60 (1.15 to 2.16)	17	1.30 (0.76 to 2.08)	11	0.92 (0.46 to 1.65)	8	2.43 (1.05 to 4.79)	
MN pleura	41	20.07 (14.40 to 27.22)	37	31.24 (21.99 to 43.06)	39	33.37 (23.73 to 45.61)	17	54.09 (31.51 to 86.60)	**
Respiratory diseases	55	1.22 (0.92 to 1.59)	38	1.32 (0.93 to 1.81)	41	1.66 (1.19 to 2.25)	20	1.97 (1.21 to 3.05)	*
Asbestosis	9	192.96 (88.23 to 366.31)	16	438.20 (250.46 to 711.61)	15	402.98 (225.53 to 664.64)	11	1045.30 (521.79 to 1870.33)	**
Cardiovascular diseases	399	1.08 (0.98 to 1.19)	236	0.96 (0.84 to 1.09)	198	0.95 (0.82 to 1.09)	76	0.86 (0.67 to 1.07)	*
Digestive diseases	58	1.27 (0.96 to 1.64)	25	0.92 (59.5 to 1.36)	29	1.25 (0.84 to 1.79)	6	0.73 (0.26 to 1.59)	
Accidents and violence	29	0.82 (0.55 to 1.17)	28	1.38 (0.92 to 2.00)	11	0.67 (0.33 to 1.19)	8	1.27 (0.55 to 2.50)	

	Time since first exposure										
	0–19		20–29		30–39		40–49		50+		Trend
	n	SMR (95% CI)	n	SMR (95% CI)	n	SMR (95% CI)	n	SMR (95% CI)	n	SMR (95% CI)	p Value
Men											
All causes	1886	0.85 (0.81 to 0.89)	3499	1.04 (1.00 to 1.07)	5131	1.06 (1.03 to 1.09)	4619	1.10 (1.07 to 1.13)	3235	1.10 (1.07 to 1.14)	**
MN	612	0.84 (0.78 to 0.91)	1483	1.15 (1.09 to 1.21)	2261	1.19 (1.15 to 1.24)	1918	1.24 (1.19 to 1.30)	1087	1.29 (1.22 to 1.37)	**
MN peritoneum	3	0.66 (0.14 to 1.93)	15	2.25 (1.26 to 3.70)	34	3.91 (2.71 to 5.46)	55	9.74 (7.34 to 12.68)	29	9.89 (6.62 to 14.20)	**
MN respiratory organs	259	1.00 (0.88 to 1.13)	661	1.40 (1.30 to 1.51)	1068	1.59 (1.50 to 1.69)	810	1.58 (1.47 to 1.69)	409	1.68 (1.52 to 1.85)	**
MN larynx	14	0.55 (0.30 to 0.92)	42	1.03 (0.74 to 1.39)	34	0.69 (0.48 to 0.96)	38	1.17 (0.83 to 1.61)	13	0.88 (0.47 to 1.51)	
MN lung	217	0.97 (0.84 to 1.11)	518	1.25 (1.14 to 1.36)	809	1.35 (1.26 to 1.45)	575	1.24 (1.15 to 1.35)	296	1.35 (1.20 to 1.51)	**
MN pleura	19	5.05 (3.04 to 7.88)	87	10.57 (8.47 to 13.04)	212	14.99 (13.04 to 17.15)	195	14.93 (12.90 to 17.17)	98	14.36 (11.66 to 17.50)	**
Respiratory diseases	71	0.86 (0.67 to 1.08)	201	1.20 (1.04 to 1.37)	379	1.33 (1.20 to 1.47)	410	1.34 (1.21 to 1.48)	352	1.30 (1.16 to 1.44)	**
Asbestosis	10	154.8 (74.2 to 284.6)	42	281.1 (202.6 to 380.0)	99	291.6 (237.0 to 355.0)	112	301.6 (248.3 to 362.9)	103	352.5 (287.7 to 427.5)	**
Cardiovascular diseases	461	0.74 (0.67 to 0.81)	938	0.83 (0.78 to 0.88)	1473	0.87 (0.83 to 0.92)	1423	0.92 (0.87 to 0.97)	1157	0.95 (0.90 to 1.01)	**
Digestive diseases	130	0.64 (0.53 to 0.76)	240	0.96 (0.84 to 1.09)	255	0.92 (0.81 to 1.04)	182	0.95 (0.82 to 1.10)	125	1.14 (0.95 to 1.36)	**
Accidents and violence	272	0.80 (0.71 to 0.91)	185	0.81 (0.70 to 0.94)	183	0.87 (0.75 to 1.00)	118	0.85 (0.70 to 1.01)	93	1.07 (0.86 to 1.30)	
Women											
All causes	87	0.90 (0.72 to 1.11)	216	1.02 (0.89 to 1.16)	479	1.13 (1.03 to 1.23)	710	1.18 (1.10 to 1.27)	1011	1.26 (1.18 to 1.34)	**
MN	40	0.95 (0.68 to 1.29)	103	1.19 (0.97 to 1.44)	178	1.22 (1.05 to 1.41)	239	1.40 (1.23 to 1.59)	258	1.55 (1.37 to 1.76)	**
MN peritoneum	–		2	2.51 (0.30 to 9.08)	3	2.16 (0.45 to 6.31)	7	4.80 (1.93 to 9.90)	23	20.01 (12.68 to 30.02)	**
MN respiratory organs	6	1.83 (0.67 to 3.98)	24	2.93 (1.88 to 4.36)	56	3.76 (2.84 to 4.88)	73	3.88 (3.04 to 4.87)	58	3.34 (2.53 to 4.32)	
MN larynx	–		–		1	2.41 (0.06 to 13.47)	–		1	2.71 (0.07 to 15.11)	
MN lung	4	1.44 (0.39 to 3.70)	13	1.83 (0.97 to 3.12)	16	1.23 (0.70 to 2.00)	25	1.52 (0.98 to 2.24)	20	1.31 (0.80 to 2.03)	
MN pleura	2	9.52 (1.15 to 34.37)	10	19.01 (9.11 to 34.95)	37	34.39 (24.21 to 47.41)	48	32.26 (23.79 to 42.77)	37	26.23 (18.46 to 36.15)	
Respiratory diseases	–		3	0.38 (0.08 to 1.12)	22	1.18 (0.74 to 1.78)	38	1.23 (0.87 to 1.69)	91	1.88 (1.51 to 2.31)	**
Asbestosis	–		–		5	222.75 (72.30 to 519.80)	11	258.00 (128.79 to 461.63)	35	689.69 (480.4 to 959.2)	**
Cardiovascular diseases	23	0.97 (0.61 to 1.45)	54	0.77 (0.58 to 1.00)	161	0.95 (0.81 to 1.11)	259	0.99 (0.87 to 1.12)	412	1.06 (0.96 to 1.17)	*
Digestive diseases	3	0.43 (0.09 to 1.25)	13	0.97 (0.52 to 1.66)	29	1.28 (0.86 to 1.84)	39	1.38 (0.98 to 1.89)	34	1.03 (0.71 to 1.44)	
Accidents and violence	13	1.47 (0.79 to 2.52)	8	0.80 (0.34 to 1.57)	13	0.85 (0.45 to 1.45)	17	0.89 (0.52 to 1.42)	25	0.99 (0.64 to 1.46)	

Number of observed deaths (n), SMR and 95% CI by duration of employment and time since first exposure.
* p<0.05; ** p<0.01; (–) no cases.

Table 4 Pooled Italian asbestos cohort study

	Duration of employment (years)											
TSFE	**0–9**			**10–19**			**20–29**			**30+**		
Causes of death	**Observed**	**Expected**	**SMR (95% CI)**	**Observed**	**Expected**	**SMR (95% CI)**	**Observed**	**Expected**	**SMR (95% CI)**	**Observed**	**Expected**	**SMR (95% CI)**
Pleural neoplasm												
0–9	0	0.73	–									
10–19	9	1.71	5.27 (2.41 to 10.01)	12	1.53	7.82 (4.04 to 13.66)						
20–29	39	3.92	9.95 (7.07 to 13.60)	34	2.54	13.39 (9.28 to 18.72)	24	2.30	10.45 (6.70 to 15.55)			
30–39	89	5.75	15.48 (12.43 to 19.05)	68	3.80	17.89 (13.89 to 22.67)	71	4.33	16.40 (12.81 to 20.69)	21	1.34	15.72 (9.73 to 24.03)
40–49	74	5.68	13.03 (10.23 to 16.35)	52	2.48	21.00 (15.68 to 27.53)	81	4.21	19.25 (15.29 to 23.93)	36	2.19	16.47 (11.53 to 22.80)
50+	31	2.60	11.93 (8.10 to 16.93)	18	1.10	16.36 (9.69 to 25.85)	37	1.95	18.96 (13.35 to 26.13)	49	2.59	18.95 (14.02 to 25.06)
Peritoneal neoplasm												
0–9	1	1.31	0.76 (0.02 to 4.26)									
10–19	0	1.84	–	2	1.78	1.13 (0.14 to 4.07)						
20–29	8	3.02	2.65 (1.14 to 5.22)	4	2.15	1.86 (0.51 to 4.77)	5	2.30	2.17 (0.71 to 5.07)			
30–39	11	3.59	3.07 (1.53 to 5.48)	10	2.23	4.49 (2.16 to 8.27)	14	3.01	4.65 (2.54 to 7.81)	2	1.27	1.58 (0.19 to 5.70)
40–49	13	2.44	5.32 (2.83 to 9.09)	10	1.20	8.32 (3.99 to 15.30)	27	2.03	13.33 (8.79 to 19.40)	12	1.43	8.39 (4.33 to 14.65)
50+	5	1.08	4.64 (1.51 to 10.83)	18	0.51	35.62 (21.1 to 56.3)	11	1.05	10.47 (5.23 to 18.73	18	1.45	12.42 (7.36 to 19.63)
Lung neoplasm												
0–9	34	45.85	0.74 (0.51 to 1.04)									
10–19	116	92.60	1.25 (1.03 to 1.50)	71	88.36	0.80 (0.63 to 1.01)						
20–29	215	166.06	1.30 (1.13 to 1.48)	179	125.36	1.43 (1.23 to 1.65)	137	130.73	1.05 (0.88 to 1.24)			
30–39	249	198.57	1.25 (1.10 to 1.42)	223	138.28	1.61 (1.41 to 1.84)	269	191.4	1.41 (1.24 to 1.58)	84	82.70	1.02 (0.81 to 1.26)
40–49	202	156.80	1.29 (1.12 to 1.48)	110	72.94	1.51 (1.24 to 1.82)	170	139.76	1.22 (1.04 to 1.41)	118	108.68	1.09 (0.90 to 1.30)
50+	77	64.38	1.20 (0.94 to 1.49)	49	28.38	1.73 (1.28 to 2.28)	65	52.73	1.23 (0.95 to 1.57)	125	89.56	1.40 (1.16 to 1.66)

Number of observed deaths, SMR and 95% 95% CI by duration of employment and time since first exposure for selected causes of death, for the total of men and women.

actually turn out to be inversely related, and if variation in intensity is large enough, longer durations may be associated with lower cumulative exposures. Furthermore, given the wide variety of occupational conditions in the different cohorts we studied, duration cannot be expected to capture more than a modest fraction of exposure variation. Estimates of time-weighted average exposure intensity by factory (cohort) and calendar period are being developed.

Early cohort and case–control studies predicted MM risk to increase according to a power of TSFE.[5 6] Peto *et al* estimated an increase of MM incidence with the third power of TSFE in a cohort of asbestos workers followed for 50 years.[4] The early studies did not explore such long latencies because no other cohorts had such a long follow-up.[6] More recently, Berry advanced the hypothesis that incidence after the initial increase has a long-time downward trend that could be modelled by a negative exponential term becoming dominant after 40 years of TSFE.[7] Berry's hypothesis was tested in other studies concluding against the hypothesis of an indefinite increase in incidence.[8–11 30 38–40] Two studies observed that pleural and peritoneal MM behaved differently, the change in trend being observed for pleural MMs only.[8 39] Our results indicate that pleural neoplasms risk was increasing only over the first four decades of TSFE; later, SMRs no longer increased for men and declined for women. The change was more evident in the first categories of employment duration, less affected by collinearity between duration and TSFE. Our results are conflicting with the hypothesis that pleural MM risk increases indefinitely and support the alternative hypothesis that it is stable or decreasing after a TSFE time of >40 years. Instead, peritoneal neoplasms risk increased over five decades of TSFE in men and over all the observation time in women. Our results for peritoneal neoplasm are similar to those presented by Reid *et al*,[8] who observed a continuing increase of risk, while in the British Asbestos Survey[30] a decrease in mortality after 50 years of TSFE was observed also for peritoneal neoplasm.

A cohort of asbestos cement workers (see online supplementary table 1, id 2), the cohort of wives of asbestos cement workers (id 43) and three cohorts of rolling-stock maintenance workers (id 24,25,26) contributed to a previous pooled study on trends in MM risk by TSFE.[8] The overlap with this study is partial as mortality follow-up of these cohorts was extended by at least 5 years. Nevertheless, we carried out a sensitivity analysis excluding these cohorts from the computation of SMRs for pleural and peritoneal malignancies and lung cancer: the same trends were observed (data not given in detail). We commented, thus, our findings on the whole pool of cohorts.

This pooled cohort includes a large number of women. Female employment in Italian asbestos industries was important, in particular in the asbestos cement and asbestos textile industries, but only limited information on asbestos exposure and asbestos-related diseases in women is usually provided. Our findings for women suggest higher SMRs than for men for lung cancer, pleural and peritoneal malignancy and asbestosis. These results may not depend on higher absolute risks or to increased sensitivity but rather on the lower female reference mortality rates from these diseases.[20] The trends by calendar period, TSFE and duration of exposure were similar in the two sexes. In women, however, mortality for all-causes and cardiovascular deaths was always higher than expected, suggesting that the HWE was less important than for men or compensated by other risk factors, such as smoking. Confounding by smoking may be more important in women, as suggested by studies on lung cancer in women living in industrial areas.[41 42]

The statistically significant increase of ovarian *cancer* mortality (43 observed vs 31.1 expected, SMR=1.38, $p<0.05$) supports the conclusion of a previous meta-analysis that estimated a meta-analytical RR of 1.77 over 18 studies (one in the present pool, table 1, N 2).[43]

No excesses were observed for tumours of the larynx. Our results do not support the conclusions of the extensive review conducted by Samet *et al*[44] and the more recent review by Peng *et al*.[45 46] Causes of disagreement could include differences in the prevalence of confounding factors, in particular smoking and alcohol, that could not be addressed in our study. The reduced mortality for cardiovascular diseases and for gastrointestinal diseases suggests a low prevalence of these factors, which would contribute to the low mortality for laryngeal cancer. We should also consider that mortality data are no longer a sensitive indicator of risk, given the high survival; therefore, further extension of the study using hospital admissions and linkage with cancer registry data is needed.

No evidence of increased risk was also observed for the tumours of pharynx, stomach, colon and rectum.

CONCLUSION

Our first results on one of the largest cohort studies of asbestos-exposed workers worldwide showed increased mortality from asbestosis and neoplasms of the lung, pleura and peritoneum, and ovarian neoplasms, but not from tumours of the larynx, pharynx, stomach, colon and rectum. Our findings, furthermore, support the hypothesis that the increase in risk of pleural malignancy according to a power of TSFE flattens out after about 40 years and may start even to decrease. These results should be taken under consideration to update the assessment of trends in MM incidence at the national population level[47] and also in the apportionment of MM risk.[48]

This huge cooperative effort is being continued with analyses and data collection along the following perspectives: estimation of exposure, collection of incident cases of MM using the record linkage with ReNaM, analyses by type of industry and by gender, analyses of specific types of cancer and diseases, modelling of cancer risk according to exposure and time-related variables, including statistical models of the risk variation with TSFE and time from cessation of exposure.

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Italian pool of asbestos workers cohorts: mortality trends of asbestos-related neoplasms after long time since first exposure

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