Mortality of Talc Miners and Millers From Val Chisone, Northern Italy

An Updated Cohort Study

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Objective: The aim of this study was to update the analysis of mortality of a cohort of talc miners and millers in Northern Italy. **Methods:** We analyzed the mortality during 1946 to 2013 of 1722 male workers in an asbestos-free talc mine (1166 miners and 556 millers) employed during 1946 to 1995. **Results:** The overall standardized mortality ratio (SMR) was 1.24 [95% confidence interval (95% CI) 1.17 to 1.32]; no deaths were observed from pleural cancer; mortality from lung cancer was not increased. Mortality from pneumoconiosis was increased (SMR 26.62; 95% CI 20.71 to 33.69), in particular among miners, and was associated with duration of employment and time since first employment. **Conclusions:** We confirmed the lack of association between exposure to asbestos-free talc, lung cancer, and mesothelioma. Increased mortality from pneumoconiosis among miners is attributable to past exposure to silica.

Talc is a lamellar structured silicate, widely used in industrial and commercial products. Although ''fibrous talc'' (ie, talc containing asbestos fibers) is considered a human carcinogen,[1] limited animal and human data are available on the potential carcinogenic effect of talc not containing asbestos. According to the International Agency for Research on Cancer (IARC), asbestos-free talc cannot be classified as to its carcinogenicity to humans (category 3), while the use of perineal talc is classified as possible human carcinogen (category 2B), based on limited evidence of an association with ovarian cancer,[2] a conclusion challenged by a recent meta-analysis[3].

As reviewed by Wild,[4] several studies of workers exposed to asbestos-free talc reported no cases of mesothelioma, and no excess risk of lung cancer.[5–8] Occasional excesses of lung cancer risk among miners, not paralleled by comparable results in millers, were attributed to coexposure to radon decay products.[7] These results contrast with an excess risk of lung cancer identified among talc workers with high-level exposure to crystalline silica.[9]

In order to provide additional evidence on risk of cancer and selected nonmalignant diseases among workers exposed to asbestos-free talc, we updated the analysis of mortality of a cohort of talc miners and millers in Val Chisone, Northern Italy,[5,10,11] one of the first occupational cohorts ever studied in Italy. Talc mined and processed in Val Chisone is free from asbestos.[12–14]

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METHODS

The cohort comprised 1822 subjects employed in the mine or the mill between 1946 and 1995. Data on date of birth, date of first employment, date of last employment, last known address, and detailed job history were obtained from personnel records at the plant. Miners ($N = 1212$) were those who worked in the mine, either exclusively or in combination with other departments; millers ($N = 610$) were those who worked in the mill or in other settings, but not in the mine. Data on smoking status were collected from 200 workers in 1993 during routine medical surveillance: 47% of miners and the 44% of millers were current smokers. In a survey of 52 workers who were employed in 2010, the prevalence of current smoking was 51%.

The follow-up for mortality was conducted by contacting the municipality of residence of cohort members; death certificates were obtained from the same source, and causes of death were coded according to the version of the International Classification of Diseases used at the time of death. Because of low reliability of cause of death certification above age 85, the follow-up was truncated when cohort members reached that age. For the present analysis, the follow-up began on January 1, 1946, or date of first employment, whichever occurred later, and ended on the date of last contact, date of death, 85th birthday, or March 31, 2013, whichever occurred earlier.

The inclusion criteria in this study were (i) valid date of birth; (ii) valid date of first employment; (iii) valid date of last employment; (iv) valid date of death, if deceased; and (v) at least 1 month of employment after January 1, 1946. The application of these criteria led to the exclusion of 65 (3.6%) subjects, of whom 37 (56.9%) were deceased. Among the excluded deceased subjects, there was one death from pharyngeal cancer, esophageal cancer, stomach cancer, lung cancer, and brain cancer each. As only 35 of 1757 (2.0%) subjects were females, the analyses were restricted to 1722 males (1166 miners and 556 millers).

Agents to which miners were exposed include talc, silica, mining gases, and radon, as well as, since 1991, diesel engine emission. Exposures of millers included talc and silica, as potential contaminant of talc. Diesel engine emissions comprise gases (SO_2, NO_x) and particulate matters, which entail exposure to polycyclic aromatic hydrocarbons (PAHs). Limited environmental measurements of respirable dust, talc, and silica are available for millers during the period 1974 to 1981; more extensive data are available between 2003 and 2014 for millers and miners. From 1991, periodical air monitoring to control diesel emission exposure was conducted. All the evaluations showed exposure levels lower than threshold limit values (TLVs) for gases and, for benzo-a-pyrene, used as a marker of PAH exposure, levels close to 1 ng/m^3. Underground radon exposure levels have been available since 1991, and were below 300 Bq/m^3.

The number of expected deaths from all causes, selected cancer sites, and selected non-neoplastic conditions were computed using male national and regional death rates for each 5-year calendar period and age group. Regional rates were used for the

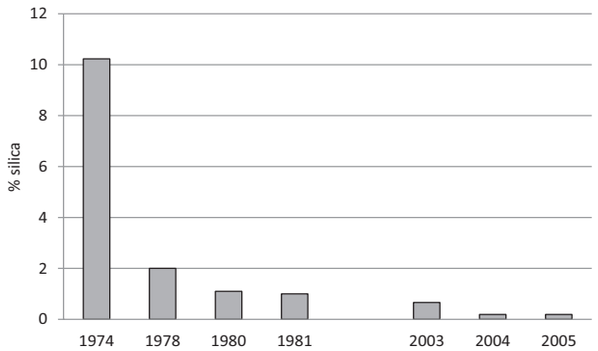

FIGURE 1. Proportion of silica over total dust by year of sampling.

period 1970 to 2013, and national death rates for the period 1950 to 1969. Rates were not available for the period 1946 to 1949, for which 1950 to 1954 national rates were used. No regional rates were available for cancers of the oral cavity and esophagus and for suicides, and national rates were used for these causes for the whole study period. We computed standardized mortality ratios (SMRs) as ratios of observed to expected deaths, and the corresponding 95% confidence intervals (CIs) were calculated according to the Poisson distribution of observed deaths.[15] We also computed SMRs by year of first employment, duration of employment, and department of employment (miners and millers). The Poisson trend statistic was used to detect trends in the SMRs, and heterogeneity between exposure subgroups (eg, miners vs millers) was examined through a χ^2 test.[15]

RESULTS

Exposure to Respirable Dust and Silica

Figure 1 summarizes the proportion of crystalline silica over total dust regarding the mill plant from 1974 to 1981 and from 2003 to 2005. Figures 2 and 3 present average exposure levels to respirable dust and silica, respectively, in miners and millers during 2007 to 2014. The increase of the dust exposure level observed in 2011 is related to drilling rock activity that took place that year. This activity is not usual and it happens only when it is necessary to reach a new talc deposit. For both agents, exposure levels were higher in miners than millers. Average silica levels were below the ACGIH-recommended TLV ($0.025\ mg/m^3$).[16]

Mortality Analysis

The 1722 cohort members contributed 59,339 person-years of observation (average duration of follow-up, 34.5 years). At the end of the follow-up, 505 subjects (29.3%) were alive (115 of whom died after they reached age 85), 1084 subjects (63.0%) were deceased [62 (5.7%) with an unknown cause of death], and 133 subjects (7.7%) were lost to follow-up.

Table 1 lists the number of observed and expected deaths, and the corresponding SMRs, for all causes, selected cancer sites, and non-neoplastic causes. Total mortality was higher than expected (SMR 1.24, 95% CI 1.17 to 1.32), while mortality from all cancers was modestly and not significantly higher than expected (SMR 1.04, 95% CI 0.92 to 1.18). No deaths were observed from pleural cancer, and two deaths were observed from peritoneal cancer (expected deaths 2.0 and 1.4, respectively; the two deaths from peritoneal cancer were not mesothelioma); mortality from lung cancer was not increased. A significant excess mortality was noticed for oral and pharyngeal cancer (SMR 3.83, 95% CI 2.62 to 5.41) and for esophageal cancer (SMR 2.13, 95% CI 1.16 to 3.57). There was a nonsignificant excess mortality from stomach (SMR 1.20, 95% CI 0.84 to 1.67) and colorectal cancer (SMR 1.03, 95% CI 0.69 to 1.50). Only two deaths from urinary bladder cancer were observed versus 11.5 expected.

We observed an increased mortality from non-neoplastic respiratory diseases (SMR 2.27, 95% CI 1.92 to 2.67) mainly due to mortality for pneumoconiosis (69 observed, 2.6 expected, SMR 26.62, 95% CI 20.71 to 33.69). Excluding observed and expected deaths from pneumoconiosis from the category of non-malignant respiratory diseases, the SMR in the latter category was reduced to 1.25 (95% CI 0.99 to 1.57). There was also an increased mortality from cirrhosis (SMR 1.87, 95% CI 1.43 to 2.39). Mortality from accidents and violent causes (suicides) was nonsignificantly higher than expected. Mortality from cardiovascular diseases (SMR 0.81; 95% CI 0.66 to 0.98), cerebrovascular diseases (SMR 0.74; 95% CI 0.57 to 0.93), and chronic obstructive pulmonary diseases (SMR 0.95; 95% CI 0.67 to 1.31) was lower than expected.

Table 2 provides results of the analysis separately for miners and millers. These results show the absence of lung cancer excess mortality in either group, and the presence of excess mortality from all causes and from cirrhosis in both. On the contrary, the excess mortality from cancers of the oral cavity and esophagus was confined to miners. The risk excess of pneumoconiosis was significantly higher in miners than in millers (63 deaths from silicosis observed in miners compared with six in millers). After excluding deaths from pneumoconiosis, the excess mortality from non-neoplastic respiratory diseases was limited to miners.

Table 3 summarizes mortality by duration of employment: the only cause of death associated with duration of employment was pneumoconiosis (*P* value of test for linear trend, 0.0005). There was a suggestion of an inverse relationship with mortality from ischemic heart disease. Mortality from alcohol-related diseases (oral, pharyngeal and esophageal cancer, cirrhosis) did not show a consistent relationship with duration of employment.

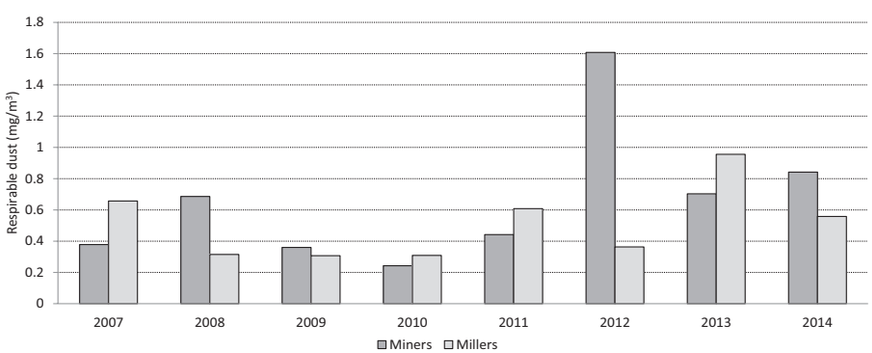

FIGURE 2. Average respirable dust level, by year and job, 2007–2014.

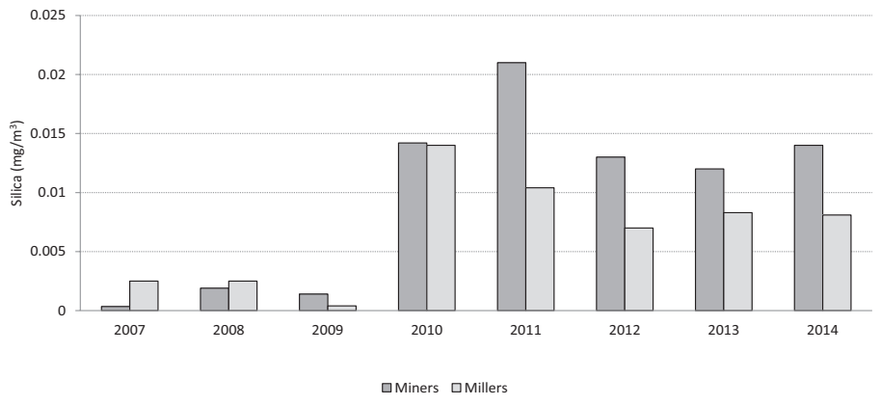

FIGURE 3. Average silica exposure level, by year and job, 2007–2014.

Results are reported according to time since first employment in Table 4: also, in this analysis, a trend was apparent only for pneumoconiosis. The analysis by year of first employment was hampered by the small number of person-years among workers first employed after 1969: in this group, however, no deaths from pneumoconiosis were observed (0.3 deaths expected).

Table 5 summarizes the results of subsequent mortality follow-ups of this cohort. In the first follow-up, to 1974,[5] there was only a weak suggestion of an increased mortality from pneumoconiosis and alcohol-related diseases, while results of the second follow-up, to 1995,[11] were similar to those of the present analysis. In none of the subsequent reports, mortality from lung cancer was notable.

DISCUSSION

Rubino et al[5] reported dust exposure levels in this mine from 1946 to 1976, and showed a progressive decrease for total respirable dust (from a range 100 to 1000 million particles per cubic foot [mmpcf] before 1955 to less than 10 mmpcf between 1960 and 1975), and estimated higher exposure to silica among miners, owing to drilling and other operations in footwall rocks with a high content of quartz.[11] In the case of millers, dust comprises almost exclusively

TABLE 1. Standardized Mortality Ratios From Selected Causes, Whole Cohort (PY = 59,339)

Cause of Death	ICD-IX Code	Obs	Exp	SMR (95% CI)
All causes	1–999	1084	870.8	1.24 (1.17–1.32)
All cancers	140–239	277	265.3	1.04 (0.92–1.18)
Oral and pharyngeal cancer	140–149	32	8.4	3.83 (2.62–5.41)
Esophageal cancer	150	14	6.6	2.13 (1.16–3.57)
Stomach cancer	151	36	29.9	1.20 (0.84–1.67)
Colorectal cancer	152–154, 159.0	28	27.1	1.03 (0.69–1.50)
Liver cancer	155	16	12.3	1.30 (0.74–2.12)
Pancreatic cancer	157	10	9.9	1.01 (0.49–1.87)
Peritoneal cancer*	158	2	1.4	1.38 (0.17–4.97)
Laryngeal cancer	161	8	8.1	0.99 (0.43–1.96)
Lung cancer	162	75	72.6	1.03 (0.81–1.30)
Pleural cancer	163	0	2.0	0 (0–1.84)
Prostate cancer	185	14	16.3	0.86 (0.47–1.44)
Bladder cancer	188	2	11.5	0.17 (0.02–0.63)
Kidney cancer	189	4	5.2	0.77 (0.21–1.98)
Brain and CNS cancer	191–192	2	6.1	0.33 (0.04–1.19)
Lympho-hematopoietic neoplasms	200–208	11	17.2	0.64 (0.32–1.15)
Lymphoma	200–202	4	7.0	0.57 (0.16–1.47)
Leukemia	204–208	7	7.5	0.93 (0.37–1.92)
Ischemic heart diseases	410–414	103	126.9	0.81 (0.66–0.98)
Cerebrovascular diseases	430–438	71	96.6	0.74 (0.57–0.93)
Chronic obstructive pulmonary diseases	490–496	37	39.0	0.95 (0.67–1.31)
Non-neoplastic respiratory diseases	460–519	147	64.8	2.27 (1.92–2.67)
Pneumoconiosis	500–508	69	2.6	26.62 (20.71–33.69)
Non-neoplastic respiratory diseases, excluding pneumoconiosis	460–496, 510–519	78	62.2	1.25 (0.99–1.57)
Liver cirrhosis	571	63	33.7	1.87 (1.43–2.39)
External causes	800–999	60	53.4	1.12 (0.86–1.45)

CI, confidence interval; CNS, central nervous system; Exp, expected deaths; ICD-IX, International Classification of Diseases, 9th version; Obs, observed deaths; PY, number of person-years; SMR, standardized mortality ratio.

*Two deaths from peritoneal cancer were from neoplasms other than mesotheliom.

TABLE 2. Standardized Mortality Ratios From Selected Causes, by Job

	Miners (PY = 41,209)			Millers (PY = 18,131)		
Cause of Death	**Obs**	**Exp**	**SMR (95% CI)**	**Obs**	**Exp**	**SMR (95% CI)**
All causes	731	562.3	1.30 (1.21–1.40)	353	308.5	1.14 (1.03–1.27)
All cancers	193	175.3	1.10 (0.95–1.27)	84	90.0	0.93 (0.74–1.16)
Oral and pharyngeal cancer	25	5.5	4.53 (2.93–6.69)	7	2.8	2.47 (0.99–5.09)
Esophageal cancer	11	4.3	2.55 (1.27–4.57)	3	2.3	1.32 (0.27–3.86)
Lung cancer	52	48.6	1.07 (0.80–1.40)	23	23.9	0.96 (0.61–1.44)
Ischemic heart diseases	65	81.2	0.80 (0.62–1.02)	38	45.7	0.83 (0.59–1.14)
Cerebrovascular diseases	44	60.2	0.73 (0.53–0.98)	27	36.4	0.74 (0.49–1.08)
Non-neoplastic respiratory diseases	120	40.8	2.94 (2.44–3.52)	27	24.0	1.13 (0.74–1.64)
Pneumoconiosis	63	1.6	38.68 (29.72–49.49)	6	1.0	6.23 (2.29–13.58)
Liver cirrhosis	41	22.0	1.86 (1.34–2.53)	22	11.7	1.87 (1.17–2.84)

CI, confidence interval; Exp, expected deaths; *N*, number of workers; Obs, observed deaths; PY, number of person-years; SMR, standardized mortality ratio.

TABLE 3. Standardized Mortality Ratios From Selected Causes, by Duration of Employment

Duration of Employment							
	<15 Years (PY = 31,196)		15–24 Years (PY = 14,913)		25+ Years (PY = 13,230)		
Cause of Death	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Test for Linear Trend**
All causes	385	1.31 (1.18–1.45)	311	1.23 (1.09–1.37)	388	1.20 (1.08–1.32)	0.22
All cancers	100	1.09 (0.89–1.33)	71	0.99 (0.77–1.25)	106	1.04 (0.85–1.26)	0.72
Oral and pharyngeal cancer	11	3.74 (1.86–6.69)	8	3.51 (1.51–6.92)	13	4.16 (2.21–7.11)	0.81
Esophageal cancer	7	3.14 (1.26–6.46)	5	2.77 (0.90–6.46)	2	0.79 (0.09–2.85)	0.08
Lung cancer	29	1.14 (0.77–1.64)	14	0.76 (0.41–1.27)	32	1.12 (0.76–1.58)	0.92
Ischemic heart diseases	42	1.03 (0.74–1.39)	28	0.74 (0.49–1.07)	33	0.69 (0.47–0.96)	0.075
Cerebrovascular diseases	24	0.83 (0.53–1.24)	15	0.50 (0.28–0.82)	32	0.85 (0.58–1.20)	0.92
Non-neoplastic respiratory diseases	40	2.00 (1.43–2.73)	44	2.20 (1.60–2.96)	63	2.54 (1.95–3.25)	0.23
Pneumoconiosis	11	14.24 (7.10–25.48)	16	19.88 (11.35–32.28)	42	41.41 (29.84–55.98)	0.0005
Liver cirrhosis	20	1.73 (1.06–2.68)	26	2.64 (1.72–3.87)	17	1.38 (0.80–2.20)	0.59

CI, confidence interval; Obs, observed deaths; PY, number of person-years; SMR, standardized mortality ratio.

TABLE 4. Standardized Mortality Ratios From Selected Causes, by Time Since First Employment

	Time Since First Employment								
	<20 Years (PY = 26,206)		20–29 Years (PY = 13,576)		30–39 Years (PY = 10,206)		40+ Years (PY = 9,352)		
Cause of Death	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Test for Linear Trend**
All causes	141	1.23 (1.04–1.46)	214	1.35 (1.17–1.54)	282	1.30 (1.15–1.46)	447	1.17 (1.07–1.29)	0.30
All cancers	23	0.85 (0.53–1.27)	48	1.05 (0.78–1.40)	79	1.16 (0.92–1.45)	127	1.02 (0.85–1.21)	0.60
Oral and pharyngeal cancer	2	1.98 (0.24–7.15)	6	3.27 (1.20–7.13)	18	7.19 (4.26–11.36)	6	2.00 (0.73–4.36)	0.97
Esophageal cancer	2	2.99 (0.36–10.79)	6	4.58 (1.68–9.98)	3	1.56 (0.32–4.56)	3	1.12 (0.23–3.28)	0.075
Lung cancer	5	0.82 (0.26–1.90)	9	0.75 (0.34–1.42)	21	1.08 (0.67–1.65)	40	1.15 (0.82–1.56)	0.25
Ischemic heart diseases	8	0.53 (0.23–1.04)	24	0.96 (0.61–1.43)	32	0.93 (0.64–1.32)	39	0.74 (0.53–1.02)	0.79
Cerebrovascular diseases	7	0.83 (0.33–1.72)	14	0.84 (0.46–1.41)	16	0.64 (0.37–1.05)	34	0.73 (0.50–1.02)	0.66
Non-neoplastic respiratory dis.	9	1.24 (0.57–2.35)	26	2.36 (1.54–3.46)	34	2.18 (1.51–3.04)	78	2.53 (2.00–3.15)	0.068
Pneumoconiosis	3	8.99 (1.85–26.25)	13	24.36 (12.96–41.65)	15	22.33 (12.49–36.84)	38	36.10 (25.54–49.55)	0.0085
Liver cirrhosis	10	1.70 (0.81–3.13)	24	2.75 (1.76–4.10)	15	1.52 (0.85–2.51)	14	1.51 (0.82–2.53)	0.87

CI, confidence interval; Obs, observed deaths; PY, number of person-years; SMR, standardized mortality ratio.

TABLE 5. Standardized Mortality Ratios for Selected Causes in Subsequent Follow-Ups of the Cohort, by Job

	Follow-up to 1974[5]		Follow-up to 1995[11]		Follow-up to 2013 [Present Analysis]	
Cause of Death	**Miners**	**Millers**	**Miners**	**Millers**	**Miners**	**Millers**
All cancers	0.77	0.92	1.08	0.83	1.10	0.93
Oral and pharyngeal cancer	—	—	6.12	3.33	4.53	2.47
Esophageal cancer	1.25	1.35	2.32	1.79	2.55	1.32
Lung cancer	0.46	0.62	1.07	0.69	1.07	0.96
Nonmalignant respiratory diseases	—	—	3.05	1.03	2.94	1.13
Pneumoconiosis	2.01	1.43	—	—	38.68	6.23
Liver cirrhosis	—	—	1.80	1.65	1.86	1.87

talc, that is, total dust equates talc exposure. The decrease in crystalline silica exposure was due to a general improvement of working conditions, including for miners improvement in ventilation and enhancing of web drilling conditions and for millers improvement in screening of the material, with a reduction in the proportion of rock over talc.

The present update of the analysis of mortality of a cohort of talc miners and millers from Northern Italy confirmed the results observed in previous follow-ups, as summarized in Table 5.[5,11] There were no cases of mesothelioma, nor an excess mortality from lung cancer in either miners or millers. These data confirm that exposure to talc not contaminated by fibers is not associated with risk of these diseases. The very long time since first employment in the present analysis (over 9000 person-years of observation, or 16% of the total, had more than 40 years since first employment) excludes the possibility that the lack of cases of mesothelioma is a consequence of insufficient latency. Data on tobacco smoking in this cohort are limited, but do not support the hypothesis of a lower prevalence of smoking in this cohort compared with regional or national data, which would mask an increase in occupationally related lung cancer. In fact, smoking prevalence was similar to that of men in Italy in the mid-1990s,[17] when data based on medical surveillance were available in this cohort.

The excess risk for oral, pharyngeal, and esophageal cancers and for cirrhosis confirms the results of earlier reports of this cohort,[5,11] and is likely related to heavy alcohol consumption.[18] The excess mortality from nonmalignant respiratory diseases is predominantly due to the high number of deaths from pneumoconiosis.

Crystalline silica is classified as human carcinogen,[1] but the presence of an excess lung cancer risk in the presence of confirmed silicosis remains open to discussion.[19–22] The lack of an increased risk of lung cancer in the absence of silicosis is compatible with the hypothesis that exposure levels required to exert a carcinogenic effect are higher than those required for silicosis development. The data of our study support this hypothesis, as we observed a high number of deaths from silicosis (69 observed vs 2.6 expected), in the absence of an excess risk for lung cancer. Deaths from pneumoconiosis observed among miners and, to a lesser extent, among millers are attributable to high silica exposure in the past, when rock drilling activities were frequent and technical prevention means had not yet been introduced.[5] In particular, deaths from pneumoconiosis reported among millers are likely a consequence of silica exposure related to the higher percentage present in talc as contaminant before 1974. The notion of a key role of high exposure in the past is confirmed by the results of the analysis by time since first employment (Table 4). No deaths from pneumoconiosis were observed among workers first employed after 1969, and no new cases of silicosis were observed during medical surveillance since 1991 (M. Coggiola, personal communication).

The absence of an excess risk of lung cancer in a cohort with a large number of silicosis cases suggests that lung fibrosis is not a necessary step in the development of the lung cancer. It is possible that the excess risk of lung cancer observed in cohorts of silicosis patients[19] is related to higher exposure levels than those required to cause silicosis, typically in the range of 0.1 mg/m^3.[23]

Among other exposures potentially experienced by miners in this cohort are radon and diesel engine exhaust. Use of diesel engines started in 1991. Although the number of miners with sufficiently long latency may not be large, the results provide no support to the hypothesis of a risk of lung cancer from diesel exhaust exposure in this cohort of underground nonmetal miners. Radon exposure levels were consistently below 300 Bq/m^3.

Strengths of our study include the large size of the cohort, the uniquely long follow-up that allows separate analyses by job title, detailed considerations of latency and other time factors, the presence of data on exposure levels in the early period of operation of the plant,[5] and the availability of some data on smoking prevalence. Limitations include the lack of individual exposure data, the lack of information on some potential confounders (eg, alcohol drinking), the lack of validation of causes of death, and of information on morbidity. However, while relying on causes of death listed on death certificates entails some misclassification, it ensures comparability with the reference (regional or national) population in the calculation of SMRs.

In conclusion, we confirmed previous results on lack of an association between exposure to talc, lung cancer, and malignant mesothelioma. Mortality from nonmalignant respiratory diseases was increased in miners, and the excess can be attributed to past exposure to silica. The absence of an excess mortality from lung cancer does not support the hypothesis of an association between silica exposure and the development of lung cancer, in the absence of silicosis.[19]

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