

Dose–response meta-analysis of silica and lung cancer

Yves Lacasse · Sylvie Martin · Dominique Gagné ·
Lajmi Lakhali

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Abstract

Objective To examine the association between occupational exposure to silica and lung cancer from 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–December 2007) for original articles published in any language. Observational studies (cohort and case–control studies) were selected if they reported the result of dose–response analyses relating lung cancer to occupational exposure to silica after appropriate adjustment for smoking.

Results Ten studies (4 cohort studies and 6 case–control studies) met the inclusion criteria of the meta-analysis, nine of which contributing to the main analysis (dose–response analysis, no lag time). We found increasing risk of lung cancer with increasing cumulative exposure to silica, with heterogeneity across studies however. Posthoc analyses identified a set of seven more homogeneous studies. Their meta-analysis resulted in a dose–response curve that was not different from that obtained in the main analysis.

Conclusion Silica is a lung carcinogen. This increased risk is particularly apparent when the cumulative exposure to silica is well beyond that resulting from exposure to the recommended limit concentration for a prolonged period of time.

Keywords Silica · Pulmonary fibrosis · Lung neoplasm · Systematic review · Meta-analysis

Introduction

From a recent meta-analysis, we estimated that, overall and after controlling for smoking, silicosis is associated with a 60% increase in risk of lung cancer [1]. Whether the association between silicosis and lung cancer is due to the effect of the fibrotic process or to the effect of respirable silica itself is unclear [2], since lung fibrosis (as it is seen in idiopathic pulmonary fibrosis and asbestosis) increases the risk of lung cancer [3, 4].

Although the International Agency for Research on Cancer (IARC) classified silica as a human lung carcinogen [5], the opinion that exposure to crystalline silica in itself (i.e., in the absence of silicosis) induces lung cancer is still challenged [6]. Our objective was to reexamine the epidemiologic evidence regarding the association between occupational exposure to silica and lung cancer through a systematic review (and meta-analysis) of the epidemiologic literature. The methods that we used are in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group's recommendations [7].

Y. Lacasse (✉) · S. Martin · D. Gagné · L. Lakhali
Centre de recherche, Centre de Pneumologie, Hôpital Laval,
Institut universitaire de cardiologie et de pneumologie de
l'Université Laval, 2725 Chemin Ste-Foy, Québec, P. Québec
G1V 4G5, Canada
e-mail: Yves.Lacasse@med.ulaval.ca

L. Lakhali
Département de mathématiques, Université Laval, Québec,
Canada

Materials and methods

Literature search

We searched Toxline, BIOSIS, Embase, and Medline [8] (1966–December 2007) for original articles published in any language using the following strategy: ([silicon dioxide, MeSH Major Topic] OR [silicosis, MeSH Major Topic]) AND [lung neoplasms, MeSH Major Topic]. All terms were exploded. We also searched for additional articles from the reference list of relevant articles obtained from the electronic search.

Study selection

Criteria for inferring causation from epidemiologic investigations have been proposed [9, 10]. These criteria include, among others, the strength of association, the consistency of results across studies, the demonstration of a biologic gradient, plausibility from mechanistic investigation, and supportive evidence from experimentation. From these criteria, the finding that an increasing cumulative exposure to respirable silica is consistently associated, with an increasing risk of cancer, would represent a strong argument supporting the IARC's conclusion that silica is carcinogenic. We therefore included published and peer-reviewed observational studies (cohort or case-control studies) that reported on dose-response analyses relating occupational exposure to silica to risk of lung cancer. In cohort studies with internal comparison, dose-response analyses are particularly appealing since workers with high exposure are compared to workers with low exposure, both groups presumably sharing similar smoking habits and clinical characteristics otherwise [11]. Cohort studies with external comparison groups and case-control studies were also considered if risks were adjusted for smoking. We included only studies in which cumulative exposure to silica was quantified in terms of mg/m^3 per years. To avoid confounding bias, studies reporting on concomitant exposures to silica and other lung carcinogens (e.g., asbestos, arsenic, uranium, radon [12]) were excluded, unless the measure of association had been adjusted for confounders. To limit selection bias, autopsy studies were also excluded [13]. In addition, narrative reviews, letters to the editor, clinical commentaries, case series, and case reports were disregarded.

Three reviewers (YL, SM, and DG) successively applied these criteria to the titles and abstracts of all citations obtained. If the title of an article or, when available, its abstract suggested any possibility that it might be relevant, the article 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 authors' names, journal, and year of publication of the articles. Those published in languages other than English and French were translated in French. Any disagreement was resolved by consensus. When we identified studies that had been reported in multiple articles, we limited our analysis to the most recent report, unless the necessary data had appeared only in an earlier article. Agreement between coders was measured using quadratic weighted Kappa statistics [14]. We kept a log of reasons for rejection of citations identified from the searches.

Information extraction

Two reviewers (YL and SM) abstracted information from all articles selected for inclusion in the meta-analysis. The abstracted information included: (1) the study design; (2) the industry and country where the occupational exposure to silica occurred; (3) the methods of exposure quantification; (4) whether patients with silicosis were excluded from the study; and (5) the risks [relative risks (RR) or odds ratios (OR), with their 95% confidence intervals (CI) or variance estimates] of lung cancer at various thresholds of exposure to silica.

Statistical analysis

Given the low event rate in the control groups, we assimilated OR to RR in case-control studies and used RR throughout the analyses. For the studies providing only RR, we transformed the confidence intervals to the log scale to estimate the variances of $\log(\text{RR})$. The standard error was estimated by dividing the transformed interval length by 3.92 and the corresponding variance then equalled to the square of the standard error [15]. Each study reported the risk of several ranges of exposure to silica with respect to a reference range. This reference range differed across studies and corresponded to the "non-exposed" (i.e., control) category. Within each category, we assigned as exposure value the median point when available or the mid-point of the corresponding range. When the highest category was open-ended, we assigned the lower point of the interval plus 20% as the exposure level [16].

Standard dose-response meta-analyses are usually conducted by performing separate analyses of each individual study first and then combining results by weighted averages. Such approach requires at least four exposure levels within each individual study when a nonlinear trend is suspected. Since several studies considered in our analysis reported less than four exposure levels, we could not apply this approach. We rather considered an alternative approach (the "prepool" method) consisting of pooling data available from all studies into a joint analysis. No assumption was made about the relationship between

log (RR) and the exposure level. Following Bagnardi et al., we considered splines regression models [17]. Heterogeneity between different studies was modeled by an additional random component of variance [18]. Models with and without the latter additional component are known as mixed-effects and fixed-effects models, respectively. We used the difference of the maximum log likelihood of these models to test the heterogeneity between studies. Both models parameters were estimated by the algorithm proposed by Stram [19]. Technical and computational details are given in Appendix 1.

A similar exposure–response meta-analysis was conducted with cumulative exposures to silica lagged by 10–20 years. In this method, for each period of follow-up, employment history in the most recent 10–20 years is ignored in order to take into account disease latency.

Sensitivity analyses

We decided a priori to conduct subgroup analyses to identify sources of heterogeneity, if any, according to the following hypotheses: (1) cohort and case–control studies would yield different results; (2) dose–response relationships would vary according to the methods of measurement of respirable silica (i.e., job-exposure matrices versus longstanding personal shift measurements). In addition, we planned a posteriori analyses to assess the impact of each individual study on heterogeneity and to examine the stability of the results. The sensitivity investigation consisted of iterative “leave-on-out” procedures. In this method, the influence of individual studies is estimated from the average dose–response curve by considering all studies except one [20].

Results

Literature search/agreement studies

A total of 1,284 separate publications were retrieved. We reduced these to a list of 449 potentially eligible articles, of which 400 were excluded for the following reasons: silicosis without specific reference to silica exposure ($n = 120$), exposure other than silica ($n = 104$), commentaries or reviews ($n = 85$), no report of measure of association ($n = 36$), autopsy studies ($n = 10$), outcome other than lung cancer ($n = 22$), animal studies ($n = 13$), other reasons ($n = 10$). Forty-nine publications from 23 studies reported on risk of lung cancer with quantitative assessment of exposure. Thirteen of these studies were excluded because of differences in quantitative assessment of exposure (Appendix 2, [21–33]). The primary reviewers finally agreed to include 12 articles [34–45] reporting on 10

studies (4 cohort studies [34–37] and 6 case–control studies [38, 39, 42–45]). Only two studies excluded patients with silicosis [38, 40]. In the remaining eight studies, the confounding effect of silicosis on the association between silica exposure and lung cancer was not assessed. Agreement among the reviewers was good (Kappa: 0.53). Disagreement was always resolved by consensus. Table 1 summarizes the 10 studies that met the inclusion criteria of the meta-analysis.

Dose–response meta-analysis

Figure 1 illustrates the contribution of the nine studies that provided data on the dose–response relationship between respirable silica exposure and lung cancer with no lag time [34–40, 42, 43]. From these data, we estimated dose–response relationship between exposure to silica and RR of lung cancer along with its confidence limit (Fig. 2). We found increasing risk of lung cancer with increasing cumulative exposure to silica. For instance, considering two levels of exposure $x_1 = 1.0 \text{ mg/m}^3$ per year and $x_2 = 6 \text{ mg/m}^3$ per year, the corresponding RRs were 1.22 (CI: 1.01–1.47) and 1.84 (CI: 1.48–2.28), respectively. The difference of these risks is significant. In fact, the risk associated with any exposure level superior to 1.84 mg/m^3 per year has a significant difference with that associated with $x = 0$. Figure 2 also suggested that the risk of lung cancer plateaus at a level exposure is greater than 6 mg/m^3 per year. The log likelihood test detected a strong heterogeneity between studies ($\chi^2 = 20.19$ on 1 degree of freedom, $p < 0.001$). The exposure–response meta-analysis of six studies with cumulative exposures to silica lagged by 10–20 years yielded similar results.

Sensitivity analyses

The separate analyses of cohort studies and case–control studies yielded similar results and also revealed heterogeneity. We also considered that all the methods of measurement of exposure to silica used to derive the cumulative exposure provided only rough estimates (Table 1). Therefore, we did not proceed with further subgroup analyses based on the methods of measurement of respirable silica. Finally, the results of the a posteriori analysis are presented in Fig. 3. Two studies generated heterogeneity in dose–response relationship estimation [37, 41]. The design and measurement methods of these two studies were different. In one cohort study, estimates of exposure to silica were based on occupational categories defined in a national census [37]. In the other (a nested case–control study conducted in industrial sand workers), exposure to silica was derived from visits to the plants, records of past changes in process and dust control, and interviews

Table 1 Characteristics of the studies included in the dose–response meta-analysis of silica and lung cancer

Reference	Study design	Type of work, Country	Method of quantification of exposure to respirable silica	Sample size
Checkoway et al. [34]	Cohort study	Diatomaceous earth industry, USA	Quantitative air monitoring data (1948–1988) obtained from the company. Job-specific exposures for years before 1948 were estimated by regression modeling based on observed temporal changes and knowledge of dates when dust exposure reduction interventions occurred	Total cohort: $n = 2,342$ (77 with lung cancer)
Steenland and Sanderson [35]	Cohort study	Industrial sand workers, USA	Job-exposure matrix based on 4,269 industrial hygiene samples collected in 1974–1995	Total cohort: $n = 4,021$ (109 with lung cancer)
Brown and Rushton [36]	Cohort study	Industrial sand industry, United Kingdom	Cumulative exposure to respirable crystalline silica was estimated using a specially developed job-exposure matrix. Exposure levels were assigned on the basis of the job, the quarry, and calendar period in which exposure occurred	Total cohort: $n = 2,272$ (81 with lung cancer)
Pukkala et al. [37]	Cohort study	No specific industry (the cohort consisted of all Finns born in 1906–1945 who participated in the 1970 national census)	Estimates based on the Finnish job-exposure matrix in which the basic dimensions of exposure assessment are occupations, agents, and calendar periods. The exposure estimates were based on the judgment of about 20 experts at the Finnish Institute of Occupational Health	Total cohort: $n = 1.6$ million (~400,000 with lung cancer)
Ulm et al. [38]	Case–control study	Stone, quarrying and ceramic industries, Germany	Estimated by an industrial hygienist using the complete occupational history, plant, or technical equipment, and calendar period	247 cases; 795 controls
Bruske-Hohlfeld et al. [39]	Case–control study	Miners, foundry and quarry workers, Germany	On the basis of job and industry codes and written job descriptions and supplementary job-specific questionnaires. Cumulative exposure was assessed by expert rating according to job-exposure matrices	513 cases; 321 controls
Cocco et al. [40] ^a	Case–control study	Mines and pottery factories, China	Industrial hygiene data were available for total dust, particle size, and percent free silica, and were used to estimate an exposure level for each job by calendar-year periods	316 cases; 1,356 controls
Chen et al. [45] ^a	Nested case–control study	Same as in Cocco, 2001 [40]	Same as in Cocco et al. [40]. More than 60% of facility, job title, and calendar year were estimated based on direct monitoring data	511 cases; 1,879 controls
Westberg and Bellander [42]	Nested case–control study	Aluminium foundries, Sweden	Air sampling made in 1992–1995 during two shifts on consecutive days. Historical measurement data were also available from the 1960s to the study	31 cases; 233 controls
Hughes et al. [41] updated by McDonald et al. [43]	Nested case–control study	Industrial sand workers, USA	Integration of job histories and job-exposure matrices (developed from visits to the plants, records of past changes in processes and dust control and interviews with long-term employees)	108 cases; 162 controls

Table 1 continued

Reference	Study design	Type of work, Country	Method of quantification of exposure to respirable silica	Sample size
Cassidy et al. [44]	Case-control study	No specific industry (all incident cases of lung cancer, with hospital controls), seven European countries	Exposure evaluated by experts, on the basis of a general questionnaire (and specialized questionnaires), and their own experience. Indices of exposure included whether the exposure occurred, the percentage of working time exposed, and the intensity of exposure	435 cases; 311 controls

^a The study by Chen et al. [45] is a follow-up study of that by Cocco et al. [40], with differences in the dose-response analyses (no lag time in Cocco et al. and 15-year lag in Chen et al.)

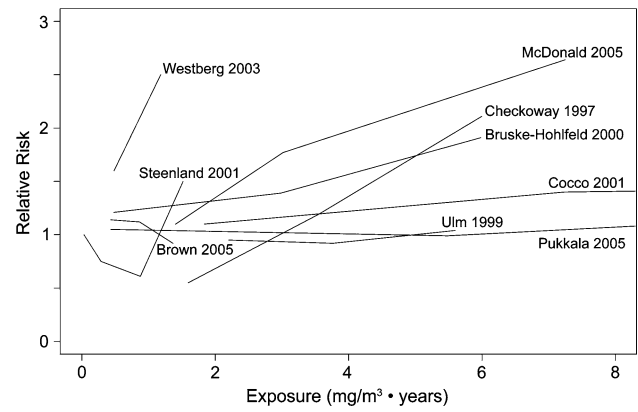


Fig. 1 Individual dose-response curves from nine studies that contributed to the dose-response meta-analysis of respirable silica exposure and lung cancer (no lag time)

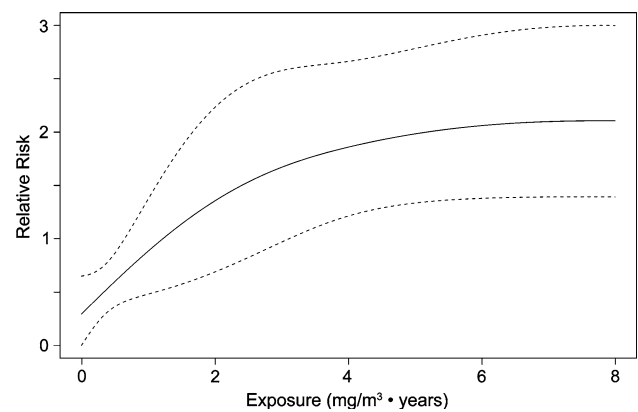


Fig. 2 Dose-response relationship between exposure to silica and RR with its 95% confidence limit (no lag time)

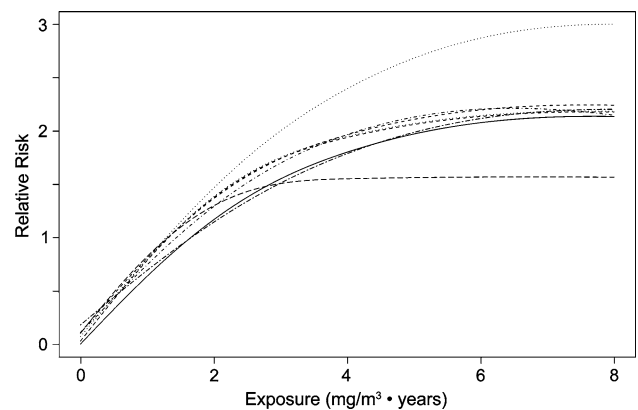


Fig. 3 Posthoc sensitivity analyses: nine different dose-response curves produced by the leave-one-out procedure

with long-term employees [41, 43]. The remaining seven studies were more homogeneous, although some heterogeneity remained ($\chi^2 = 4.45$ on 1 degree of freedom, $p = 0.035$). Overall, their meta-analysis yielded the same results as those obtained in the main analysis.

Discussion

From a systematic review of the literature and a meta-analysis, we found that an increasing cumulative exposure to respirable silica is associated, across high-quality epidemiological studies, with an increasing risk of lung cancer. The interpretation of our meta-analysis is restricted by our finding of significant heterogeneity across studies.

Heterogeneity is however inherent to the purpose and methods of meta-analysis. Primary studies may differ considerably in their designs, data collection processes, and definitions of exposure and confounders [46]. Important sources of heterogeneity include variability in exposure characterization, study design and quality, and control for confounding [47]. Although heterogeneity is often seen as a limitation to meta-analysis, its exploration may improve understanding of the degree of comparability among studies, identify stratifying variables to remove heterogeneity, and generate hypotheses for further research [47, 48]. None of our a priori hypotheses satisfactorily explain heterogeneity. Subgroup analyses were however limited by the small number of studies included.

Another source of heterogeneity is exposure measurement error [49]. Unfortunately, exposure-measurement error is frequently ignored in epidemiologic studies [50]. In addition, different methods to measure silica exposure exist [51] and variation in cutpoints across studies are also problematic in meta-analysis [49]. Cumulative exposure to respirable silica was most often estimated from job descriptions and historical data to create job-exposure matrices (Table 1). In the main analysis (i.e., dose–response analysis, no lag time), only three studies [34, 40, 42] included contemporary—although limited—air sampling from which cumulative estimates of exposure were based. The effect of measurement error on the study results was formally tested in only one study [42]. In all studies, cumulative exposure quantification could therefore only represent rough estimates that could certainly account, in part, for heterogeneity. Also, measurement error probably accounted for some of the uncertainty regarding the carcinogenicity of silica following small cumulative exposure, where the relative risk of lung cancer is around 1.0. It is nevertheless reassuring to observe at least a trend in the dose–response relationship between cumulative silica exposure and the risk of lung cancer in most individual studies (Fig. 1).

Another limitation of the studies that met the inclusion criteria of the meta-analysis is that, with two exceptions [38, 40], patients with silicosis were not excluded. The meta-analysis of these two case–control studies lacked statistical power and could not demonstrate any dose–response relationship between silica exposure and lung cancer (data not shown). Since silicosis is a risk factor for lung cancer [1], this situation may overestimate the

association between silica exposure and lung cancer. However, the magnitude of this error is unknown because the proportion of silicotics among patients exposed to silica was not specified in any of the studies. The statistical model describing the association between silica exposure and lung cancer with silicosis as an intermediate outcome is a typical illness–death model [52]. Advanced statistical methods are employed to investigate such models, and these methods have not been adapted to meta-analysis.

In a pooled exposure–response analysis of 10 silica-exposed cohorts to investigate the association with lung cancer, Steenland et al. also concluded that silica is carcinogenic [11]. Although pooled and meta-analyses both aim at reconciling previously conducted studies that yielded inconsistent results [46], fundamental differences exist between the two types of reviews. A pooled analysis results from the collaboration of investigators who share individual data from related studies. Exposure measures and other covariates can be applied uniformly across the studies combined [53]. A meta-analysis combines aggregated data from studies retrieved from a systematic search of the literature. Pooled and meta-analyses on the same topic may therefore be conducted on quite different sets of studies. For instance, only two published studies [34, 35] were common to Steenland’s pooled analysis and our meta-analysis. In addition, 6 of the 10 studies that met the inclusion criteria of our review became available after Steenland’s publication. “Participation bias” in pooled analysis has been assimilated to “publication bias” in meta-analysis [53]. Few head-to-head comparison between pooled and meta-analyses has been published. A rare instance is the study by Gordon et al. of sinonasal cancer among wood workers [53]. Overall, both analyses yielded similar results, as did Steenland’s and ours.

Our results and those of Steenland et al. bring only partial guidance to compensatory boards evaluating patients with lung cancer and past exposure to respirable silica. It is now well established that silicosis is a risk factor for lung cancer [1]. 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 [2]. Although there is a dose–response relationship between cumulative exposure to respirable silica and lung cancer, the increased risk is especially apparent when the cumulative exposure to silica is extremely high and well beyond that resulting from exposure to the limit concentration recommended by the National Institute of Occupational Safety and Health (0.05 mg/m^3 as a time-weighted average for up to 10-h workday during 40-h workweek [54]) for a prolonged period of time (>30 years). Such cumulative exposures are unlikely in developed countries where strict occupational safety and health regulations exist. The risk of lung cancer at lower cumulative exposure remains uncertain.

Conclusion

From our results and those of Steenland et al. [11], we would concur with the IARC that silica is a lung carcinogen. Our results indicate that there is an exposure–response relationship between silica and lung cancer above a threshold level estimated to be >1.84 mg/m³ per year. The interpretation of our findings by compensatory boards is however limited by the wide range of exposure to respirable silica reported in the original studies, the heterogeneity across studies, and the confounding effect of silicosis that cannot be fully assessed.

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Appendices

Appendix 1: statistical methods for meta-analysis

Let $I = 1, \dots, I$ indexes independent studies and $J = 1, \dots, n_i$ indexes exposure levels within studies. Let $Y_{ij} = \log(\text{RR}_{ij})$ be the estimated log risk ratio corresponding to exposure level x_{ij} . The fixed-effects model is then written as

$$Y_{ij} = f(x_{ij}) + \varepsilon_{ij} + e_{ij}, \quad i = 1, \dots, I, \quad J = 1, \dots, n_i,$$

model 1

where f is a smooth continuous function, describing the relationship between the exposure level and the log relative risk response. $\varepsilon_{ij} \rightarrow N(0, s_{ij}^2)$ are the sampling errors in Y_{ij} since the latter are estimated rather than observed. Estimated s_{ij}^2 are given by individual studies. Finally, $e_{ij} \rightarrow N(0, \sigma^2)$ are the overall error terms. It is assumed that ε_{ij} and e_{ij} are independent.

For the mixed-effects model, a random effect term γ_i common to points of the same study is added. This yield

$$Y_{ij} = f(x_{ij}) + \gamma_i + \varepsilon_{ij} + e_{ij}, \quad i = 1, \dots, I, \quad J = 1, \dots, n_i,$$

model 2

where $\gamma_i \rightarrow N(0, \tau^2)$ and are independent from ε_{ij} and e_{ij} . Testing heterogeneity corresponds them to performing the following:

$$H_0 : \tau^2 = 0 \quad \text{vs.} \quad H_1 : \tau^2 > 0.$$

The null hypothesis H_0 is rejected at level α if

$$-2\{\log(\text{maximum likelihood model 1}) - \log(\text{maximum likelihood model 2})\} \geq \chi_{1,\alpha}^2,$$

where $\chi_{1,\alpha}^2$ satisfies $P(\chi_1^2 > \chi_{1,\alpha}^2) = \alpha$. In both models, f is left completely unspecified providing flexibility. It is nonparametrically estimated by a spline of order 3 [17]:

$$f(x) = \beta_{01}x + \beta_{02}x^2 + \beta_{03}x^3 + \sum_{1 \leq i \leq C-1} \beta_{i3}(x - k_i)_+^3,$$

where $(x - k_i)_+ = \max(x - k_i, 0)$ is the positive part and $\{k_i, i = 1, \dots, C - 1\}$ are knots. We set $C = 3$. The models parameters $\{\beta_{01}, \beta_{02}, \beta_{03}, \beta_{13}, \beta_{23}, \tau^2, \sigma^2\}$ are estimated by the algorithm given by Stram [19].

Appendix 2 Reasons for exclusion of observational studies with dose–response analysis of silica and lung cancer

Reference	Reason for exclusion
Hnizdo et al. [21]	Lung cancer in relation to exposure to silica and uranium production in underground gold miners. Radon daughter measurement not available
Checkoway et al. [22]	Cohort study with external comparison group
Chen and Chen [23]	Exposure to arsenic
Calvert et al. [24]	Qualitative assessment of exposure to crystalline silica
Kauppinen et al. [25]	Qualitative assessment of exposure to crystalline silica
Menvielle et al. [26]	Exposure expressed in “centiles based on the distribution among controls”
Attfield and Costello [27]	Cohort study with external comparison group; no adjustment for smoking
Smailyte et al. [28]	Cohort study with external comparison group
L’Abbate et al. [29]	Qualitative assessment of exposure to crystalline silica
Baccarelli et al. [30]	Autopsy study
Chen et al. [31]	Cohort study with external comparison group
Zeka et al. [32]	Qualitative assessment of exposure to crystalline silica
Yu et al. [33]	Cohort study limited to silicotics, with external comparison group

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