

Review Article

# Silicosis and Smoking Strongly Increase Lung Cancer Risk in Silica-Exposed Workers

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**Abstract:** It remains controversial whether silica is a human lung carcinogen. In this study, we estimated the relative risks of lung cancer due to silica and silicosis by meta-analysis. We collected papers published from 1966–2001 which epidemiologically reported on the relationship between silica/silicosis and lung cancer. We removed papers which did not exclude the effects of asbestos and radioactive materials including radon. We selected the most recent one if some papers were based on the same cohort. Based on the selected papers, we summarized the lung cancer risks from silica, silicosis and non-silicosis with exposure to silica, by meta-analysis using a random effects model. The pooled relative risks were 1.32 (95% confidence interval (CI), 1.23–1.41) for silica, 2.37 (95% CI, 1.98–2.84) for silicosis and 0.96 (95% CI, 0.81–1.15) for non-silicosis with exposure to silica. Since some papers on silica did not exclude silicosis, the risk due to silica itself may be smaller than 1.32. It was less possible that silica exposure directly increases lung cancer risk. On the other hand, the relative risk, 2.37 for silicosis suggested that silicosis increases lung cancer risk. Meta-analysis also revealed that cigarette smoking strongly increased the lung cancer risk in silicotic patients (relative risk, 4.47; 95% CI, 3.17–6.30). Thus, the present study suggested the great importance of preventing silicosis and smoking cessation in reducing lung cancer incidence in silica-exposed workers.

**Key words:** Crystalline silica, Silicosis, Lung cancer, Occupational exposure, Relative risk, Smoking

## Introduction

Since the 1980s, there have been a lot of epidemiological studies investigating the relationship between crystalline silica and silicosis in lung cancer risk. Some cohort and case-control studies showed a positive significant relationship between silica exposure and lung cancer risk and/or between silicosis and lung cancer risk, but some other studies indicated no significant association. In addition, some reports did

not adequately take into account potential confounding factors, including smoking and concomitant exposure to other carcinogens such as radon, asbestos and polycyclic aromatic hydrocarbons (PAH). At present, it is controversial whether silica and silicosis increase the lung cancer risk.

In 1997, the International Agency for Research on Cancer (IARC) classified respirable crystalline silica from occupational sources as a group 1 carcinogen, meaning there is ‘sufficient evidence of carcinogenicity to humans’<sup>1)</sup>.

However, this decision did not settle the controversial discussion and has generated further debate. On the other hand, these days, epidemiological reports which take the confounding factors more carefully into account are

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**Table 1. Characters of 17 cohort studies presenting the lung cancer risk from silica exposure**

| author                     | yr   | place                 | subjects                                       | valuables controlled for              | index | observed death | number of subjects | ref. |
|----------------------------|------|-----------------------|--|---------------------------------------|-------|----------------|--------------------|------|
| 1 Costello <i>et al.</i>   | 1988 | Vermont, US           | granite workers                                | age, sex, race, region, calendar time | SMR   | 118            | 5,414              | 2    |
| 2 Guenel <i>et al.</i>     | 1989 | Denmark               | stone workers                                  | age, sex, region                      | SIR   | 44             | 2,071              | 3    |
| 3 Mehnert <i>et al.</i>    | 1990 | GDR                   | slate quarry workers                           | age, sex                              | SMR   | 27             | 2,476              | 4    |
| 4 Merlo <i>et al.</i>      | 1991 | Genova, Italy         | brick workers                                  | age, sex, calendar period             | SMR   | 28             | 1,022              | 5    |
| 5 Sherson <i>et al.</i>    | 1991 | Denmark               | foundry workers                                | age, sex, calendar period             | SIR   | 166            | 6,144              | 6    |
| 6 Cocco <i>et al.</i>      | 1994 | Sardinia, Italy       | lead and zinc miners                           | age, sex, calendar period             | SMR   | 86             | 4,740              | 7    |
| 7 Costello <i>et al.</i>   | 1995 | continental USA       | crush stone operation                          | age, sex, race, calendar period       | SMR   | 51             | 3,246              | 8    |
| 8 Dong <i>et al.</i>       | 1995 | China                 | silica brick workers                           | age, sex                              | SMR   | 65             | 6,266              | 9    |
| 9 Steenland <i>et al.</i>  | 1995 | South Dacota, US      | gold miners                                    | age, sex                              | SMR   | 115            | 3,328              | 10   |
| 10 Meijers <i>et al.</i>   | 1996 | Netherlands           | ceramic workers                                | age, sex, calendar period             | SMR   | 30             | 1,794              | 11   |
| 11 Rasfnsson <i>et al.</i> | 1997 | Iceland               | diatomaceous plant                             | age, sex, calendar period             | SIR   | 5              | 1,342              | 12   |
| 12 Cherry <i>et al.</i>    | 1998 | United Kingdom        | pottery, refractory & sandstone workers        | age, sex, calendar period             | SMR   | 68             | 4,822              | 13   |
| 13 de Klerk <i>et al.</i>  | 1998 | Kalgoorlie, Australia | gold miners                                    | age, sex, calendar period             | SMR   | 138            | 2,297              | 14   |
| 14 Checkoway <i>et al.</i> | 1999 | Lompoc, CA, US        | diatomaceous earth mining & processing factory | age, sex, race, calendar period       | SMR   | 48             | 1,798              | 15   |
| 15 McDonald <i>et al.</i>  | 2001 | US and Canada         | sand producing plant                           | age, calendar period                  | SMR   | 83             | 2,670              | 16   |
| 16 Steenland <i>et al.</i> | 2001 | US                    | industrial sand workers                        | n.a.                                  | SMR   | 109            | 4,269              | 17   |
| 17 Stern <i>et al.</i>     | 2001 | US and Canada         | construction plasterer & cemalet mason         | age, calendar period                  | SMR   | 1,386          | 12,873             | 18   |

n.a.: not available; ref.: reference; SMR: standardized mortality rate; SIR, standardized incidence rate; GDR: German Democratic Republic.

increasing in number.

In this study, we summarized the data from the epidemiological reports by meta-analysis, to investigate whether crystalline silica and silicosis increase the risk of lung cancer.

## Methods

### Study selection

We searched the MEDLINE database (from January 1966 through October 2001) for literature with the key words: “‘silica’ or ‘silicosis’ or ‘pneumoconiosis’” and ‘lung cancer’. We also looked for Japanese studies in the Japanese Journal of Industrial Health, Journal of Science Labour and the Japanese Journal of Traumatology and Occupational Medicine, which publish many Japanese epidemiological studies on occupational medicine, but are not listed in MEDLINE. We included cohort and case-control studies if they evaluated lung cancer incidence or mortality in subjects exposed to silica exposure or with silicosis. All the potentially relevant studies were independently reviewed and rated by three investigators. Disagreements were resolved by discussion. Only studies rated as fair or good quality were used for our analysis. Studies were excluded if they did not

adequately take into account potential confounding factors including smoking and concomitant exposure to other carcinogens such as radon, asbestos and PAH. Some papers had investigated the same cohorts or the same subjects. In such cases, the most recent analysis on the same cohort or subjects was selected for our analysis, as long as they were not of lower quality than the less recent analyses.

### Lung cancer risks from silica exposure, silicosis and non-silicosis with silica exposure

As a result, we chose 30 studies in 25 papers which stated a relationship between silica exposure and lung cancer risk: 17 cohort studies in 17 papers<sup>2-18)</sup> (Table 1) and 13 case-control studies in 8 papers<sup>13, 19-25)</sup> (Table 2). We also chose 16 studies (11 cohort<sup>4, 9, 11, 15, 26-32)</sup> and 5 case-control studies<sup>19, 33-36)</sup> which stated a relationship between silicosis and lung cancer risk (Tables 3 and 4). In addition, we selected 8 studies which presented lung cancer risk in non-silicotic subjects exposed to silica as well as silicotic subjects<sup>4, 9, 11, 15, 19, 31, 33, 37)</sup> (Table 5). We evaluated the common lung cancer risks from silica exposure, silicosis and non-silicosis with exposure to silica from these studies by meta-analysis.

**Table 2. Characters of 13 case-control studies presenting the risk of lung cancer from silica exposure**

| author                          | yr   | place                         | subjects  | valuables controlled for  | index | observed death | case              | control           | ref. |
|---------------------------------|------|-------------------------------|---|---|-------|----------------|-------------------|-------------------|------|
| 18 Forastiere <i>et al.</i>     | 1986 | Civitacastellana Italy        | quarry worker   | age, calendar period, smoking                                     | MHRR  | 5              | 29                | 225               | 19   |
| 19 Forastiere <i>et al.</i>     | 1986 | Civitacastellana Italy        | ceramic worker  | age, calendar period, smoking                                     | MHRR  | 33             | 137               | 225               | 19   |
| 20 McLaughlin <i>et al.</i>     | 1992 | Hubei, China                  | iron-copper miner   | age, sex, mine  | OR    | 57             | 74                | 343               | 20   |
| 21 McLaughlin <i>et al.</i>     | 1992 | Jiangxi, Henan & Hunan, China | potteries worker  | age, sex, factory   | OR    | 51             | 62                | 238               | 20   |
| 22 McLaughlin <i>et al.</i>     | 1992 | Guangxi, China                | tin miner   | age, sex, mine  | OR    | 66             | 87                | 371               | 20   |
| 23 McLaughlin <i>et al.</i>     | 1992 | Jiangxi & Hunan, China        | tungsten miner  | age, sex, mine  | OR    | 69             | 93                | 400               | 20   |
| 24 DeStefani <i>et al.</i>      | 1996 | Uruguay                       | various workers with silica exposure                              | age, residence, education, cigarette smoking, alcohol consumption | OR    | 125            | 653               | 270               | 21   |
| 25 Cherry <i>et al.</i>         | 1998 | UK                            | pottery, refractory & sandstone workers                           | age, sex  | OR    | n.a.           | 52                | 195               | 13   |
| 26 Ulm <i>et al.</i>            | 1999 | Germany                       | ceramic workers   | age, sex, smoking habit, area of residence, type of industry      | OR    | n.a.           | 247 <sup>*a</sup> | 795 <sup>*a</sup> | 22   |
| 27 Ulm <i>et al.</i>            | 1999 | Germany                       | quarry workers  | age, sex, smoking habit, area of residence, type of industry      | OR    | n.a.           |                   |                   |      |
| 28 Bruske-Holfeld <i>et al.</i> | 2000 | Germany                       | workers with silica exposure (ie, miners, foundry, quarry worker) | age, sex, region of residence                                     | OR    | 819            |                   |                   |      |
| 29 Martin <i>et al.</i>         | 2000 | France                        | electricity and gas workers <sup>*c</sup>                         | age, sex, calendar, period, economic status, asbestos exposure    | OR    | 128            | 310               | 1,225             | 24   |
| 30 S-Stanczyk <i>et al.</i>     | 2001 | Poland                        | pulp and paper workers <sup>*c</sup>                              | age, sex, year of hire  | OR    | 29             | 79                | 237               | 25   |

ref.: reference; OR: odds ratio; MHRR: Mantel-Haenzel relative risk; n.a.: not available; <sup>\*a</sup>: includes both ceramic workers and quarry workers; <sup>\*b</sup>: includes both case and control; <sup>\*c</sup>: with exposure to silica in their work environment.

**Table 3. Characters of 11 cohort studies presenting the lung cancer risk from silicosis**

|    | yr                            | place | subjects                | valuables controlled for                         | index                           | observed death | number of subjects | ref.  |    |
|----|-------------------------------|-------|-------------------------|--|---------------------------------|----------------|--------------------|-------|----|
| 1  | Infante-Rivard, <i>et al.</i> | 1989  | Quebec, Canada          | silicotic patients                               | age, sex, calendar period       | SMR            | 83                 | 1,072 | 26 |
| 2  | Ebihara, <i>et al.</i>        | 1990  | Tokyo & Shizuoka, Japan | silicosis patients                               | age, sex, calendar period       | SMR            | 31                 | 803   | 27 |
| 3  | Mehnert, <i>et al.</i>        | 1990  | GDR                     | slate quarry workers                             | age, sex                        | SMR            | 9                  | n.a.  | 4  |
| 4  | Amandus, <i>et al.</i>        | 1995  | North Carolina, US      | dusty trades workers                             | age, sex, race                  | SMR            | 35*                | 760   | 28 |
| 5  | Dong, <i>et al.</i>           | 1995  | China                   | silica brick workers                             | age, sex                        | SMR            | 35                 | 1,827 | 9  |
| 6  | Meijers, <i>et al.</i>        | 1996  | Neitherland             | ceramic workers                                  | age, sex, calendar period       | SMR            | 10                 | 124   | 11 |
| 7  | Brown, <i>et al.</i>          | 1997  | Sweden                  | silicotic patients                               | age, sex, calendar period       | SMR            | 41                 | 1,130 | 29 |
| 8  | Oksa, <i>et al.</i>           | 1997  | Finland                 | silicotic patients                               | age, sex, calendar period       | SIR            | 15                 | 170   | 30 |
| 9  | Finkelstein, <i>et al.</i>    | 1998  | Ontario, Canada         | miners and other workers exposed to silica       | age, calendar period            | SMR            | 13                 | 2,091 | 35 |
| 10 | Checkoway, <i>et al.</i>      | 1999  | Lompoc, CA, US          | diatomaceous earth mining and processing factory | age, sex, race, calendar period | SMR            | 4                  | 81    | 15 |
| 11 | Chan, <i>et al.</i>           | 2000  | Hong Kong               | silicotic patients                               | sex                             | SMR            | 33                 | 1,502 | 32 |

ref.: reference; SMR: standardized mortality rate; SIR: standardized incidence rate; GDR: German Democratic Republic; n.a.: not available; \*: calculated value.

**Table 4. Characters of 5 case-control studies presenting the lung cancer risk from silicosis**

|    | yr                         | place | subjects                | valuables controlled for      | index                                    | observed death | case | control | ref.  |    |
|----|----------------------------|-------|-------------------------|-------------------------------|--|----------------|------|---------|-------|----|
| 12 | Forastiere, <i>et al.</i>  | 1986  | Civitacastellana, Italy | ceramic worker                | age, sex, calendar period, smoking       | MHRR           | 15   | 40      | 225   | 19 |
| 13 | Mastrangelo, <i>et al.</i> | 1988  | Belluno, Italy          | lung cancer patients admitted | date of birth, sex, area, admission date | MHRR           | 50   | 80      | 357   | 33 |
| 14 | Hnizdo, <i>et al.</i>      | 1997  | South Africa            | gold miners                   | age                                      | RR             | 15   | 78      | 386   | 34 |
| 15 | Finkelstein, <i>et al.</i> | 1998  | Ontario, Canada         | workers exposed to silica     | age                                      | OR             | 12   | 23      | 145   | 35 |
| 16 | Cocco, <i>et al.</i>       | 2000  | China                   | miners and factory workers    | age, facility type                       | OR             | 77   | 316     | 1,356 | 36 |

ref.: reference; OR: odds ratio; RR: relative risk; MHRR: Mantel-Haenzel relative risk.

**Table 5. Characters of 6 cohort studies (A) and 2 case-control studies (B) presenting the lung cancer risk from silicosis**

| (A) | yr                         | place | subjects                | valuables controlled for                         | index                                    | observed death | number of subjects | ref.    |      |    |
|-----|----------------------------|-------|-------------------------|--|--|----------------|--------------------|---------|------|----|
| 1   | Mehnert, <i>et al.</i>     | 1990  | GDR                     | slate quarry workers                             | age, sex                                 | SMR            | 18                 | n.a.    | 4    |    |
| 2   | Amandus, <i>et al.</i>     | 1992  | North Carolina, US      | dusty trades workers                             | age, sex, race                           | SMR            | 2                  | 107     | 37   |    |
| 3   | Dong, <i>et al.</i>        | 1995  | China                   | silica brick workers                             | age, sex                                 | SMR            | 30                 | 4,176   | 9    |    |
| 4   | Finkelstein, <i>et al.</i> | 1995  | Ontario, Canada         | miners and other workers exposed to silica       | age, calendar period                     | SMR            | 12                 | 1,568   | 31   |    |
| 5   | Meijers, <i>et al.</i>     | 1996  | Neitherland             | ceramic workers                                  | age, sex, calendar period                | SMR            | 20                 | 1,670   | 11   |    |
| 6   | Checkoway, <i>et al.</i>   | 1999  | Lompoc, CA, US          | diatomaceous earth mining and processing factory | age, sex, race, calendar period          | SMR            | 48                 | 1,798   | 15   |    |
| (B) | yr                         | place | subjects                | valuables controlled for                         | index                                    | observed death | case               | control | ref. |    |
| 7   | Forastiere, <i>et al.</i>  | 1986  | Civitacastellana, Italy | ceramic worker                                   | age, sex, calendar period, smoking       | MHRR           | 18                 | 97      | 225  | 19 |
| 8   | Mastrangelo, <i>et al.</i> | 1988  | Belluno, Italy          | lung cancer patients admitted                    | date of birth, sex, area, admission date | MHRR           | 86                 | 181     | 357  | 33 |

n.a.: not available; ref.: reference; GDR: German Democratic Republic; SMR: standardized mortality rate; MHRR: Mantel-Haenzel relative risk.

#### *Lung cancer risk based on the radiographic category of silicosis*

We evaluated the relationship between the radiographic category of silicosis and lung cancer risk. This category is defined by the Japanese Classification of Radiographs of Pneumoconiosis (1960), and is almost the same in categories I–III as the classification of the International Labor Organization but includes a category IV for large opacities. We selected 7 studies and evaluated the common relative risks of lung cancer in each category<sup>9,27,32,38–41</sup>. We evaluated the dose-effect trend in the relationship by the Cochran-Armitage trend test.

#### *Lung cancer risk from silicosis in smokers and non-smokers*

We evaluated the lung cancer risks in both smokers and non-smokers from 6 cohort and 2 nested case-control studies

in 8 papers and proceedings<sup>9,26,27,30,33,34,41,42</sup>, which presented both risks in each cohort.

#### *Analysis*

Relative risk was used as a measure of the relationship between silica exposure or silicosis and lung cancer risk. For case-control studies, the relative odds ratio was used as a surrogate measure of the corresponding relative risk. Because the absolute risks of lung cancer are low in both silica-exposed workers and the general public, the relative odds ratio approximately represents the relative risk. We treated the relative risk and the relative odds ratio equally in this study. Many cohort studies showed a standardized mortality rate (SMR), while some studies showed a standardized incidence rate (SIR). In this paper, we pooled these values together, because the values of SIR and SMR

for cancers of all sites and lung cancer in silicotic patients were reported to be very similar<sup>30</sup>. In fact, the differences between SIR and SMR for lung cancers in the studies we selected were very small in silica-exposed subjects and in silicotic patients.

Among the papers we selected, some showed a 95 % confidence interval (CI) with relative risk, but others did not. In the latter case, we estimated the CI using other values presented in the paper, on the basis of a Poisson distribution<sup>43</sup>. From the presented or estimated CI, i.e., the lower and upper limits (LL, UL) of 95% CI, we calculated standard error:  $SE = \log(UL/LL)/(1.96*2)$ . Based on the SE, we estimated the weight of each study and pooled the risks with a meta-analysis using a random effects model<sup>44</sup>.

Two papers on silicosis in non-smokers<sup>26, 30</sup> showed that the observed death number was zero and so SMR was zero. If we simply used the method shown above, these studies would be ignored because the weights of the studies would be calculated as zero. To avoid this, we set the LL at 95% CI assuming the degree of freedom at 1 instead of twice the observed death number (=0) in  $\chi$  square distribution ( $=\chi(97.5\%, 1)/(2*\text{expected death number})$ ) and calculated SMR from the LL and the UL ( $=\sqrt{LL*UL}$ ), instead of zero, although it was very small and almost zero.

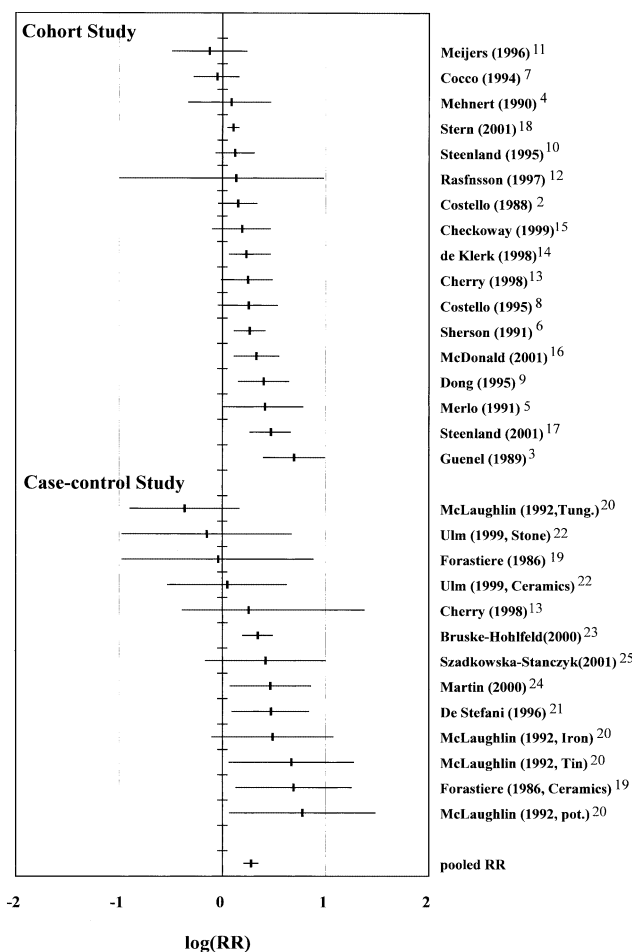
#### Publication bias

We examined the potential for publication bias by constructing a 'funnel plot'. We also examined this by analyzing the association between effect estimates and their variances by the Kendall rank correlation test, as described by Begg and Mazundar<sup>45</sup>. Moreover, we analyzed the association between standardized effects and precision with the intercept of the regression line by linear regression test, as described by Egger *et al.*<sup>46</sup>.

## Results

#### Lung cancer risk from silica exposure

We included 17 cohort studies and 13 case-control studies in a meta-analysis investigating the lung cancer risk from silica exposure. The characteristics of the cohort studies and the case-control studies are presented in Tables 1 and 2, respectively. The relative risks of the studies with the presented or estimated 95% CIs are demonstrated in Fig. 1. The common risks summarized from the cohort studies and the case-control studies were 1.29 (95% CI, 1.20–1.40) and 1.42 (95% CI, 1.22–1.65), respectively. The estimated common risk from silica exposure summarized from all 30



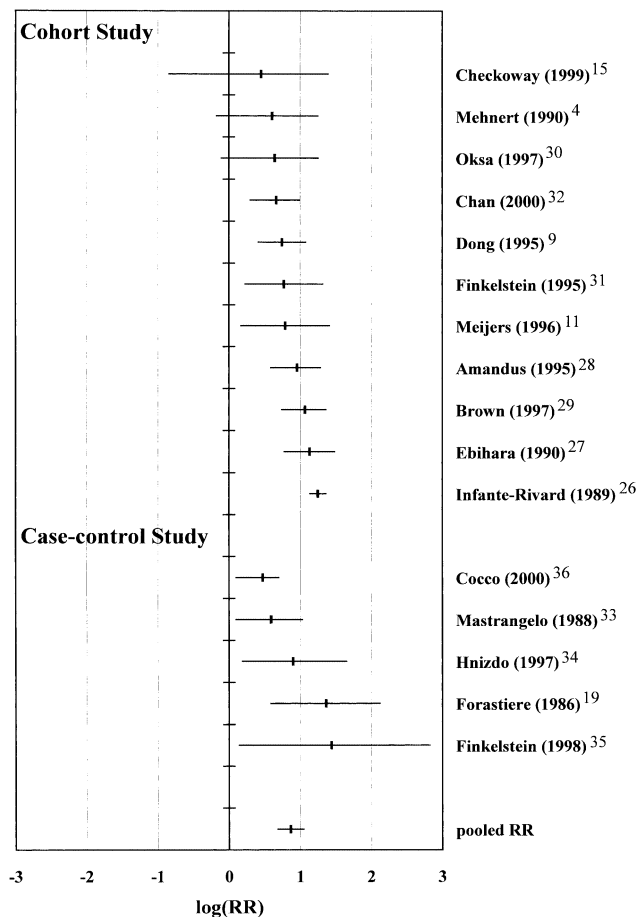
**Fig. 1. Relative risk (RR) plot for lung cancer in subjects exposed to crystalline silica.**

Pooled RR, 1.32 (95% confidence interval, 1.23–1.41), was summarized from 17 cohort studies and 13 case-control studies by meta-analysis using a random effects model. Each horizontal line represents a 95% confidence interval. The first author's name, year of publication and reference number of each study are shown in the right side of the figure. The characteristics of these studies are shown in Tables 1 and 2.

studies was 1.32 (95% CI, 1.24–1.41) (Fig. 1).

#### Lung cancer risk from silicosis

We included 11 cohort studies and 5 case-control studies in a meta-analysis investigating the lung cancer risk from silicosis. The characteristics of the cohort studies and the case-control studies are presented in Tables 3 and 4, respectively. Figure 2 shows the relative risks of the studies with the presented or estimated 95% CIs. The common risks summarized from the cohort studies and the case-control studies were 2.49 (95% CI, 2.08–2.99) and 1.89 (95% CI, 1.45–2.48), respectively. The estimated common risk from silicosis summarized from all 16 studies was 2.37 (95% CI,



**Fig. 2. Relative risk (RR) plot for lung cancer in silicotic patients.** Pooled RR, 2.37 (95% confidence interval, 1.98–2.84), was summarized from 11 cohort studies and 5 case-control studies by meta-analysis using a random effects model. Each horizontal line represents a 95% confidence interval. The first author's name, year of publication and reference number of each study are shown in the right side of the figure. The characteristics of these studies are shown in Tables 3 and 4.

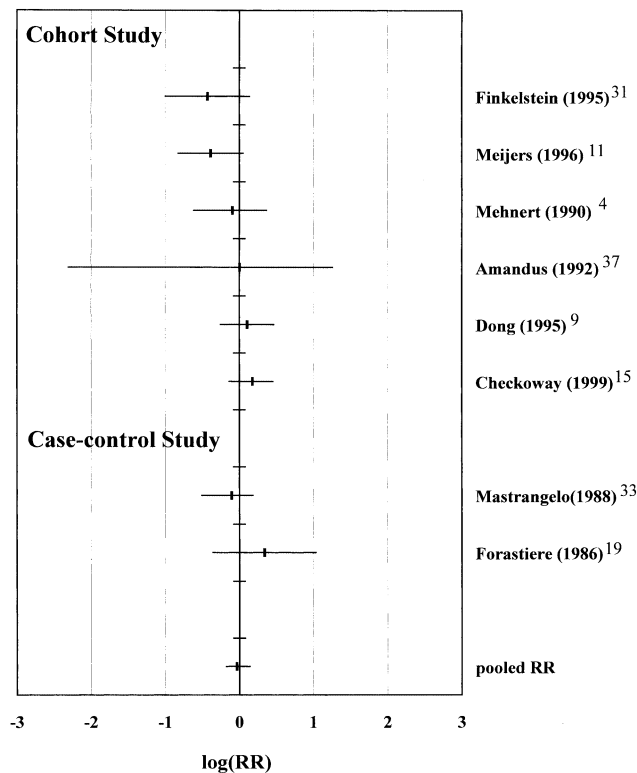
1.98–2.84) (Fig. 2).

#### *Lung cancer risk in non-silicotic subjects with silica exposure*

We chose 6 cohort studies and 2 case-control studies for a meta-analysis to investigate the lung cancer risk in non-silicotic subjects with silica exposure (Table 5). The relative risks of the studies with the presented or estimated 95% CIs are demonstrated in Fig. 3. The estimated common risk from silica exposure was 0.96 (95% CI, 0.81–1.15), summarized from all 8 studies (Fig. 3).

#### *Lung cancer risk based on the radiographic category of silicosis*

We collected 7 studies that presented a lung cancer risk from silicosis classified by the radiographic category: 5



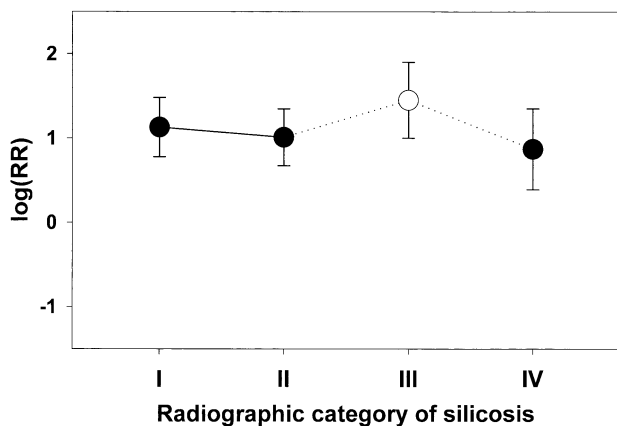
**Fig. 3. Relative risk (RR) plot for lung cancer in non-silicotic subjects exposed to silica.**

Pooled RR, 0.96 (95% confidence interval, 0.81–1.15), was summarized from 6 cohort studies and 2 case-control studies by meta-analysis using a random effects model. Each horizontal line represents a 95% confidence interval. The first author's name, year of publication and reference number of each study are shown in the right side of the figure.

studies<sup>9, 27, 38, 40, 41</sup>) showed a risk of lung cancer in categories I–IV, and 2 studies<sup>32, 39</sup>) showed the risk in categories I–III. We summarized the common risk in each category (Fig. 4). Since publication bias may exist in the selection of studies for category III as described below, we just showed the calculated common risk in category III in the open circle and dotted line in Fig. 4, and evaluated the dose-effect trend only in categories I, II and IV. The Cochran-Armitage trend test showed no significant trend between the category and the common risk of lung cancer ( $P=0.86$ ).

#### *Lung cancer risk from silicosis in smokers and non-smokers*

Finally, we summarized the common risk of lung cancer in smokers and non-smokers with silicosis from 6 cohort studies and 2 case-control studies. Figure 5 shows the relative risks of the studies with the presented or estimated 95% CIs in smokers and non-smokers with silicosis, respectively. The estimated common risks summarized from all 9 studies were



**Fig. 4. Pooled relative risk (RR) of lung cancer based on the radiographic category of silicosis.**

The pooled RRs were calculated by meta-analyses using a random effects model. The analyses of categories I–III (I, II, closed circle; III, open circle) were based on 7 studies<sup>9, 27, 32, 38–41</sup>. The analysis of category IV (closed circle) was based on 5 studies<sup>9, 27, 38, 40, 41</sup>. Since publication bias may exist in the selection of studies for category III, the calculated common risk in category III was shown in the open circle and dotted line. Error bars show the 95% confidence intervals. There was no significant dose-effect trend between RRs and categories I, II, and IV (closed circles), by the Cochran-Armitage trend test (P=0.86).

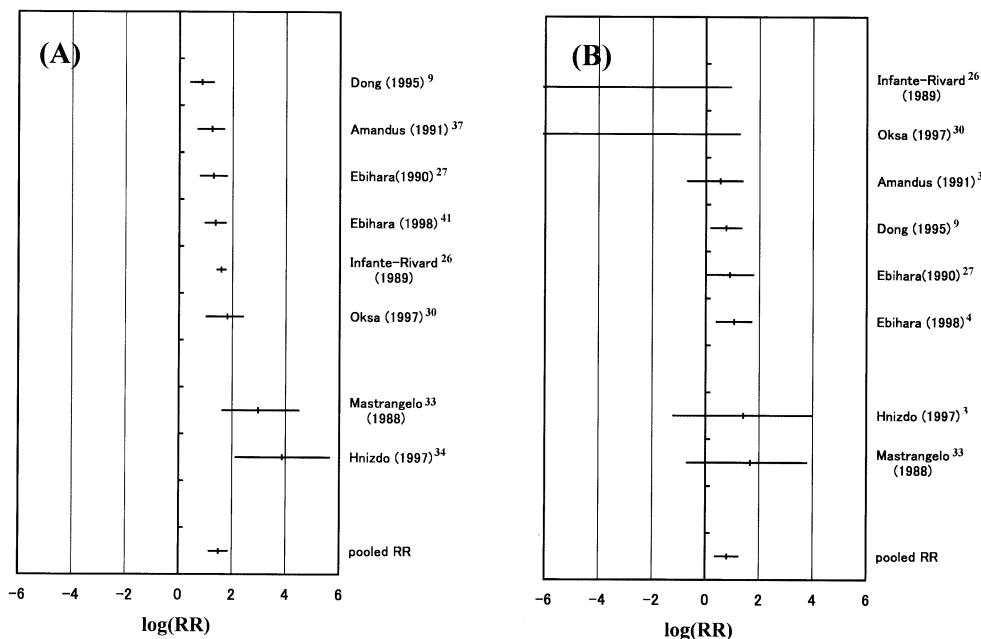
4.47 (95% CI, 3.17–6.30) in smokers with silicosis and 2.24 (95% CI, 1.46–3.43) in non-smokers with silicosis (Fig. 5).

*Publication bias*

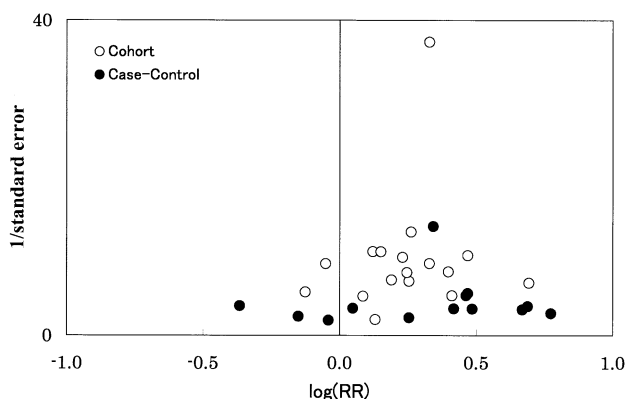
There was no evidence of publication bias in the meta-analysis of the lung cancer risk from silica exposure in a funnel plot (Fig. 6). The Kendall rank correlation coefficient between effect estimates and their variances by the method of Begg and Manzundar was 0.054 (P=0.96). The intercept of the regression line in the linear regression test on the association between precision and standardized effects by the method of Egger *et al.* was -0.27 (95% CI, -1.03 – 0.49, P=0.48).

There was no evidence of publication bias in the meta-analysis of the lung cancer risk from silicosis in a funnel plot (not shown). The Kendall rank correlation coefficient by the method of Begg and Manzundar was 0.81 (P=0.42). The intercept of the regression line by the method of Egger *et al.* was -1.64 (95% CI, -2.95 – 0.38, P=0.18).

There was no evidence of publication bias in the meta-analysis of lung cancer risk in non-silicotic subjects with silica exposure in a funnel plot (not shown). The Kendall rank correlation coefficient by the method of Begg and Manzundar was -0.25 (P=0.80). The intercept of the regression line by the method of Egger *et al.* was -0.59 (95%



**Fig. 5. Relative-risk (RR) plot for lung cancer in silicotic patients of smokers (A) and non-smokers (B).** Both pooled RRs were calculated from 6 cohort studies and 2 case-control studies. Each horizontal line represents a 95% confidence interval. The first author’s name, year of publication and reference number of each study are shown in the right side of each figure.



**Fig. 6. Funnel plot for 17 cohort studies (open circle) and 13 case-control studies (closed circle) presenting the lung cancer risk from silica exposure.**

Relative risks of these studies are shown in Fig. 1. The characteristics of these studies are shown in Tables 1 and 2.

CI,  $-3.29 - 2.11$ ,  $P=0.61$ ).

The Kendall rank correlation coefficients by the method of Begg and Manzundar for the meta-analyses of lung cancer risk on radiographic category I, II, III and IV were  $-0.75$  ( $P=0.45$ ),  $0.75$  ( $P=0.45$ ),  $-2.25$  ( $P<0.05$ ) and  $-0.49$  ( $P=0.62$ ), respectively, indicating that publication bias may exist in the analysis of category III but not in the analyses of the other categories. The intercepts of the regression line by the method of Egger *et al.* for the meta-analyses were  $-0.31$  (95% CI,  $-2.6 - 3.27$ ,  $P=0.80$ ),  $-1.09$  (95% CI,  $-7.30 - 5.12$ ,  $P=0.67$ ),  $-2.18$  (95% CI,  $-3.14 - -1.21$ ,  $P<0.01$ ) and  $-1.94$  (95% CI,  $-0.95 - 4.83$ ,  $P=0.12$ ), respectively, indicating that publication bias may exist in the analyses of category III but not in the analyses of the other categories. Taken together, we concluded that publication bias may exist in the selected studies for the analysis of category III. Accordingly, we excluded the calculated common risk of category III from the analysis testing the dose-effect tendency between the category and lung cancer risk.

There were no publication biases in the meta-analyses of lung cancer risk in smokers and non-smokers with silicosis in funnel plots (not shown). The rank correlation coefficients by the method of Begg and Manzundar were  $1.485$  ( $P=0.14$ ) in smokers with silicosis and  $-1.237$  ( $P=0.22$ ) in non-smokers with silicosis. The intercepts of the regression line by the method of Egger *et al.* were  $0.56$  (95% CI,  $-2.29 - 3.41$ ,  $P=0.65$ ) and  $-0.96$  (95% CI,  $-2.52 - 0.60$ ,  $P=0.18$ ) in smokers and non-smokers with silicosis, respectively.

## Discussion

We estimated the common risk of lung cancer from exposure to crystalline silica based on 30 studies (Tables 1, 2 and Fig. 1). The risk was  $1.32$  (95% CI,  $1.24 - 1.41$ ). This indicated that, even if silica is carcinogenic to humans, the effect is suggested to be rather weak. We also estimated the common risk of lung cancer from silicosis based on 16 studies (Tables 3, 4 and Fig. 2). The risk was  $2.37$  (95% CI,  $1.98 - 2.84$ ). This value was similar to the risks in previous reports using meta-analysis. Tsuda *et al.* reported that the estimated risk was  $2.74$  (95% CI,  $2.60 - 2.90$ ) in 1997<sup>47</sup>. Smith *et al.* estimated the risk to be  $2.2$  (95% CI,  $2.1 - 2.4$ ) in 1995<sup>48</sup>. Therefore, in the present study, we conclude that silicosis is one of the risk factors of lung cancer.

As described above, the risk of lung cancer was calculated as  $1.32$  in subjects exposed to silica (Fig. 1). Most papers we selected in the meta-analysis only mentioned that subjects were exposed to silica, but did not indicate whether or not they were silicotic. That is, the subjects in some of the studies theoretically include silicotic patients as well as non-silicotic subjects. Since the risk of lung cancer from silicosis is estimated to be  $2.37$  (Fig. 2), the lung cancer risk from silica exposure itself is suggested to be less than  $1.32$ . In fact, the risk of lung cancer in non-silicotic subjects exposed to silica was only  $0.96$  (Fig. 3), although papers on which the meta-analysis was based were limited in number ( $n=8$ , Table 5). Consequently, it is hard to say from the present study that exposure to crystalline silica directly increases lung cancer risk.

Whether 'silica itself' or 'silicosis induced by silica' increases lung cancer risk in human is a very interesting question from a purely academic perspective. It is also very significant when we take actual measures to prevent lung cancer in silica-exposed workers. As a matter of fact, the question has been tested by many investigations over the last 20 yr. In 1982, Goldsmith *et al.* suggested three hypotheses in terms of the relationship between silica/silicosis and lung cancer: (1) silica is a direct carcinogen, (2) silicosis is an intermediate pathological state leading to lung cancer (scar cancer) and (3) silica with absorbed PAH impairs lung clearance and causes lung cancer<sup>49</sup>.

Since the IARC classified silica as a human carcinogen (Class 1) in 1997, some people believe that 'silica itself' increases lung cancer risk in humans, despite the IARC's annotation of limitations in the epidemiologic data. This might be proven to be true in the future. However, our analyses in this study on the basis of papers up to the present did not support it. The pooled risk of lung cancer in silica-

exposed subjects in our analysis was only 1.32, and the subjects also inevitably included silicotic patients. In 2001, an IARC group and their colleagues supported their classification by showing a monotonic trend in pooled exposure-response analyses for lung cancer in silica-exposed workers based on 10 cohort studies<sup>50</sup>). Indeed, the monotonic trend strongly suggested that 'silica itself' causes lung cancer in humans, but the odds ratios they presented were 1.0, 1.0, 1.3, 1.5 and 1.6 for graded cumulative exposures (from '< 0.4' to '12.8 +' (mg/m<sup>3</sup> · yr)), which were almost the same level as the risk shown by our analysis (Fig. 1). In addition, they did not exclude silicotic patients, either. Therefore, considering the present analyses about the lung cancer risks of silicotic and non-silicotic subjects exposed to silica (Figs. 2 and 3), silica itself may induce lung cancer indirectly, probably through silicosis, in humans.

Some papers, reporting animal experiments, might support the idea that silica itself is a human carcinogen. It was observed that exposure of rats to high doses of silica either by intra-tracheal instillation or by inhalation can produce lung cancer<sup>51-53</sup>), suggesting that silica itself is carcinogenic in rats. However, our meta-analysis suggested that 'silicosis induced by silica', rather than 'silica itself', increases lung cancer risk in humans, which was also supported by the following evidence: 1) when Saffiotti *et al.* observed in detail the lung tissue of rats injected with crystalline silica into the trachea, they found that adenocarcinomas of alveolar type II origin were developed near granulomas with fibrosis in the lung<sup>54</sup>). In their words, the tumor was 'associated with areas of pulmonary fibrosis (silicosis)'. 2) Inhalation of titanium dioxide, not classified as a human carcinogen by the IARC (Class 3), induces lung fibrosis and increases lung cancer incidence in rats<sup>55-58</sup>), similarly to silica. 3) Cryptogenic fibrosing alveolitis, of course not due to silica, increases the risk of lung cancer in humans<sup>59</sup>). 4) Moreover, according to Koshi and Koshi (2001), there was no evidence showing the genotoxicity of crystalline silica<sup>60</sup>). In addition, we believe species differences are very important in interpretation of the results in animal experiments investigating the carcinogenicity of silica, because it was reported that after exposure to high doses of crystalline silica in hamsters no tumor outcome was observed in contrast with an observation in rats<sup>53</sup>).

The present study suggested that silicosis, rather than silica itself, increased lung cancer risk in silica-exposed workers. Therefore, to reduce lung cancer incidence in silica-exposed workers, first of all, we should try to completely prevent silicosis. At present, to prevent silicosis in silica-exposed workers, various measures are taken in many countries,

including control of silica concentration in the work environment, proper usage of protective equipment for the respiratory airway, periodic medical check-up for silicosis, and transfer to a different workplace based on the medical check-up. These measures may have to be reconsidered from the point of view of preventing lung cancer complicated with silicosis. Furthermore, silicotic patients should be continuously followed-up in a strict cancer screening program.

Although we found the relationship between silicosis and lung cancer risk to be strong, the risk of lung cancer was not dependent on the radiographic category of silicosis (Fig. 4). As reported by Chan *et al.*<sup>32</sup>), we should mention that in the progression of silicosis, only patients who have not contracted lung cancer in the earlier categories can contract lung cancer in the later categories. Thus, patients who contract lung cancer in the earlier categories of silicosis should theoretically contract it in the later categories with a high probability. Therefore, we cannot deny that silicosis is a risk factor of lung cancer because the risk of lung cancer was independent of the radiographic category of silicosis.

We compared the risk of lung cancer from silicosis between smokers and non-smokers (Fig. 5). The lung cancer risk in smokers with silicosis was estimated to be 4.47, which was 2.00 times as high as the estimated risk of 2.24 in non-smokers with silicosis. The data in the present study did not seem to indicate that the effects of silicosis and smoking on lung cancer risk are multiplicative. Many studies showed lung cancer risks from cigarette-smoking ranging from 3 to more than 10, which depended on the amount and duration of smoking, the age of starting smoking and race<sup>61-63</sup>). In comparison, the risk rate of lung cancer in smokers to non-smokers (2.00 times) in silicotic patients seemed smaller. In the case of asbestosis, it is now unclear whether the effects of smoking are additive or multiplicative, although they were believed to be multiplicative for 30 yr until recently<sup>64-67</sup>). Thus, further strict studies are necessary to examine precisely whether the effects of silicosis with smoking are additive, multiplicative or other. Of greater importance are the results that cigarette-smoking increased the risk of lung cancer in silicotic patients and that the lung cancer risk in smokers with silicosis was rather high (4.47). Therefore, silicotic patients should be strongly recommended to stop smoking in order to prevent lung cancer.

Funnel plots did not show publication biases in the meta-analyses of lung cancer risks from silica exposure (Fig. 6), silicosis and silica exposure, as well as from silicosis in smokers and non-smokers (not shown). The Kendall rank correlation coefficient by the method of Begg and

Manzundar<sup>45)</sup> and the intercept of the regression line in the linear regression test by the method of Egger *et al.*<sup>46)</sup> did not show significant publication biases in the meta-analyses, either, except in the analysis of lung cancer risk in radiographical category III of silicosis, which we excluded from our analysis of a dose-effect trend as described above. Additionally, using a random effects model, we corrected the heterogeneity of the studies in the meta-analyses.

In conclusion, the meta-analyses in this study revealed that silicosis is a risk factor of lung cancer. They also showed a small risk of lung cancer in subjects exposed to silica including silicotic patients. This suggested that crystalline silica induces lung cancer indirectly in humans. In addition, the analyses showed that smoking strongly increased the lung cancer risk in silicotic patients. Preventing silicosis and encouraging smoking cessation may be the most effective measures to reduce lung cancer incidence in silica-exposed workers.

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