ORIGINAL ARTICLE

Retrospective mortality cohort study of Italian workers compensated for silicosis

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Objectives: To estimate cause specific mortality in a large cohort of Italian workers compensated for silicosis.

Methods: The cohort included 14 929 subjects (14 098 men and 831 women) compensated for silicosis between 1946 and 1979, alive on 1 January 1980, and resident in Tuscany (a region of central Italy with 3 547 000 inhabitants). Mortality follow up ranged from 1980 to 1999. Vital status and the causes of death were determined by linkage with the regional mortality registry and with the national mortality database. The cohort mortality rates were compared to the rates of the local reference population. SMRs and their 95% confidence intervals were computed assuming a Poisson distribution of the observed deaths. Specific SMR analyses were performed according to the level of disability, the year of compensation assignment, and the job type.

Results: A significant excess mortality was observed in male silicotics for cancer of the lung, trachea, and bronchus and cancer of the liver, respiratory diseases (silicosis, asbestosis, antracosilicosis, and other pneumoconiosis), and for tubercolosis. Statistically significant mortality excess was observed in female silicotics for respiratory diseases (specifically silicosis and other pneumoconiosis) and tuberculosis. Analyses for period of compensation assignment showed a twofold increased SMR for biliary tract cancer among female workers and for liver cancer among male workers compensated before 1970.

Conclusions: The excess mortality from respiratory tract cancers and respiratory tract diseases detected in Italian compensated silicotics are in agreement with previous epidemiological studies. Although the twofold increased risk for liver cancer among males is suggestive of a possible association with silica dust exposure, the finding needs to be confirmed.

The International Agency for Research on Cancer has classified crystalline silica as a human carcinogen in 1996[1] following a systematic review of the evidence reported by epidemiological studies conducted in silica exposed workers and silicotics in the USA,[2 3] Italy,[4 5] UK,[6–9] and China.[10 11] Studies conducted in silicotics[12–15] have shown increased risk of lung cancer with increasing duration of follow up since diagnosis. For workers who may have been exposed to crystalline silica, there have been infrequent reports of statistically significant excesses of non-respiratory tract cancers.[16] Evidence of an association of autoimmune diseases and renal diseases with silica exposure has recently been suggested.[17 18] In Italy, after an individual claim for silicosis compensation is made, the National Workers' Compensation Authority (INAIL) carries out inspections for insurance premium applications. Criteria for silicosis compensation assignment are radiographic findings consistent with pneumoconiosis, a verified history of occupational exposure to silica dust, and a level of general working inability exceeding 10% (reflecting a respiratory inability of 35%).[19] The aim of this study is to estimate the cause specific mortality in a large cohort of Italian workers compensated for silicosis with reference to specific job categories, period of compensation assignment, and degree of working inability.

METHODS

The cohort includes 14 929 subjects (14 098 men and 831 women) compensated for silicosis between 1946 and 1979 by INAIL, who were alive on 1 January 1980 and lived in Tuscany, a region of central Italy of about 3 547 000 inhabitants. The follow up period ranged between 1 January 1980 and 31 December 1999 and the study subjects contributed for a total of 237 178 person-years of observation. INAIL and the Regional Mortality Registry of Tuscany (RMR) databases were used to ascertain the vital status for all subjects and retrieve the causes of death for those who died during the follow up period. A total of 8521 deaths occurred among 14 929 compensated subjects. The cause of death was ascertained via RMR for 6451 subjects; for the remaining 2070 individual records were linked to the anonymous Italian mortality file by the Italian Agency for New Technologies, Energy and the Environment (ENEA). Record linkage was based on the following keys: gender, place and date of birth, place and date of death. The linkage procedure identified 1273 causes of death. Overall, the cause of death was ascertained for 7724 (90.6%) out of 8521 deceased subjects and it was unknown for 797 (9.4%). Causes of death were coded according to the International Classification of Diseases (ICD) Ninth Revision. As recently suggested[20] we assumed that the cause specific distribution of the 797 deaths with unknown cause was the same as that observed for those whose cause of death was known and the results under this assumption are reported in text and tables. Statistical analyses have been carried out also with a ''unknown cause of death'' category, but findings are not presented in the tables.

Expected number of deaths were estimated by applying age, gender, calendar period, and cause specific regional

Abbreviations: ICD9, International Classification of Diseases, Ninth Revision; RMR, Regional Mortality Registry; SMR, standardised mortality ratio

Table 1 Cause specific mortality among workers compensated for silicosis, Tuscany, Italy, between 1946 and 1979: observed and expected deaths, standardised mortality ratios (SMRs), 95% confidence interval (95% CI)

ICD9 Code	Cause of death	Sex	Observed	Expected	SMR	95% CI
000.0–999.9	All causes	M	8162.00	8820.51	0.93	0.91–0.95
		F	359.00	419.61	0.86	0.77–0.95
000.1–139.8	Infectious diseases	M	74.34	41.79	1.78	1.42–2.23
		F	5.50	1.77	3.11	1.38–7.01
010.0–018.9	Tuberculosis	M	51.38	17.76	2.89	2.20–3.80
		F	4.40	0.42	10.47	4.24–25.85
140.0–239.9	All cancers	M	2551.62	2734.44	0.93	0.90–0.97
		F	72.62	93.60	0.78	0.62–0.98
140.0–145.9	Lip, oral cavity and pharynx	M	6.56	49.12	0.13	0.06–0.28
150.0–159.9	Digestive organs and peritoneum	M	947.84	1053.65	0.90	0.84–0.96
		F	34.11	42.88	0.80	0.57–1.11
150.0–150.9	Oesophagus	M	54.66	54.42	1.00	0.77–1.31
151.0–151.9	Stomach	M	311.57	379.26	0.82	0.74–0.92
		F	7.70	12.95	0.59	0.30–1.19
153.0–154.8	Colorectal	M	214.27	256.22	0.84	0.73–0.96
		F	12.10	11.62	1.04	0.60–1.82
155.0–155.2	Liver	M	158.52	73.84	2.15	1.84–2,51
		F	2.20	2.26	0.97	0.28–3.36
156.0–156.9	Gallbladder and extrahepatic bile ducts	M	21.86	27.37	0.80	0.53–1.21
		F	4.40	2.54	1.73	0.70–4.27
157.0–157.9	Pancreatic	M	97.30	101.08	0.96	0.79–1.17
		F	4.40	4.85	0.91	0.37–2.24
158.0–158.9	Peritoneum	M	4.37	12.02	0.36	0.15–0.90
160.0–165.9	Respiratory tract	M	875.68	813.53	1.08	1.01–1.15
		F	7.70	7.05	1.09	0.55–2.18
160.0–160.9	Nose	M	2.19	2.09	1.05	0.30–3.63
161.0–161.9	Larynx	M	57.94	65.78	0.88	0.68–1.14
162.0–162.9	Trachea, bronchus and lungs	M	798.06	723.88	1.10	1.03–1.18
		F	6.60	6.16	1.07	0.51–2.26
163.0–163.9	Pleural mesothelioma	M	9.84	13.42	0.73	0.40–1.36
172.0–172.9	Melanoma	M	15.31	13.81	1.11	0.67–1.82
174.0–174.9	Breast	F	8.80	12.53	0.70	0.37–1.34
179.0–182.8*	Uterus	F	4.40	4.50	0.98	0.40–2.41
185.0–185.0	Prostate	M	194.60	232.27	0.84	0.73–0.96
188.0–188.9	Bladder	M	135.56	142.82	0.95	0.80–1.12
189.0–189.9	Kidney	M	64.50	61.83	1.04	0.82–1.33
191.0–191.9	Brain	M	14.21	38.45	0.37	0.22–0.62
201.0–201.9	Hodgkin's disease	M	3.28	7.27	0.45	0.16–1.27
203.0–203.0	Multiple myeloma	M	18.59	20.30	0.92	0.58–1.44
204.0–208.9	Leukaemia	M	63.41	73.47	0.86	0.68–1.10
250.0–250.9	Diabetes mellitus	M	112.60	176.74	0.64	0.53–0.77
		F	16.50	15.59	1.06	0.66–1.71
390.0–459.9	Cardiovascular diseases	M	2526.47	3862.76	0.65	0.63–0.68
		F	160.64	218.47	0.74	0.63–0.86
401.0–405.9	Hypertension	M	64.50	118.82	0.54	0.43–0.69
		F	15.40	9.63	1.60	0.98–2.62
410.0–414.9	Ischaemic heart diseases	M	868.03	1244.32	0.70	0.65–0.75
		F	49.51	50.77	0.98	0.74–1.29
430.0–438.9	Cerebrovascular diseases	M	811.18	1239.40	0.65	0.61–0.70
		F	42.91	79.49	0.54	0.40–0.73
460.0–519.9	Respiratory system diseases	M	1835.54	737.87	2.49	2.38–2.60
		F	48.41	21.63	2.24	1.69–2.96
490.0–496.0	Chronic obstructive pulmonary disease	M	334.53	425.90	0.79	0.71–0.87
		F	5.50	9.13	0.60	0.27–1.36
490.0–492.9	Bronchitis	M	300.64	358.36	0.84	0.75–0.94
		F	4.40	7.19	0.61	0.25–1.51
493.0–493.9	Asthma	M	15.31	31.50	0.49	0.30–0.80
500.0–500.0	Anthracosilicosis	M	2.19	0.09	25.34	7.31–87.90
501.0–501.0	Asbestosis	M	2.19	0.26	8.48	2.44–29.40
502.0–502.0	Silicosis	M	1303.14	59.97	21.73	20.58–22.94
		F	31.91	0.06	536.75	380.04–758.08
503.0–505.0	Other pneumoconiosis	M	38.26	1.94	19.69	14.36–27.00
520.0–579.9	Digestive system diseases	M	378.26	402.22	0.94	0.85–1.04
		F	12.10	16.91	0.72	0.41–1.25
571.0–571.9	Liver cirrhosis	M	172.73	183.65	0.94	0.81–1.09
577.0–577.9	Pancreatic diseases	M	18.59	15.88	1.17	0.75–1.84
		F	2.20	0.78	2.81	0.81–9.72
580.0–629.9	Genitourinary system diseases	M	94.02	134.49	0.70	0.57–0.86
		F	6.60	5.02	1.31	0.62–2.77
580.0–589.9	Nephritis, nephrotic syndrome and nephrosis	M	72.15	76.09	0.95	0.75–1.19
		F	6.60	3.43	1.92	0.91–4.06
780.0–799.9	Undefined conditions	M	77.62	146.75	0.53	0.42–0.66
		F	6.60	11.77	0.56	0.27–1.18
800.0–999.9	Injury and poisoning	M	251.44	322.43	0.78	0.69–0.88
		F	17.60	15.60	1.13	0.71–1.79

Only causes of death with at least two deaths are reported.
*Code 181.0 not included.

mortality rates to the quinquennial age (20–24; …; 80–84; 85+) and calendar year specific (1980–84; …; 1995–99) person-years of observations. Standardised mortality ratios (SMRs) and their 95% confidence interval (95% CI) were computed assuming a Poisson distribution of the observed deaths.

Specific SMR analyses were performed according to the year of compensation assignment (before and after 1970, that is, with more or less than 10 years from the start of follow up) and the level of working disability more or less than 31% (equal to 55% of respiratory inability for INAIL criteria) and in the subcohorts of male miners and glass workers. The categories for ''year of compensation'' and ''working inability'' variables in the subcohort analyses have been chosen to have an equal distribution of person-years of observations.

RESULTS

Mean age at compensation was 52.6 (SD 9.5) years without significant differences between gender. In the subgroup of subjects who died before the end of follow up, the mean time elapsed between compensation and death was 21.1 (SD 7.1) years for males and 23 (SD 8) years for female workers. More than 50% of the subjects had a compensation with the lower level of disabililty (that is, 21% of working ability lost corresponding to a 45% of respiratory inability). Silicotics with at least 31% disability were less than 20% of the entire cohort. The most frequent professional categories in male silicotics were miners, generic workers, glass workers, masons, and ceramic workers. This latter category was the most frequent occupation among women. About 40% of the entire cohort was compensated for silicosis more than 10 years before the start of follow up.

Table 1 shows the SMRs and their 95% CI in males and females for specific categories of causes of death. Only causes with at least two deaths have been reported. A significant excess mortality was observed in males for cancer of the liver, lung, trachea, and bronchus, non-malignant respiratory tract diseases (silicosis, asbestosis, antracosilicosis, and other pneumoconiosis), and for tubercolosis. Other excesses were observed among males including melanoma, kidney, nasal, and oesophageal cancers, and pancreatic diseases. Statistically significant excess mortality was observed in females for non-malignant respiratory diseases (SMR = 2.24), specifically silicosis (SMR = 536.75), and tuberculosis (SMR = 10.47) despite the reduced overall mortality (SMR = 0.86). Pancreatic diseases, nefritis, and biliary tract cancer mortality was also increased among female silicotics.

Specific analyses were carried out for male miners and glass workers, the job categories with the majority of the cohort members (2780 and 1255 subjects respectively). They showed (not reported in tables) a major mortality for respiratory system diseases (SMR = 3.11; 95% CI 2.86 to 3.39 and SMR = 1.78; 95% CI 1.44 to 2.21 respectively) and liver cancer (SMR = 1.60; 95% CI 1.09 to 2.34 and SMR = 1.90; 95% CI 1.10 to 3.29 respectively). Silicotics with a level of working inability equal or higher than 31% experienced increased mortality for tubercolosis, liver cancer, respiratory tract cancer, and respiratory system diseases than the referent population and the whole cohort of silicotics. Analyses for period of compensation assignment showed a significantly increased SMR for biliary tract cancer among females and for tubercolosis, silicosis, other pneumoconiosis, and liver cancer among males compensated before 1970 (more than 10 years before the start date of follow up). Deaths from asbestosis occurred only in the group with less than 10 years from the date of compensation assignment to the beginning of follow up.

DISCUSSION

The study detected a significant excess mortality for lung cancer among silicotics, a finding that is consistent with the results of other epidemiological studies.[15 21 22] Recently, a meta-analysis of 27 published cohort studies of lung cancer among silicotics showed a pooled SMR value of 2.45 (95% CI 1.63 to 3.66).[23] Fourteen studies used compensation for silicosis as the cohort definition criteria and the SMR ranged between 1.4 and 3.8. When interpreting the results it should be considered that for the group of deceased with unknown cause, we assumed the same distribution by cause of the observed ones, without adjustment for added uncertainty. This assumption is correct if there is no reason for a different pattern of cause of death among observed and unknown. In the analyses with an ''unknown cause of death'' class, the SMRs decrease by about 5% with the same extent for confidence intervals. Information on smoking of the subjects in the cohort was not available in our study, preventing any SMR analysis accounting for smoking habits. If the silicotics in our study had smoked more than the general population, the results would have to be considered with regard to the confounding effect of smoking. However, in a previous meta-analysis,[24] four studies showed a lung cancer risk adjusted for smoking higher than the unadjusted suggesting that the risk was not attributable to smoking.[12 24–27] A previous study conducted on Italian silicotics, with a similar design, showed that silicotics' smoking prevalence was similar to that reported for the general population.[28] Furthermore the possible role of smoking as a confounder of the increase in lung cancer mortality should be considered in view of the absence of an increment in other smoking related causes of death (that is, lip, oral cavity, and pharynx cancer, cardiovascular diseases, bronchitis, and chronic obstructive pulmonary diseases[29]). The use of local rates for comparison, the absence of an increase for smoking related diseases, and the relevant epidemiological evidence suggest an occupational origin of the observed increase in lung cancer mortality.

In our cohort a significantly reduced mortality for all causes of death was detected both in male and female silicotics, while mortality for respiratory system diseases and tuberculosis was significantly increased. The absence of an effect on life expectancy for silicotics is probably attributable to the presence in the cohort of a well known selection bias—the healthy workers effect.[20] The association between silicosis and tubercolosis (TB), that has been reported by many epidemiological studies,[30] is consistent with our results. The excess mortality for asbestosis in our silicotics cohort confirms the circumstance of a possible exposure to asbestos and silica dust in occupations such as mining, construction, manufacture, and building maintenance[31] but should be verified by a specific survey.

Although previous studies in silicotics have not reported any increased risk for liver cancer, an increase has been observed in workers exposed to silica containing dust. In China, in a cohort of 68 241 workers exposed to dust in metal mines and pottery factories,[32] increased mortality was observed among those exposed to high levels of total dust. A recent update showed that liver cancer mortality increased with increasing levels of cumulative exposure to silica mixed dust.[33] In a cohort of Chinese tin miners (1113 subjects who were employed in underground work for at least one year) the observed cases of liver cancer were higher than expected, both with national and local populations as reference.[34] A case control study on primary liver cancer in Sweden reported an increased risk for liver cancer (adjusted for alcohol consumption) in workers potentially exposed to high levels of inorganic dust, mostly stone dust containing silica.[35]

The twofold higher risk for liver cancer detected in male silicotics (and in those compensated before 1970) is unlikely

to be attributable solely to a higher consumption of alcohol by cohort members, because no excess was observed for other alcohol related diseases such as cancer of the upper aero-digestive tract or liver cirrhosis. The epidemiological evidence on the association between silica exposure and liver cancer is not consistent, and in industrialised countries about 75% of liver cancer cases are attributable to risk factors that are not occupational (alcohol consumption, B and C hepatitis, aflatoxin infection).[36] An experimental study on rats[37] and few observational studies on workers exposed to crystalline silica reported hepatic changes and liver diseases, including hepatocellular carcinoma.[38] Thus the observed mortality excess for liver cancer must be considered with caution and our findings need to be further investigated with a cumulative exposure variable estimation.

In conclusion, in a large cohort of workers compensated for silicosis we observed a significant excess in mortality among males for cancer of the lung, trachea, and bronchus, tuberculosis, and liver cancer. Excess mortality from liver cancer was more than twofold higher than in the reference population suggesting a possible association with silica dust exposure. Mortality from non-malignant respiratory diseases and tuberculosis was increased among females compensated for silicosis.

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