Original article
Scand J Work Environ Health 2005;31(6):450-458
doi:10.5271/sjweh.949

Meta-analysis of silicosis and lung cancer
by Lacasse Y, Martin S, Simard S, Desmeules M

Affiliation: Centre de Pneumologie, Hôpital Laval, 2725 Chemin Ste-Foy, Ste-Foy, P Quebec, G1V 4G5, Canada. Yves.Lacasse@med.ulaval.ca

Key terms: lung cancer; lung neoplasm; meta-analysis; pulmonary fibrosis; review; silica; silicosis; systematic review

This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/16425586
Meta-analysis of silicosis and lung cancer

by Yves Lacasse, MD, Sylvie Martin, MSc, Serge Simard, MSc, Marc Desmeules, MD

Lacasse Y, Martin S, Simard S, Desmeules M. Meta-analysis of silicosis and lung cancer. Scand J Work Environ Health 2005;31(6):450–458.

Objectives This study examined the association between silicosis and lung cancer in a systematic review (and meta-analysis) of the epidemiologic literature, with special reference to the methodological quality of observational studies.

Methods We searched Medline, Toxline, BIOSIS and Embase (1966–May 2004) for original articles published in any language and systematically reviewed the bibliographies of the retrieved articles. Observational studies (cohort and case–control studies) were selected if they reported a measure of association [standardized mortality ratio (SMR), relative risk or odds ratio] relating lung cancer to silicosis.

Results Thirty-one studies (27 cohort studies, 4 case–control studies) met the inclusion criteria of the meta-analysis. Without any adjustment for smoking, the meta-analysis of the cohort studies indicated that the common SMR was 2.45 [95% confidence interval (95% CI) 1.63–3.66; homogeneity P<0.0001]. When the results of the cohorts for which mortality data were adjusted for smoking were pooled, the common SMR was 1.60 (95% CI 1.33–1.93; homogeneity P=0.52). In a “dose–response” analysis, the profusion of small and large opacities found in chest X-rays correlated with the risk of death from lung cancer. Overall, the case–control studies were more conservative in their conclusions.

Conclusions Because of biases inherent to observational studies, it is likely that the risk of lung cancer among silicosis patients is overestimated in the current literature. There is nevertheless evidence, from data restricted to never-smokers and from a “dose–response” analysis, that silicosis and lung cancer are associated.

Key terms lung neoplasm; pulmonary fibrosis; silica; systematic review.

Silicosis is a parenchymal lung disease caused by the inhalation of crystalline silicon dioxide, or silica (1). Such exposure occurs in a wide variety of occupations, among which foundry workers, miners, quarriers, and sandblasters are the most at risk (2). In jurisdictions in which occupational exposure standards have been specified, the incidence of silicosis has dramatically diminished (3). Nevertheless, currently recommended exposure limits for occupational exposure to silica are still associated with a significant risk of silicosis (4). In the province of Quebec (Canada), silicosis remains the third most common cause of compensation for work-related respiratory disorders, following occupational asthma and asbestos-related diseases.

The association between silicosis and lung cancer has long been suggested by clinical observations and case series (5–7). However, more recent epidemiologic studies have often provided conflicting results. The interpretation of this epidemiologic evidence has been hampered by shortcomings that include the noncomparability of reference groups, detection bias, and the confounding effect of other carcinogenic risk factors, such as cigarette smoking and exposure to other known occupational carcinogens (8).

We sought to reexamine the epidemiologic evidence regarding the association between silicosis and lung cancer through a systematic review (and meta-analysis) of the epidemiologic literature, with special reference to the methodological quality of the observational studies. The methods that we used are in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group’s recommendations (9).

Material and methods

Literature search

We searched Toxline, BIOSIS, Embase and Medline (10) (1966–May 2004) for original articles published in
any language using the following strategy: ([silicosis, MeSH Major Topic] OR [silicon dioxide, MeSH Major Topic]) AND [lung neoplasms, MeSH Major Topic]. We also searched for additional articles from the reference list of relevant papers obtained from the electronic search.

Study selection

Observational studies (cohort and case–control studies) were selected if they reported a measure of association [standardized mortality ratio (SMR), relative risk or odds ratio (OR)] relating lung cancer to silicosis. Proportional mortality studies were excluded because of their potential for a systematic overestimation of risk (11). To limit selection bias, we also excluded autopsy studies (12). In addition, narrative reviews, letters to the editor, clinical commentaries, case series, and case reports were disregarded.

Two reviewers (YL and SM) successively applied these criteria to the titles and abstracts of all the citations obtained. If the title of an article or, when available, its abstract suggested any possibility that it might be relevant, the paper was retrieved and independently assessed by the same reviewers for a final decision about its inclusion into the meta-analysis. Throughout this process, the reviewers were blinded to the authors’ names, the journal name, and the year of publication of the papers. Those published in languages other than English and French were translated into French. Any disagreement was resolved by consensus or by consulting a third reviewer (MD). When we identified studies that had been reported in multiple papers, we limited our analysis to the most recent report, unless the necessary data had appeared only in an earlier paper. Agreement between coders was measured using quadratic weighted kappa statistics (13). We kept a log of the reasons for rejecting citations identified from the searches. Publication bias was investigated by visual inspection of a plot of the magnitude of risk in a study versus the number of silicotics in the study (14). We determined a priori that the effect of publication bias should be slight if this plot showed a rough, symmetric funnel shape.

Study evaluation for methodological quality

We evaluated study validity by systematically considering the following three important sources of bias in observational studies: (i) selection bias, which stems from the absence of comparability between the groups being studied; (ii) information bias, which results from an incorrect (or differential) determination of exposure or outcome; and (iii) confounding bias, which is likely when the results can be accounted for by the presence of a factor associated with both the exposure and the outcome rather than directly involved in the causal pathway (15).

Information extraction

Two reviewers (YL and SM) abstracted information from all of the selected papers for inclusion in the meta-analysis. The abstracted information included (i) the study design, (ii) the industry and country where the occupational exposure to silica that led to silicosis had occurred, (iii) the period during which new cases of silicosis were included in the cohort and the length of follow-up, (iv) the record source, (v) whether confounders were accounted for, (vi) whether the comparison group was from the general population or consisted of any other group of workers, and (vii) the actual data reported in the paper. In case of missing data, we did not attempt to contact any of the authors for additional information.

Analysis of cohort studies

For each study, we calculated the SMR from the observed and expected number of deaths from lung cancer among the silicosis patients and the unexposed (SMR=observed/expected) and computed the corresponding 95% confidence interval (16). Since the lung cancer incidence rate approaches its mortality rate (17), standardized incidence ratios (SIR) were analyzed similarly and pooled with the SMR values. In addition, we noted that several studies had reported the SMR value after adjustment for smoking according to the method described by Axelson (18). For these studies, we computed the expected number of deaths from lung cancer from the number of deaths actually observed and the adjusted SMR reported in the study. In addition, we noted that several authors controlled for smoking by restricting the analysis to silicosis patients who had never smoked. We therefore conducted three separate meta-analyses, one with the unadjusted SMR, another with the adjusted SMR according to Axelson’s method, and a third one of the SMR restricted to never-smokers. The SMR values were weighted by the inverse of their variance and combined according to a random-effects model (19). Homogeneity was tested by the method described by Fleiss (19). Subgroup analyses were indicated when significant heterogeneity was found among the primary study results. Statistical significance was set at P<0.05.

Subgroup analyses and a priori hypotheses explaining heterogeneity among studies. In meta-analyses that did not meet the criteria for homogeneity, we conducted subgroup analyses in an effort to identify the source of heterogeneity according to the following hypotheses: (i) studies of silicosis patients who acquired their lung disease from underground mining (with potential exposure to co-carcinogens such as radon daughters) result in higher risks of lung cancer, (ii) the longer the follow-up period, the higher the risk of lung cancer, and (iii) studies of compensation registries result in higher risks of lung cancer.
Silicosis and lung cancer

Dose–response analysis. In conducting this review, we realized that several authors reported SMR values according to the International Labour Organization’s (ILO) radiographic classification of pneumoconioses (20). In this classification, cases of silicosis are categorized according to the presence and profusion of small (≤1 cm) and large (>1 cm) opacities. Categories 1, 2, and 3 represent an increasing profusion of small opacities, as defined by standard radiographs. Categories A, B, and C are defined in terms of the dimension of large opacities. The comparison of the risks of lung cancer among silicosis patients was appealing since it allowed an "exposure–response analysis" in which workers with high exposure were compared with workers with low exposure, both groups presumably sharing similar smoking habits and clinical characteristics otherwise (21).

Because there was no clear evidence from the literature that smoking predisposes to the development or the progression of silicosis (22), this analysis does not seem to be confounded by smoking. This analysis was conducted according to the method for the meta-analysis of epidemiologic dose–response data described by Berlin et al (23). In this method, a weighted least-square estimate of the regression slope (β) of the logarithm of the risk versus exposure (ILO category) is computed for each study (log [risk]=β · exposure). The inverse of the variance of log [risk] is used as the regression weight. The regression slopes are then combined according to a random-effects model (19). Finally, we converted back the common logarithm into natural units expressed in terms of relative risk. Homogeneity was also tested by the method described by Fleiss (19).

Analysis of case–control studies

The case–control studies that met the inclusion criteria of the meta-analysis used different statistical methods to report the risk of lung cancer among silicosis patients. We restricted our statistical analysis to unadjusted data. The unadjusted odds ratios were weighted by the inverse of their variance and combined according to a random-effects model (19). Statistical significance was tested by the method described by Fleiss (19). Validity assessment

Validity assessment

Cohort studies. With one exception (37), the cohort studies included in the meta-analysis presented SMR (or SIR) values computed from national mortality rates for lung cancer. In two studies, separate analyses were conducted using comparison groups that were not from the general population (8, 38). Since the general population rates were used for calculating expected deaths and the smoking prevalence rate among blue collars is higher than in the general population (52, 53), the unadjusted SMR values should be interpreted cautiously. Accordingly, in unadjusted analyses, lung cancer SMR values tend to be overestimated for smoking and underestimated when the analysis is limited to nonsmokers. Fourteen cohorts were from compensation registries (12, 24–26, 29–31, 33, 34, 36, 39, 45–47). Compensation for silicosis largely depends on disability (selection bias) (38, 40, 54, 55) and, therefore, on smoking (confounding bias). Another difficulty in interpreting several of the available epidemiologic investigations was the combined exposure with other lung carcinogens, such as radon daughters in underground mining and polycyclic aromatic hydrocarbons in foundries (confounding bias). Most of the studies reported on silicosis patients whose diagnosis was made in the 1960s; this approach increased the likelihood of misdiagnoses among patients with pre-existing diffuse lung disease (information bias). In all of the studies, misclassification may have resulted in the inclusion of other pneumoconioses in silicosis patients (information bias). In addition, periodic surveillance in cohorts of compensated silicosis patients may have increased the likelihood of a lung cancer diagnosis for these patients (information bias). Overall, these potential sources of bias favor the finding of a positive association between silicosis and lung cancer.

Case–control studies. One case–control study (49) was hospital-based and at risk of Berkson’s (or admission) bias, which comes into play whenever there are differences in admission rates between exposed (ie, silicosis patients) and unexposed persons (selection bias) (56). Otherwise, the selection of controls and data collection
Lacasse et al

were appropriate, without clear indication of a differential determination of exposure or outcome. In all of the studies, smoking was accounted for, either in stratified or logistic regression analyses.

Analysis of cohort studies

A total of 23,305 silicosis patients contributed to the analysis of the cohort (table 2). We did not find any clear indication of publication bias from the visual inspection of the funnel plot (figure 1). Without any adjustment for smoking or any other co-carcinogen, the pooled SMR value was 2.45 (95% CI 1.63–3.66). However, significant heterogeneity was found among the study results (P<0.0001). We could not explain this heterogeneity by excluding the cohorts of underground miners from the analysis (table 3). It is also noteworthy that excluding studies of compensation registries did not result in a lower risk of lung cancer (table 3). In addition, we could not find any correlation between the length of follow-up and the overall risk of lung cancer.

When the results of the cohorts were pooled in which mortality data were adjusted for smoking according to Axelson’s method, the pooled SMR value was 1.60. The results of the studies that contributed to this analysis were homogeneous. When the results of the cohorts restricted to never-smokers were pooled, the SMR value was 1.52. The results of the studies that contributed to this analysis were also homogeneous. In the latter analysis, because the unexposed populations included smokers, this result probably represents an underestimate of the risk of lung cancer among silicosis patients.

In the three studies that conducted analyses using comparison groups that were not from the general population, the risk of lung cancer among silicosis patients was increased. In Amandus & Costello’s study (8), the age-adjusted lung cancer risk for silicosis patients was 1.56 (95% CI 0.91–2.68) times higher than that of non-silicotic metal miners. In the study by Dong et al (37), the lung cancer risk of silicosis patients was 2.10 times higher (P<0.01) than that of workers from rough rolling steel mills (37). Finally, in Finkelstein’s study (38),

Table 1. Characteristics of the cohort studies included in the systematic review of lung cancer in silicosis patients.

| Study                  | Country          | Source of diagnosis | Type of work                     | Number of patients | Period at risk (years)* |
|-----------------------|------------------|---------------------|----------------------------------|--------------------|------------------------|
| Cohort studies        |                  |                     |                                  |                    |                        |
| Finkelstein et al, 1987 (24) | Canada           | Compensation registry | Any                             | 276                | 22.5                   |
| Zambon et al, 1987 (25)  | Italy            | Compensation registry | Any                             | 1313               | 23.0                   |
| Puntoni et al, 1988 (12) | Italy            | Compensation registry | Refractory brick industry       | 138                | 19.0                   |
| Infante-Rivard et al, 1989 (26) | Canada        | Compensation registry | Any                             | 1072               | 24.5                   |
| Chen et al, 1990 (27)   | China            | Screening           | Underground mining               | 1355               | 6.0                    |
| Chiyotani et al, 1990 (28) | Japan           | Hospitalized        | Unclear                         | 1941               | 14.5                   |
| Ebihara et al, 1990 (29) | Japan            | Compensation registry | Mining, tunneling, quarrying     | 698                | 5.0                    |
| Mehmet et al, 1990 (30) | Canada           | Compensation registry | Quarrying                       | 493                | 16.0                   |
| Ng 1990 (31)           | Hong Kong        | Compensation registry | Quarrying                       | 1184               | 6.0                    |
| Amandus & Costello, 1991 (8) | USA             | Screening           | Underground mining               | 369                | 15.0                   |
| Amandus et al, 1991 (32) | USA              | Screening           | Mining, tunneling quarrying      | 655                | 21.5                   |
| Chia et al, 1991 (33)   | China            | Compensation registry | Quarrying                       | 159                | 7.0                    |
| Morinaga et al, 1991 (34) | Japan            | Compensation registry | Foundries, stone workers         | 248                | 13.0                   |
| Shima et al, 1991 (35)  | Japan            | ?                   | Ceramic workers                  | 960                | –                      |
| Partanen et al, 1994 (36) | Finland         | Compensation registry | Foundries, mining, quarrying, stone, glass and ceramic industry | 811                | 34.5                   |
| Dong et al, 1995 (37)   | China            | Screening           | Refractory brick industry        | 1827               | 31.5                   |
| Finkelstein, 1995 (38)  | Canada           | Screening           | Any                             | 523                | 35.0                   |
| Goldsmith et al, 1995 (39) | USA             | Compensation registry | Any                             | 590                | 30.5                   |
| Merlo et al, 1995 (40)  | Italy            | Hospitalized        | Tunneling, quarrying, refractory brick industry | 450               | 16.0                   |
| Meijers et al, 1996 (41) | Netherlands      | Screening           | Ceramic workers                  | 124                | 14.0                   |
| Wang et al, 1996 (42)   | China            | Screening           | Any                             | 4271               | 9.0                    |
| Brown et al, 1997 (43)  | Sweden           | Hospitalized        | Not mentioned                    | 1130               | 15.0                   |
| Okazaki et al, 1997 (44) | Finland         | Screening           | Any                             | 163                | 13.0                   |
| Checkoway et al, 1999 (45) | USA             | Screening           | Diatomatous products            | 81                 | 29.5                   |
| Chan et al, 2000 (46)   | Hong Kong        | Compensation registry | Surface workers only             | 1490               | 8.5                    |
| Ulm et al, 2000 (47)    | Germany          | Compensation registry | Mining, tunneling quarrying      | 282                | –                      |
| Carta et al, 2001 (48)  | Italy            | Compensation registry | Any                             | 724                | 30.0                   |
| Case-control studies   |                  |                     |                                  |                    |                        |
| Hessel et al, 1986 (50) | South Africa     | Compensation registry | Gold mines                      | 399                | –                      |
| Mastrangelo et al, 1988 (49) | Italy        | Compensation registry | Mining, tunneling quarrying      | 618                | –                      |
| Fu et al, 1994 (48)     | China            | Screening           | Tin mines                       | 267                | –                      |
| Forastiere et al, 1986 (51) | Italy          | Compensation registry | Ceramic industry and quarrying   | 40                 | –                      |

* Period at risk determined either (i) from the mean follow-up period (number of persons × years at risk / total number of silicosis patients) or (ii) from the midpoint of the period during which new cases of silicosis were included in the cohort up to the end of the follow-up.
Silicosis and lung cancer

Table 2. Summary of the 27 cohort studies that met the inclusion criteria of the meta-analysis. The standardized mortality ratios (SMR) are unadjusted. Homogeneity P<0.0001. (O = observed, E = expected, 95% CI = 95% confidence interval)

| Reference | N   | O   | E   | Weight (%) | SMR  | 95% CI          |
|-----------|-----|-----|-----|------------|------|-----------------|
| Finkelstein et al, 1987 (24) | 276 | 16  | 5.3 | 1.9        | 3.02 | 1.73–4.90       |
| Zambon et al, 1987 (25)      | 1313| 70  | 29.3| 8.3        | 2.39 | 1.86–3.02       |
| Punttila et al, 1988 (12)    | 136 | 6   | 3.6 | 0.7        | 1.67 | 0.61–3.64       |
| Infante-Rivard et al, 1989 (26) | 172 | 83  | 23.9| 9.9        | 3.47 | 2.76–4.30       |
| Chen et al, 1990 (27)        | 1335| 14  | 2.7 | 1.7        | 5.24 | 2.87–8.80       |
| Chiyotani et al, 1990 (28)   | 1941| 44  | 7.3 | 5.2        | 6.03 | 4.38–8.09       |
| Ebihara et al, 1990 (29)     | 698 | 26  | 9.0 | 3.1        | 2.89 | 1.89–4.24       |
| Mehmert et al, 1990 (30)     | 493 | 9   | 4.9 | 1.1        | 1.83 | 0.84–3.48       |
| Ng 1990 (31)                 | 1184| 23  | 12.3| 2.7        | 1.87 | 1.18–2.80       |
| Amandus & Costello, 1991 (8) | 369 | 14  | 8.1 | 1.7        | 1.73 | 0.94–2.90       |
| Amandus et al, 1991 (32)     | 655 | 34  | 13.7| 4.0        | 2.48 | 1.72–3.47       |
| Chia et al, 1991 (33)        | 159 | 9   | 4.5 | 1.1        | 2.01 | 0.92–3.81       |
| Morinaga et al, 1991 (34)    | 248 | 10  | 2.7 | 1.2        | 3.70 | 1.78–6.81       |
| Shima et al, 1991 (35)       | 960 | 9   | 4.2 | 1.1        | 2.14 | 0.98–4.07       |
| Partanen et al, 1994 (36)    | 811 | 101 | 34.9| 12.0       | 2.89 | 2.36–3.52       |
| Dong et al, 1995 (37)        | 1287| 35  | 16.7| 4.2        | 2.10 | 1.66–2.99       |
| Finkelstein, 1995 (38)       | 523 | 13  | 6.0 | 1.5        | 2.16 | 1.15–3.30       |
| Goldsmith et al, 1995 (39)   | 590 | 39  | 20.5| 4.6        | 1.90 | 1.35–2.60       |
| Merlo et al, 1995 (40)       | 450 | 35  | 10.0| 4.2        | 3.50 | 2.44–4.87       |
| Meijers et al, 1996 (41)     | 124 | 10  | 4.6 | 1.2        | 2.20 | 1.05–4.04       |
| Wang et al, 1996 (42)        | 4271| 104 | 44.0| 12.4       | 2.37 | 1.93–2.87       |
| Brown et al, 1997 (43)       | 1130| 41  | 14.1| 4.9        | 2.91 | 2.09–3.95       |
| Oksa et al, 1997 (17)        | 163 | 15  | 5.6 | 1.8        | 2.70 | 1.51–4.46       |
| Checkoway et al, 1999 (44)   | 81  | 4   | 2.6 | 0.5        | 1.57 | 0.43–4.02       |
| Chan et al, 2000 (45)        | 1490| 33  | 17.0| 3.9        | 1.94 | 1.34–2.73       |
| Ulm et al, 2000 (46)         | 282 | 9   | 4.5 | 1.1        | 1.98 | 0.91–3.76       |
| Carta et al, 2001 (47)       | 724 | 34  | 24.9| 4.0        | 1.37 | 0.95–1.91       |
| Total                     | 23305| 100 | 2.45| 1.63–3.66  |

Figure 1. Study of publication bias (funnel plot). The two outliers are the studies by Chiyotani et al (28) and Chen et al (27). See the text for discussion.

Analysis of case–control studies

The authors of the four case–control studies that met the inclusion criteria of the meta-analysis used different statistical methods to report the risk of lung cancer among silicosis patients. The raw data are given in table 4. The meta-analysis indicated that silicosis increases the risk of lung cancer (common OR 1.70, 95% CI 1.15–2.53, P_homogeneity=0.23). However, stratified or logistic regression analyses resulted in conflicting interpretations. Hessel et al (50) found no statistically significant association between silicosis and lung cancer after matching cases and controls by age and smoking. Forastière et al (51) reported an increased risk of lung cancer (Mantel-Haenszel rate ratio 3.9, 95% CI 1.8–8.3) after control for age and smoking. After adjusting for smoking, Mastrangelo et al (49) found a twofold increase in lung cancer risk for workers compensated for silicosis (Mantel-Haenszel rate ratio 1.8, 95% CI 1.1–2.8). Fu et al (48) found that the presence of silicosis did not contribute to the prediction of risk for lung cancer independently of the years spent underground.

Discussion

Because of biases inherent to observational studies, it is likely that the SMR values reported in the cohort studies that met the inclusion criteria of this meta-analysis represent overestimates of the real risk of lung cancer among silicosis patients. The results of four case–control studies were more conservative. There is nevertheless evidence, from data restricted to never-smokers, from cohort studies using appropriate comparison groups, and from a "dose–response" analysis, that silicosis and lung cancer are truly associated.
conducted by independent reviewers (61). Sources of discordance include differences in study selection, data extraction, assessment of the ability to combine studies, and the choice of control groups. 

Table 3. Results of the meta-analysis of the cohort studies. (SMR = standardized mortality ratio, 95% CI = 95% confidence interval)

| Analysis                                      | Number of Studies | Silicosis patients (N) | SMR   | 95% CI       | Homogeneity (P-value) |
|-----------------------------------------------|-------------------|------------------------|-------|--------------|-----------------------|
| All studies included, without adjustment for smoking | 27                | Amandus & Costello (8), Puntoni et al (12), Oksa et al (17), Finkelstein et al (24), Zambon et al (25), Infante-Rivard et al (26), Chen et al (27), Chiyotani et al (28), Ebihara et al (29), Mehnert et al (30), Ng (31), Amandus et al (32), Chia et al (33), Morinaga et al (34), Shimma et al (35), Partanen et al (36), Dong et al (37), Finkelstein (38), Goldsmith et al (39), Merlo et al (40), Mejers et al (41), Wang et al (42), Brown et al (43), Checkoway et al (44), Chan et al (45), Ulm et al (46), Carta et al (47) | 23 305 | 2.45 | 1.63–3.66   | <0.0001               |
| After adjustment for smoking                  | 4                 | Goldsmith et al (39), Merlo et al (40), Checkoway et al (44), Chan et al (45) | 2 611 | 1.60 | 1.33–1.93   | 0.52                   |
| After exclusion of smokers                    | 10                | Amandus & Costello (8), Oksa et al (17), Zambon et al (25), Infante-Rivard et al (26), Ebihara et al (29), Amandus et al (32), Chia et al (33), Partanen et al (36), Dong et al (37), Wang et al (42) | 614  | 1.52 | 1.02–2.26   | 0.25                   |
| After exclusion of underground miners         | 24                | Puntoni et al (12), Oksa et al (17), Finkelstein et al (24), Zambon et al (25), Infante-Rivard et al (26), Chiyotani et al (28), Ebihara et al (29), Mehnert et al (30), Ng (31), Amandus et al (32), Chia et al (33), Morinaga et al (34), Shimma et al (35), Partanen et al (36), Dong et al (37), Finkelstein (38), Goldsmith et al (39), Merlo et al (40), Mejers et al (41), Wang et al (42), Brown et al (43), Checkoway et al (44), Chan et al (45), Ulm et al (46) | 20 877 | 2.47 | 1.76–3.48   | <0.0001               |
| After exclusion of studies of compensation registries | 13                | Amandus & Costello (8), Oksa et al (17), Chiyotani et al (28), Amandus et al (32), Shimma et al (35), Dong et al (37), Finkelstein (38), Merlo et al (40), Mejers et al (41), Wang et al (42), Brown et al (43), Checkoway et al (44) | 13 829 | 2.67 | 1.68–4.25   | <0.0001               |

Relation with previous studies

Our systematic review differs from that published in 1997 by Tsujda et al (57). In their meta-analysis, all types of pneumoconioses (with the exception of asbestosis) were included. However, our results are in agreement with previous meta-analyses published by Smith et al (58) and Steenland & Stayner (59). Smith et al (58) reported a summary relative risk of 2.2 (95% CI 2.1–2.4) from 23 cohort and case–control studies. In this meta-analysis, 12 of the 27 cohort studies that met the inclusion criteria of our review became available after their publication. These authors considered three cohort studies that we excluded from our analysis because we could not ascertain that the study populations consisted of silicosis patients. On the contrary, we included the study of Chiyotani et al on hospitalized silicosis patients (28), whereas Smith et al (58) rejected it on the basis of the likelihood of selection bias (silicosis patients with lung cancer being more likely to be admitted to the hospital than silicosis patients without lung cancer). Steenland & Stayner (59) reported a summary relative risk of 2.3 (95% CI 2.2–2.6) from 19 cohort and case–control studies.

Similarly, our study complements a more recent review published by Kurihara & Wada (60), in which the literature search covered the period 1966–2001 and focused on Japanese studies. Sixteen epidemiologic studies met their inclusion criteria. Overall, the results reported by Kurihara & Wada are in agreement with ours. An important difference between the two studies is that these authors could not find any trend between the radiographic category of silicosis and the risk of lung cancer. Such differences are not unusual in meta-analyses conducted by independent reviewers (61). Sources of discordance include differences in study selection, data extraction, assessment of the ability to combine studies, and the choice of control groups.
Silicosis and lung cancer

and statistical methods for data synthesis (61). In the “dose–response” analysis, we used a set of studies that differs from the one in the Japanese review. Neither the radiographic classification of silicosis nor the statistical methods were the same in both studies. Nevertheless, Kurihara & Wada (60) concluded that silicosis increases lung cancer risk.

Publication bias

We limited our analysis of publication bias to a visual inspection of the funnel plot because the statistical methods used to judge its symmetry have been questioned (14). We found no clear indication of publication bias from the visual inspection of the funnel plot (figure 1). Publication bias would have modified the shape of the funnel. If small statistically nonsignificant studies had been omitted, a “bite” would have been taken out of the display for effects near zero (i.e., SMR 1.00). The two outliers are the study by Chiyotani et al (28) on hospitalized patients and that by Chen et al (27) on underground miners. The authors of the latter study commented that their results may have been confounded by exposure to radon daughters. The two studies accounted for less than 7% of the total weight of the studies that we included in our analysis. Both contributed only to the unadjusted analyses (figure 1 and table 3) and were not included in the dose–response analysis. The exclusion of both studies from the meta-analysis did not have a significant impact on its results (data not shown).

Clinical and medicolegal implications

Our finding of a “dose–response gradient” among silicosis patients deserves further comments. Whether this result reflects a real dose–response relationship between silicosis and lung cancer remains uncertain. On one hand, lung fibrosis (as seen in idiopathic pulmonary fibrosis and asbestosis) increases the risk of lung cancer (62, 63). On the other hand, whether the association between silicosis and lung cancer is due to the effect of the fibrotic process or to the effect of quartz dust itself is unclear (64). Some data suggest that the progression of silicosis may be determined by total accumulated silica dust exposure (65). If silica was a true carcinogen, our finding would rather be interpreted as an indication of the dose–response relationship between silica exposure and lung cancer (66). Such a distinction is, however, irrelevant for compensatory boards in their assessment of patients with silicosis and lung cancer. It is however relevant for the compensation of patients with occupational exposure to silica (without silicosis) and lung cancer.

Concluding remarks

We conclude that silicosis increases the risk of lung cancer. This association does not necessarily imply that silica is a lung carcinogen. A better and modern understanding of the relationship between silica exposure and lung cancer requires additional investigations and dose–response analyses, including exposures in the range of currently recommended exposure limits.

Acknowledgments

The Institute de Recherche en Santé et Sécurité au Travail du Québec (IRSST) (Grant 99–163) granted funding for this study.

We thank Dr Marc Baril from the IRSST for his support during all steps of this project. We acknowledge the contributions of Hélène Girard and Jocelyne Bellemare, the first a technician in documentation and the second a librarian at Laval Hospital. We are also indebted to Dr Miyako Yamamoto and Mr Vladimir Kurin for their translation of the original papers.

References

1. Ziskind M, Jones RN, Weill H. Silicosis. Am Rev Respir Dis 1976;113:643–65.
2. Valiante DJ, Rosenman KD. Does silicosis still occur? JAMA
3. De Klerk NH, Ambrosini GL, Pang SC, Musk AW. Silicosis compensation in Western Australian gold miners since the introduction of an occupational exposure standard for crystalline silica. Ann Occup Hyg 2002;46:687–92.

4. Steenland K, Brown D. Silicosis among gold miners: exposure—response analyses and risk assessment. Am J Public Health 1995;85:1372–7.

5. Cochrane AL, Moore F. A 20-year follow-up of men aged 55–64 including coal-miners and foundry workers in Stavely, Derbyshire. Br J Ind Med 1980;37:226–9.

6. Kolev K, Bakardjiev T. Interrelation between silicosis and lung cancer: preliminary report. Med Lav 1973;64:241–4.

7. Vervuurt VH, Krijn JW. Pneumoconiosis and pulmonary carcinoma. Am J Pathol 1938;14:49–58.

8. Amandus HE, Shy C, Wing S, Blair A, Heineman EF. Silicosis and smoking [review]. Scand J Work Environ Health 2005, vol 31, no 6 suppl 2:77–80.

9. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000;283:2008–12.

10. Gehanno JF, Paris C, Thirion B, Caillard JF. Assessment of bibliographic databases performance in information retrieval for occupational and environmental toxicology. Occup Environ Med 1998;55:562–6.

11. Decoufle P, Thomas TL, Pickle LW. Comparison of the portionate mortality ratio and standardized mortality ratio risk measures. Am J Epidemiol 1980;111:263–9.

12. Puntoni R, Goldsmith DF, Valero F, Vercelli M, Bonassi S, Di Giorgio F, et al. A cohort study of workers employed in a refractory brick plant. Tumori 1988;74:27–33.

13. Kramer MS, Feinstein AR. Clinical biostatistics LIV. The biostatistics of concordance. Clin Pharmacol Ther 1981;29:111–23.

14. Steenland K, Nolian M, Guyatt GH. Publication bias: a brief review for clinicians. Mayo Clin Proc 2000;75:1284–8.

15. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet 2002;359:248–52.

16. Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol 1990;131:373–5.

17. Oksa P, Pukkala E, Karjalainen O, Ojajärvi A, Huuskonen P. Lung cancer among workers exposed to silica dust in Chinese refractory plants. Scand J Work Environ Health 1995;21 suppl 2:69–72.

18. Axelsson O. Aspects on confounding in occupational health epidemiology [letter to the editor]. Scand J Work Environ Health 1978;4:98–102.

19. Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res 1993;2:121–45.

20. International Labour Organisation (ILO). Guidelines for the use of the ILO International Classification of Radiographs of Pneumoconiosis. Revised ed. In: ILO, editor. Occupational Safety and Health Series. Geneva: ILO; 1980. Occupational Safety and Health Series p 46–8.

21. Steenland K, Miettinen A, Bottella P, Stanley L, Attfield M, Chen J, et al. Pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multicentre study. Cancer Causes Control 2001;12:773–83.

22. Hessel PA, Gamble JF, Nicolich M. Relationship between silicosis and smoking [review]. Scand J Work Environ Health 2003;29(5):329–36.

23. Berlin JA, Longnecker M, Greenland S. Meta-analysis of epidemiologic doses-response data. Epidemiology 1993;4:218–28.

24. Finkelstein M, Liss GM, Krammer F, Kusiak RA. Mortality among workers receiving compensation awards for silicosis in Ontario 1940–85. Br J Ind Med 1987;44:588–94.

25. Zambon P, Simonato L, Mastrangelo G, Winkelmann R, Saia B, Crepet M, et al. Mortality of workers compensated for silicosis during the period 1959–1963 in the Veneto region of Italy. Scand J Work Environ Health 1987;13:118–23.

26. Infante-Rivard C, Armstrong B, Petticler M, Cloutier LG, Theriault G. Lung cancer mortality and silicosis in Quebec, 1938–85. Lancet 1989;2:1504–7.

27. Chen SY, Hayes RB, Liang SR, Li QG, Steward PA, Blair A. Mortality experience of haematite mine workers in China. Br J Ind Med 1990;47:175–81.

28. Chiyotani K, Saito K, Okubo T, Takahashi K. Lung cancer risk among pneumoconiosis patients in Japan, with special reference to silicotics. Lyon: International Agency for Research on Cancer (IARC); 1990. IARC Scientific Publications no 97, p 95–104.

29. Ebihara I, Shinokawa E, Kawami M, Kurosawa T. A retrospective cohort mortality study of pneumoconiosities. J Sci Lab Occup Med 1990;66:399–407.

30. Mehnen WH, Staneckez W, Mohner M, Konetzke G, Muller W, Ahlendorf W et al. A mortality study of a cohort of slate quarry workers in the German Democratic Republic. Lyon: International Agency For Research on Cancer (IARC); 1990. IARC Scientific Publications 97, p 55–64.

31. Ng TP, Chan SL, Lee J. Mortality of a cohort of men in a silicosis register: further evidence of an association with lung cancer. Am J Ind Med 1990;17:163–71.

32. Amandus HE, Shy C, Wing S, Blair A, Heineman EP. Silicosis and lung cancer in North Carolina dusty trades workers. Am J Ind Med 1991;20:57–70.

33. Chia S-E, Chia K-S, Phoon W-H, Lee H-P. Silicosis and lung cancer among Chinese granite workers. Scand J Work Environ Health 1991;17:170–4.

34. Morinaga K, Sakatanai M, Yokoyama K, Yasui I, Hara I, Sera Y. Silicosis and lung cancer: a retrospective cohort study of compensated patients with silicosis in Osaka. Jpn J Traumatol Occup Med 1991;39:192–7.

35. Shima S, Arakawa T, Kato Y, Yoshida T, Taniwaki H, Nao-gakura K, et al. Epidemiological studies on the risk of pulmonary tuberculosis or lung cancer in ceramic workers with pneumoconiosis. J Sci Lab Occup Med 1991;67:565–73.

36. Partanen T, Pukkala E, Vainio H, Kurppa K, Koskinen H. Increased incidence of lung and skin cancer in Finnish silicotic patients. J Occup Med 1994;36:616–22.

37. Dong D, Xu G, Sun Y, Hu P. Lung cancer among workers exposed to silica dust in Chinese refractory plants. Scand J Work Environ Health 1995;21 suppl 2:69–72.

38. Finkelstein MM. Radiographic abnormalities and the risk of lung cancer among workers exposed to silica dust in Ontario. Can Med Assoc J 1995;152:37–43.

39. Goldsmith DF, Beaumont JJ, Morrin LA, Schenker MB. Respiratory cancer and other chronic disease mortality among silicotics in California. Scand J Work Environ Health 1995;21 suppl 2:77–80.

40. Merlo F, Fontana L, Reggiardo G, Ceppi M, Barisione G, Moril L, et al. Mortality and lung cancer in workers exposed to silica and other dusts in a refractory brick plant. Tumori 1988;74:27–33.
Silicosis and lung cancer

42. Wang Z, Dong D, Liang X, Qu G, Wu J, Xu X. Cancer mortality among silicotics in China’s metallurgical industry. Int J Epidemiol 1996;25:913–7.

43. Brown LM, Gridley G, Olsen JH, Mellekjaer L, Linet MS, Fraumeni JF Jr. Cancer risk and mortality patterns among silicotic men in Sweden and Denmark. J Occup Environ Med 1997;39:633–8.

44. Checkoway H, Hughes JM, Weill H, Seixas NS, Demers PA. Crystalline silica exposure, radiological silicosis, and lung cancer mortality in diatomaceous earth industry workers. Thorax 1999;54:56–9.

45. Chan CK, Leung CC, Tam CM, Yu TS, Wong TW. Lung cancer mortality among a cohort of men in a silicotic register. Int Arch Occup Environ Health 2001;74:69–75.

46. Ulm K, Ehnes H, Guldner K, Kieser D, Gerein P, Eigenthaler J, et al. Exposure to quartz, silicosis and lung cancer—description of the study; results of the mortality analysis. Arbeitsmed Sozialmed Umweltmed 2000;35:97–101.

50. Hessel PA, Sluis-Cremer GK, Hnizdo E. Cohort mortality study of North American industrial sand workers, I: mortality from lung cancer, silicosis and other causes. Ann Occup Hyg 2001;45:193–9.

55. McDonald JC. Silica, silicosis, and lung cancer. Br J Ind Med 1989;46:289–91.

56. Sackett DL. Bias in analytic research. J Chronic Dis 1979;32:51–63.

57. Tsujda T, Babazono A, Yamamoto E, Mino Y, Matsuoka H. A meta-analysis on the relationship between pneumoconiosis and lung cancer. J Occup Health 1997;39:285–94.

58. Smith AH, Lopipero PA, Barroga VR. Meta-analysis of studies of lung cancer among silicotics. Epidemiology 1995;6:617–24.

59. Steenland K, Stayner L, Silica, asbestos, man-made mineral fibers, and cancer. Cancer Causes Control 1997;8:491–503.

60. Kurihara N, Wada O. Silicosis and smoking strongly increase lung cancer risk in silica-exposed workers. Ind Health 2004;42:303–14.

62. Hughes JM, Weill H. Asbestosis as a precursor of asbestos related lung cancer: results of a prospective mortality study. Br J Ind Med 1991:48:229–33.

63. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis: a population-based cohort study. Am J Respir Crit Care Med 2000;161:5–8.

64. Koskela RS, Klockars M, Järvinen E, Rossi A, Kolaru PJ. Cancer mortality of granite workers 1940–1985. Lyon: International Agency For Research on Cancer (IARC); 1990. IARC Scientific Publications 97, p 43–53.

65. Hughes JM, Jones RN, Gilson JC, Hammad YY, Samimi B, Hendrick DJ, et al. Determinants of progression in sandblasters’ silicosis. Ann Occup Hyg 1982;26:701–12.

Received for publication: 15 March 2005