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# Mortality among silicotics in Genoa, Italy, from 1961 to 1987

by Franco Merlo, PhD,[1] Luigi Fontana, MD,[2] Giorgio Reggiardo, BSc,[1] Marcello Ceppi, PhD,[1] Giovanni Barisione, MD,[2] Elsa Garrone, BSc,[1] Marina Doria, MD[3]

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A historical cohort mortality study conducted among 515 silicotic subjects revealed higher than expected risks for all causes [standardized mortality ratio (SMR) 1.89], respiratory tract diseases (SMR 8.89), silicotuberculosis (SMR 27.00), respiratory tract cancers (SMR 3.14), and lung cancer (SMR 3.50). Mortality from cardiovascular diseases was lower than that expected (SMR 0.51). Lung cancer risk increased with duration of occupational exposure (SMR 2.80, 2.99, and 5.02 for 14, 15—29, and 30 years of employment, respectively). Lung cancer risk was higher for the silicotics without tuberculosis (SMR 3.72) than for those with tuberculosis (SMR 2.83). Indirect adjustment for smoking habits, including number of cigarettes smoked per day, showed that smoking would have been responsible for a maximum risk of 1.77. Thus smoking may have explained 50% of the observed excess mortality from lung cancer.

*Key terms* epidemiology, Italian silicotics, pulmonary tuberculosis, respiratory tract cancer, smoking.

In 1986, the International Agency for Research on Cancer (IARC) critically examined all published studies investigating the link between exposure to silica dusts and lung cancer. It concluded that there was sufficient evidence for the carcinogenicity of crystalline silica in experimental animals and limited evidence for its carcinogenicity in humans (1).

Despite the fact that most human studies have reported an increased lung cancer risk, their interpretation has been hampered by serious study design problems, such as the choice of appropriate reference populations, the lack of knowledge concerning smoking habits, and concomitant exposure to other occupational carcinogens (2). Studies of silicotic subjects suffer from all these limitations and from potential selection and disease misclassification biases. Selection bias may increase the probability of workers (exposed to silica) seeking and receiving compensation for silicosis when other exposures (eg, smoking) are actually responsible for symptomatic lung function impairment (3), while the disease misclassification may result in the inclusion of other pneumoconioses (eg, asbestosis) in the group of true silicotics (4). Both biases have been suspected to increase the estimated epidemiologic measures of association between silicosis and lung cancer. However, recently published data from humans (5—9) showed that smoking habits and disease misclassification bias had a marginal role, if any, in the lung cancer risk estimated for silicotics. Moreover, mechanistic studies of carcinogenicity showed direct damage by crystalline silica through binding to the phosphate backbone of the DNA (deoxyribonucleic acid) strand (Daniel et al and Williams & Saffiotti this issue).

## Subjects and methods

Our unit previously reported findings of a historical mortality study of 520 silicotic subjects diagnosed at the Department of Occupational Health of the San Martino Hospital, Genoa, Italy, between 1961 and 1980 and followed through 1981. This research showed increased mortality from respiratory tract diseases [standardized mortality ratio (SMR) 13.36] and respiratory cancers (SMR 6.85) (10). We used the same methods (10) to evaluate the 515 silicosis patients whose follow-up was extended from 1981 through 1987 in this study. SMR values and their 95% confidence intervals (95% CI) were computed for overall mortality and specific causes of death by using EPILOG (11).

## Results

The vital status of the 515 silicotic subjects and of a subcohort of 450 individuals for which information on year of first employment, duration of employment, and type of exposure was available is reported in table 1. For the latter subcohort, mean age at entry into follow-up was 55.3 (SD 11.1) years and age at the beginning of employment was 23.4 (SD 8.55) years. The mean length between first employment and the diagnosis of silicosis was 31.9 (SD 13.5) years and the mean length of follow-up was 11.56 (SD 9.6) years. Pulmonary tuberculosis was diagnosed for 117 (26%) silicotics, who contributed 1215 person-years of observation (24% of the total number of person-years).

Table 2 shows the overall and cause-specific SMR values for the entire cohort of silicotics. The overall mortality (SMR 1.66,

1 IST — Istituto Nazionale per la Ricerca sul Cancro, CSTA — Centre for the Study of Environmental Cancer, Division of Environmental Epidemiology and Biostatistics, Genoa, Italy.
2 Occupational Health Department, Ospedali Civili S Martino, Genoa, Italy.
3 Local Health Unit II, San Remo, Italy.

Reprint requests to: Dr F Merlo, Centre for the Study of Environmental Cancer, Division of Epidemiology and Biostatistics, IST-Istituto Nazionale per la Ricerca sul Cancro, Viale Benedetto XV, 10, 16132 Genoa, Italy.

**Table 1.** Vital status of the cohort of silicotics followed from 1961 through 1987 and the person-years of observation at the date of termination of the study.

| Vital status | All silicotics | | Silicotics with complete data | |
|---|---|---|---|---|
| | Number | % | Number | % |
| Alive | 172 | 33.4 | 160 | 35.6 |
| Deceased | 301 | 58.4 | 290 | 64.4 |
| All cancer deaths | 58 | 19.3 | 56 | 19.3 |
| Lung cancer | 37 | 63.8[a] | 35 | 62.5[a] |
| Respiratory tract diseases | 127 | 42.2 | 122 | 42.1 |
| Other diseases | 45 | 14.9 | 45 | 15.5 |
| Silicotuberculosis | 35 | 11.6 | 34 | 11.7 |
| Lost to follow-up | 42 | 8.2 | — | 0 |
| Total | 515 | 100 | 450 | 100 |
| Person-years | 6214 | | 5141 | |

[a] Percentage of all cancer deaths.

**Table 2.** Mortality from selected causes among all the silicotics from 1961 through 1987. [O = observed deaths, E = expected deaths based on age and calendar-year-specific death rates of the male population of Italy (1961—1987), SMR = standardized mortality ratio, 95% CI = 95% confidence interval]

| Cause of death[a] | O | E | SMR | 95% CI |
|---|---|---|---|---|
| Malignant neoplasms (140—208) | 58 | 44.0 | 1.32 | 1.0—1.70 |
| Respiratory tract (161—165) | 39 | 13.8 | 2.82 | 2.01—3.86 |
| Lung (162) | 37 | 11.7 | 3.15 | 2.22—4.35 |
| Respiratory tract diseases (460–519) | 127 | 16.8 | 7.57 | 6.29—8.97 |
| All deaths (0—999) | 301 | 181.3 | 1.66 | 1.48—1.86 |

[a] Code from the ninth revision of the International Classification of Diseases in parentheses.

**Table 3.** Mortality from selected causes among the silicotics with complete data (N = 450). [O = observed deaths, E = expected deaths based on age and calendar-year-specific death rates of the male population of Italy (1961—1987), SMR = standardized mortality ratio, 95% CI = 95% confidence interval]

| Cause of death[a] | O | E | SMR | 95% CI |
|---|---|---|---|---|
| Malignant neoplasms (140—208) | 56 | 34.9 | 1.61 | 1.26—2.15 |
| Buccal cavity, pharynx (140—149) | 2 | 1.18 | 1.69 | 0.20—6.11 |
| Stomach (151) | 5 | 5.8 | 0.87 | 0.28—2.02 |
| Respiratory tract (161—165) | 37 | 11.8 | 3.14 | 2.21—4.33 |
| Larynx (161) | 2 | 1.36 | 1.47 | 0.18—5.31 |
| Lung (162) | 35 | 9.99 | 3.50 | 2.44—4.87 |
| Prostate (185) | 3 | 2.46 | 1.22 | 0.25—3.57 |
| Bladder (188) | 1 | 1.76 | 0.57 | 0.01—3.16 |
| Kidney (189) | 1 | 0.56 | 1.78 | 0.05—9.92 |
| Lymphatic, hemopoietic (200—208) | 1 | 2.07 | 0.48 | 0.01—2.68 |
| Cardiovascular diseases (390—459) | 35 | 68.2 | 0.51 | 0.36—0.71 |
| Respiratory tract diseases[b] (460—519) | 122 | 13.7 | 8.89 | 7.38—10.6 |
| Digestive tract diseases (520—579) | 23 | 10.9 | 2.10 | 1.33—3.16 |
| Ill-defined conditions (780—799) | 6 | 3.51 | 1.71 | 0.63—3.72 |
| Violent causes (800—999) | 3 | 5.55 | 0.54 | 0.11—1.5 |
| Other diseases[c] | 45 | 29.2 | 1.54 | 1.12—2.06 |
| Silicotuberculosis (11.4) | 34 | 1.25 | 27.0 | 18.8—38.0 |
| All deaths (0—999) | 290 | 152.9 | 1.89 | 1.69—2.12 |

[a] Code from the ninth revision of the International Classification of Diseases in parentheses.
[b] 96 deaths from silicosis.
[c] Includes two deaths from chronic renal failure (ICD code 585.0).

95% CI 1.48—1.86) was significantly higher than the expected. Mortality from all malignant neoplasms was also higher than the expected (SMR 1.32, 95% CI 1.0—1.70). Particularly elevated mortality risks were observed for respiratory tract diseases (SMR 7.57, 95% CI 6.29—8.97), for respiratory tract cancers (SMR 2.82, 95% CI 2.01—3.86), and for lung cancer (SMR 3.15, 95% CI 2.22—4.35). The exclusion of four lung cancer deaths that occurred within the first year of the diagnosis of silicosis did not significantly alter the lung cancer risk (SMR 2.82, 95% CI 1.94—3.96).

Table 3 shows the overall and cause-specific SMR value for the subcohort of silicotics with complete data. Excess mortality was observed for all causes (SMR 1.89, 95% CI 1.69—2.12), pulmonary tuberculosis (SMR 27.00, 95% CI 18.80—38.00), respiratory tract diseases (SMR 8.89, 95% CI 7.38—10.6), all cancers (SMR 1.61, 95% CI 1.26—2.15), lung cancer (SMR 3.50, 95% CI 2.44—4.87), and respiratory tract cancers (SMR 3.14, 95% CI 2.21—4.33). The analyses for site-specific, smoking-related malignancies did not reveal a significant excess mortality for oropharyngeal (SMR 1.69, 95% CI 0.20—6.11), laryngeal (SMR 1.47, 95% CI 0.18—5.31), or bladder (SMR 0.57, 95% CI 0.01—3.16) cancer. No deaths from esophageal-pancreatic cancer were observed. Mortality from prostate cancer (SMR 1.22, 95% CI 0.25—3.57), kidney cancer (SMR 1.78, 95% CI 0.05—9.92), and lymphatic and hemopoietic neoplasms (SMR 0.48, 95% CI 0.01—2.68) was not found to differ significantly from the expected level. The observed excess mortality from nonmalignant respiratory diseases was largely attributable to silicosis: 96 (80.7%) of the 119 respiratory deaths. Mortality from cardiovascular diseases was significantly lower than the expected value (SMR 0.51, 95% CI 0.36—0.71). The increased mortality from digestive tract diseases (SMR 2.10, 95% CI 1.33—3.16) was mainly due to cirrhosis of the liver (18 deaths). Mortality from other diseases was higher than the expected value (SMR 1.54, 95% CI 1.12—2.06) due to the excess mortality from silicotuberculosis (SMR 27.00, 95% CI 18.80 — 38.00). No deaths from autoimmune diseases and two deaths from chronic renal failure were observed.

Table 4 shows the SMR values for selected causes of death by the pulmonary tuberculosis status as ascertained at the time of the medical examination. Silicotics diagnosed as having pulmonary tuberculosis had a strikingly higher mortality from silicotuberculosis (SMR 72.70, 95% CI 47.90—105.70) than the remaining subjects (SMR 7.99, 95% CI 3.21—16.46). Mortality from lung

**Table 4.** Mortality from selected causes among the silicotics according to the pulmonary tuberculosis status. (O = observed deaths, SMR = standardized mortality ratio, 95% CI = 95% confidence interval)

| Cause of death | Pulmonary tuberculosis | | | | | |
|---|---|---|---|---|---|---|
| | Yes[a] | | | No[b] | | |
| | O | SMR | 95% CI | O | SMR | 95% CI |
| All deaths | 93 | 1.83 | 1.48—2.24 | 197 | 1.93 | 1.66—2.22 |
| All cancers | 9 | 0.93 | 0.43—1.77 | 47 | 1.86 | 1.37—2.48 |
| Lung cancer | 7 | 2.83 | 1.14—5.83 | 28 | 3.72 | 2.47—5.38 |
| Silicotuberculosis | 27 | 72.7 | 47.9—105.7 | 7 | 7.99 | 3.21—16.46 |
| Respiratory tract diseases | 34 | 6.84 | 4.74—9.56 | 88 | 10.1 | 8.07—12.39 |

[a] N = 117, person-years = 1214.
[b] N = 333, person-years = 3927.

cancer and from respiratory diseases was lower among the silicotics with tuberculosis than among those with tuberculosis. For the former group the observed number of cancer deaths did not differ from those expected from the Italian population cancer death rate.

An analysis by type of occupation (data not shown) revealed higher mortality from all cancers (SMR 2.58, 95% CI 1.53—4.08) and from lung cancer (SMR 4.83, 95% CI 2.32—8.89) among the foundry and coke oven workers. These subjects were likely to have had greater occupational exposure to polynuclear aromatic hydrocarbons (12) than refractory, ceramic, and excavation workers (SMR 1.86, 95% CI 0.96—1.87, and SMR 2.78, 95% CI 1.81—4.07, for all cancers and lung cancer, respectively).

The SMR values for all cancers and lung cancer by length of employment and years since first employment are reported in table 5. Increased risks for lung cancer were detected for silicotics with 15—29 years of employment for the latency period 15—29 years (SMR 8.12, 95% CI 2.64—18.94) and with ≥ 30 years of employment for the latency period 30 years (SMR 5.06, 95% CI 2.77—8.49). No cancer deaths were observed for the latency period ≤ 14 years (not reported in table 5). The lung cancer risk increased with increasing length of employment (SMR 2.80, 2.99, and 5.02 for ≤ 14, 15—29, and ≥ 30 years of employment, respectively).

Smoking habits were indirectly adjusted for (13) on the basis of the proportions of smokers, ex-smokers, and nonsmokers of the Italian male population (14), as well as on the basis of the proportions of subjects who smoked ≤ 10, 11—20, 21—40, and > 40 cigarettes per day. These proportions and the associated relative risks (15) that were used to estimate the expected excess mortality from lung cancer due to smoking habits are reported in table 6. Since smoking data were not available for 83 silicotics (16.1%) and the number of cigarettes smoked per day was lacking for 47 smokers (9.1%) in the study group and for 0.6% of the reference population, indirect adjustment was done on the assumption that all the subjects classified as having "unknown" habits in the study group were smokers and that smokers with an "unknown number of cigarettes smoked per day" in the study group were heavy smokers (> 40 cigarettes per day), while in the reference population they were considered light smokers (ie, they smoked ≤ 10

**Table 5.** All cancer and lung cancer mortality by the length of employment and years since first employment. (O = observed deaths, SMR = standardized mortality ratio, 95% CI = 95% confidence interval)

| Cause of death | Years since first employment | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 15—29 | | | ≥ 30 | | | Total | | |
| | O | SMR | 95% CI | O | SMR | 95% CI | O | SMR | 95% CI |
| All cancers | | | | | | | | | |
| Employed ≤ 14 years | 3 | 1.57 | 0.32—4.61 | 12 | 1.59 | 0.82—2.78 | 15 | 1.55 | 0.87—2.55 |
| Employed 15—29 years | 5 | 2.61 | 0.85—6.08 | 13 | 1.01 | 0.54—1.73 | 18 | 1.21 | 0.72—1.92 |
| Employed ≥ 30 years | — | . | .. | 23 | 2.24 | 1.42—3.36 | 23 | 2.24 | 1.42—3.36 |
| Total | 8 | 2.06 | 0.89—4.06 | 48 | 1.57 | 1.15—2.08 | 56 | 1.61 | 1.26—2.15 |
| Lung cancer | | | | | | | | | |
| Employed ≤ 14 years | 2 | 3.27 | 0.40—11.81 | 6 | 2.77 | 1.02—6.02 | 8 | 2.80 | 1.21—5.51 |
| Employed 15—29 years | 5 | 8.12 | 2.64—18.94 | 8 | 2.15 | 0.93—4.25 | 13 | 2.99 | 1.60—5.12 |
| Employed ≥ 30 years | — | . | .. | 14 | 5.06 | 2.77—8.49 | 14 | 5.02 | 2.74—8.42 |
| Total | 7 | 5.60 | 2.63—11.54 | 28 | 3.24 | 2.15—4.68 | 35 | 3.50 | 2.44—4.87 |

**Table 6.** Crude estimates of the lung cancer rate ratio attributable to differences in smoking habits in the study group and in the Italian male population.

| | Risk | Study group | | | Reference population | | |
|---|---|---|---|---|---|---|---|
| | | Smoking habits[a] | Assumption | | Smoking habits[d] | Assumption | |
| | | | First[b] | Second[c] | | First[e] | Second[f] |
| Smokers | 15 | 48.9 | | | 45.6 | | |
| 1—10 cigarettes/day | 4.6 | 20.6 | 30.2 | 20.6 | 14.6 | 14.8 | 15.2 |
| 11—20 cigarettes/day | 7.5 | 15.0 | 22.0 | 15.0 | 23.1 | 23.4 | 23.1 |
| 21—40 cigarettes/day | 13.1 | 3.6 | 5.26 | 3.6 | 6.8 | 6.9 | 6.8 |
| > 40 cigarettes/day | 16.6 | 0.6 | 0.78 | 25.2 | 0.5 | 0.5 | 0.5 |
| Unknown | | 9.1 | . | . | 0.6 | . | . |
| Ex-smokers | 4 | 20.6 | . | . | 13.5 | . | . |
| Nonsmokers | 1 | 14.4 | . | . | 40.9 | . | . |
| Unknown | . | 16.1 | . | . | . | | |
| Rate ratio | . | 1.066[1] | 1.146[2] | 1.767[3] | 1 | 1 | 1 |

[a] Smoking habits of the silicotics.
[b] Assuming that those with unknown smoking habits in the study group (16.1%) were all smokers equally distributed within each cigaretters/day group.
[c] Assuming that both "unknown" in the study group (16.1% + 9.1%) smoked > 40 cigarettes/day.
[d] Smoking habits of the referents (14).
[e] Assuming that smokers with unknown cigarette consumption in the reference population (0.6%) were equally distributed with each cigarettes/day group.
[f] Assuming that smokers with unknown cigarette consumption in the reference population (0.6%) smoked ≤ 10 cigarettes/day.
[1] a vs d, [2] b vs e, [3] c vs f.

cigarettes per day). According to these assumptions, the mortality risk from lung cancer attributable solely to smoking ranged between 1.066 and 1.767. Thus the maximum lung cancer risk explainable by smoking was (3.5-1.767)/3.5 or 50%.

## Discussion

The findings of our study show that clinically diagnosed silicotics experience a higher than expected mortality from all cancers, lung cancer, silicotuberculosis, silicosis, and digestive tract diseases. Excess mortality from lung cancer and silicotuberculosis is consistent with the results of other studies on silicotic subjects, particularly that by Infante-Rivard et al (16). An analysis by length of employment suggested that exposure to silica dusts may increase the risk of lung cancer among workers who develop silicosis. The observed dose-response relationship between lung cancer risk and length of employment is suggestive of a causal role played by exposure to silica dusts and lung cancer development, although the role of other occupational carcinogens may be important as well. Indirect adjustment for smoking explained about 50% of the excess mortality from lung cancer. The marginal role of smoking in causing the observed excess of lung cancer was confirmed also by the significantly lower mortality from cardiovascular diseases and by the lack of excess risk for smoking-related neoplasms other than lung cancer.

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