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Meta-analysis of silicosis and lung cancer

by Yves Lacasse, MD,¹ Sylvie Martin, MSc,¹ Serge Simard, MSc,¹ Marc Desmeules, MD¹

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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

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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 but not 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 ($SMR = \text{observed/expected}$) 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.

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 ($\log[\text{risk}] = \beta \cdot \text{exposure}$). The inverse of the variance of $\log[\text{risk}]$ 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-effect model (19). Homogeneity was tested by the method described by Fleiss (19). Statistical significance was set at $P < 0.05$. We reported the results of the stratified or logistic regression analyses in a narrative fashion.

Results

Literature search and agreement studies

Altogether 1071 separate publications were retrieved. We reduced these to a list of 286 potentially eligible papers, of which 225 were excluded for the following reasons: silica exposure without specific reference to

silicosis (N=87), exposure other than silica (N=46), commentaries or reviews (N=46), no report of measure of association (N=20), autopsy studies (N=10), outcome other than lung cancer (N=10), animal studies (N=4), and proportional mortality studies (N=2). Both primary reviewers agreed to include 31 studies [27 cohort studies (8, 12, 17, 24–47), 4 case-control studies (48–51)] reported in 51 articles (quadratic weighted kappa: 0.84, 95% CI 0.71–0.97). Disagreement was always resolved by consensus. Table 1 summarizes the 31 studies that met the inclusion criteria of the meta-analysis.

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

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) ^a
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	136	19.0
Infante-Rivard et al, 1989 (26)	Canada	Compensation registry	Any	1072	24.5
Chen et al, 1990 (27)	China	Screening	Underground mining	1335	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
Mehnert 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
Oksa et al, 1997 (17)	Finland	Screening	Any	163	13.0
Checkoway et al, 1999 (44)	USA	Screening	Diatomaceous products	81	29.5
Chan et al, 2000 (45)	Hong Kong	Compensation registry	Surface workers only	1490	8.5
Ulm et al, 2000 (46)	Germany	Compensation registry	Mining, tunneling quarrying	282	–
Carta et al, 2001 (47)	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	–
Forastière et al, 1986 (51)	Italy	Compensation registry	Ceramic industry and quarrying	40	–

^a 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.

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 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)	1 313	70	29.3	8.3	2.39	1.86–3.02
Puntoni et al, 1988 (12)	136	6	3.6	0.7	1.67	0.61–3.64
Infante-Rivard et al, 1989 (26)	1 072	83	23.9	9.9	3.47	2.76–4.30
Chen et al, 1990 (27)	1 335	14	2.7	1.7	5.24	2.87–8.80
Chiyotani et al, 1990 (28)	1 941	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
Mehnert et al, 1990 (30)	493	9	4.9	1.1	1.83	0.84–3.48
Ng 1990 (31)	1 184	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)	1 827	35	16.7	4.2	2.10	1.46–2.92
Finkelstein, 1995 (38)	523	13	6.0	1.5	2.16	1.15–3.69
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)	4 271	104	44.0	12.4	2.37	1.93–2.87
Brown et al, 1997 (43)	1 130	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)	1 490	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	23 305			100	2.45	1.63–3.66

after adjustments were made for mining sectors and cumulative radon exposure, the miners with radiographic abnormalities suggestive of silicosis were found to be at substantially greater risk of lung cancer than those with normal radiographic findings (OR 6.88, 95% CI 1.89–25.00) (38).

“Dose–response” analysis. Five studies reported the risk of lung cancer according to the radiological severity of silicosis (29, 31, 37, 45, 47). One was excluded from the analysis because of a lack of data (42). For simple silicosis (ILO categories 1, 2 and 3), for one-category increments, the risk of lung cancer increased by 1.33 (95% CI 1.16–1.53, $P_{\text{homogeneity}} = 0.002$). The small number of studies precluded meaningful subgroup analyses. For complicated silicosis (ILO categories A, B and C), for one-category increments, the risk of lung cancer increased by 1.67 (95% CI 1.52–1.83, $P_{\text{homogeneity}} = 0.86$) (figure 2).

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, $P_{\text{homogeneity}} = 0.23$). 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 tobacco consumption. Forastière et al (51) reported an increased risk of lung cancer for silicosis patients (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.

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

Analysis	Number of studies	Studies	Silicosis patients (N)	SMR	95% CI	Homo-geneity (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), Ebi-hara et al (29), Mehnert et al (30), Ng (31), Amandus et al (32), Chia et al (33), Morinaga et al (34), Shima et al (35), Partanen et al (36), Dong et al (37), Finkelstein (38), Goldsmith et al (39), Merlo et al (40), Meijers 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), Ebi-hara 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 1990 (28), Ebi-hara et al (29), Mehnert et al (30), Ng (31), Amandus et al (32), Chia et al (33), Morinaga et al (34), Shima et al (35), Partanen et al (36), Dong et al (37), Finkelstein (38), Goldsmith et al (39), Merlo et al (40), Meijers 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), Chen et al (27), Chiyotani et al (28), Amandus et al (32), Shima et al (35), Dong et al (37), Finkelstein (38), Merlo et al (40), Meijers 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 Tsujida et al (57). In their meta-analysis, all types of pneumoconiosis (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

Figure 2. Dose-response analysis of silicosis and lung cancer. Small and large opacities refer to the International Labour Organization's radiographic classification of pneumoconiosis. (closed circles = Ebi-hara et al (29), triangles = Ng et al (31), open circles = Dong et al (37), closed squares = Chan et al (45), open squares = Carta et al (47).

conducted by independent reviewers (61). Sources of discordance include differences in study selection, data extraction, assessment of the ability to combine studies,

Table 4. Summary of the four case-control studies that met the inclusion criteria of the meta-analysis. The odds ratios (OR) are unadjusted. Homogeneity $P=0.23$. (95% CI = 95% confidence interval)

Reference	Cases		Controls		Weight (%)	OR	95% CI
	Silicosis	No silicosis	Silicosis	No silicosis			
Hessel et al, 1986 (50)	24	109	45	221	31.1	1.08	0.6–1.79
Forastière et al, 1986 (51)	15	57	25	294	12.5	3.09	1.45–5.82
Mastrangelo et al, 1988 (49)	50	259	30	279	31.5	1.80	1.08–2.81
Fu et al, 1994 (48)	37	42	56	132	24.9	2.08	1.17–3.43
Total (homogeneity $P=0.23$)					100	1.70	1.15–2.53

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 (ie, 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.

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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*

- 1989;262:3003–7.
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 Staveley, 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. Vorwald AJ, Karr JW. Pneumoconiosis and pulmonary carcinoma. *Am J Pathol* 1938;14:49–58.
8. Amandus H, Costello J. Silicosis and lung cancer in U.S. metal miners. *Arch Environ Health* 1991;46:82–9.
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 proportionate mortality ratio and standardized mortality ratio risk measures. *Am J Epidemiol* 1980;111:263–9.
12. Puntoni R, Goldsmith DF, Valerio 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. Montori VM, Smieja 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 A, Ojajarvi A, Huuskonen MS. Cancer incidence and mortality among Finnish asbestos sprayers and in asbestosis and silicosis patients. *Am J Ind Med* 1997;31:693–8.
18. Axelson 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, Mannetje A, Boffetta P, Stayner 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, Petitclerc 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 pneumoconiotics. *J Sci Lab* 1990;66:399–407.
30. Mehnert WH, Staneczek 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 EF. 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, Sakatani 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, Nagaoka K, et al. Epidemiological studies on the risk of pulmonary tuberculosis or lung cancer in ceramic workers with pneumoconiosis. *J Sci Lab* 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. *Am J Ind Med* 1995;28:459–67.
40. Merlo F, Fontana L, Reggiardo G, Ceppi M, Barisione G, Garrone E, et al. Mortality among silicotics in Genoa, Italy, from 1961 to 1987. *Scand J Work Environ Health* 1995;21 suppl 2:77–80.
41. Meijers JMM, Swaen GMH, Slangen JJM. Mortality and lung cancer in ceramic workers in the Netherlands: Preliminary results. *Am J Ind Med* 1996;30:26–30.

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, Møller J, 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. *J Occup Environ Med* 2000;42:69-75.
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.
47. Carta P, Aru G, Manca P. Mortality from lung cancer among silicotic patients in Sardinia: an update study with 10 more years of follow up. *Occup Environ Med* 2001;58:786-93.
48. Fu H, Gu X, Jin X, Yu S, Wu K, Guidotti TL. Lung cancer among tin miners in southeast China: silica exposure, silicosis, and cigarette smoking. *Am J Ind Med* 1994;26:373-81.
49. Mastrangelo G, Zambon P, Simonato L, Rizzi P. A case-referent study investigating the relationship between exposure to silica dust and lung cancer. *Int Arch Occup Environ Health* 1988;60:299-302.
50. Hessel PA, Sluis-Cremer GK, Hnizdo E. Case-control study of silicosis, silica exposure, and lung cancer in white South African gold miners. *Am J Ind Med* 1986;10:57-62.
51. Forastiere F, Lagorio S, Michelozzi P, Cavariani F, Arca M, Borgia P, et al. Silica, silicosis and lung cancer among ceramic workers: a case-referent study. *Am J Ind Med* 1986;10:363-70.
52. Covey LS, Wynder EL. Smoking habits and occupational status. *J Occup Med* 1981;23:537-42.
53. Sterling TD, Weinkam JJ. Smoking characteristics by type of employment. *J Occup Med* 1976;18:743-54.
54. McDonald AD, McDonald JC, Rando RJ, Hughes JM, Weill H. 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. Tsujida 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.
61. Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. *Can Med Assoc J* 1997;156:1411-6.
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 Crit Care Med* 2000;161:5-8.
64. Koskela RS, Klockars M, Järvinen E, Rossi A, Kolari 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.
66. de Klerk NH, Musk AW. Silica, compensated silicosis, and lung cancer in Western Australian goldminers. *Occup Environ Med* 1998;55:243-8.

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