

Research Article

Occupational Exposure to Silica and Lung Cancer: Pooled Analysis of Two Case-Control Studies in Montreal, Canada

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Abstract

Background: Respirable crystalline silica is a highly prevalent occupational exposure and a recognized lung carcinogen. Most previous studies have focused on selected high-exposure occupational groups. This study examines the relationship between occupational exposure to silica and lung cancer in an occupationally diverse male population.

Methods: Two large population-based case-control studies of lung cancer were conducted in Montreal, one in 1979-1986 (857 cases, 533 population controls, 1,349 cancer controls) and the second in 1996-2001 (738 cases and 899 controls). Interviews provided descriptive lifetime job histories, smoking histories, and other information. Industrial hygienists translated job histories into histories of exposure to a host of occupational substances, including silica. Relative risk was estimated, adjusting for several potential confounders, including smoking.

Results: The odds ratio for substantial exposure to silica was 1.67 (95% confidence interval, 1.21-2.31) and for any exposure was 1.31 (95% confidence interval, 1.08-1.59). Joint effects between silica and smoking were between additive and multiplicative, perhaps closer to the latter. In this population, it is estimated that approximately 3% of lung cancers were attributable to substantial silica exposure.

Conclusions: The carcinogenicity of inhaled crystalline silica was observed in a population with a wide variety of exposure circumstances.

Impact: The finding of carcinogenicity across a wide range of occupations complements prior studies of specific high-exposure occupations. This suggests that the burden of cancer induced by silica may be much greater than previously thought. *Cancer Epidemiol Biomarkers Prev*; 19(6); 1602-11. ©2010 AACR.

Introduction

Inhaled crystalline silica represents one of the most common occupational exposures worldwide (1). In a recent review of global burden of disease due to occupational carcinogens, silica showed the highest proportion of workers exposed and the highest weighted relative risk (relative risk weighted by proportion exposed) for lung cancer among eight lung carcinogens tabulated (2). Several studies, including pooled analyses and meta-analyses, have reported an association between respirable silica and lung cancer (3-8). Several cohort studies have reported relative risks of lung cancer of approximately 1.3 to 1.4 among silica-exposed workers, with significant and/or monotonic dose-response relationships (4, 8). Although most cohort studies did not

have reliable lifetime smoking histories, those that did have some smoking data found that smoking did not confound the silica-lung cancer relationship (4). Relative risks of lung cancer have been particularly high (1.7-2.7) among silicotics. A working group of the International Agency for Research on Cancer (IARC) has evaluated inhaled crystalline silica as a group 1 lung carcinogen (9).

Most of the pivotal studies of occupational silica exposure have focused on specific occupational groups such as miners and brick, diatomaceous earth, pottery, sand, and stone workers, and on individuals known to have silicosis. These occupational groups and silicotics are those in which silica exposure has been highest. This has increased the power to detect an effect of silica exposure, but because the vast majority of silica-exposed workers are exposed in occupations with lower levels of exposure, it leaves open the question of whether there is a detectable excess risk of lung cancer among the majority of silica-exposed workers. Further, the studies that have been conducted among cohorts of workers in specific industries may have been susceptible to confounding by coexposures within the industry. Examples are arsenic (10, 11) and radon among miners (12) and polycyclic aromatic hydrocarbons (PAH) among ceramic workers (10, 11). Because of the diversity of coexposure profiles across different industries, it is plausible that

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population-based studies may be less vulnerable to such industry-specific confounding.

An association between inhaled crystalline silica and lung cancer has important public health implications, not only for the small number of high-exposure industries that have been targeted in cohort studies, but also for the much larger number of workers exposed in other industries. The few population-based studies that evaluated silica exposure have suggested an elevated risk of lung cancer with occupational silica exposure (13-15).

In the early 1980s, we carried out a population-based case-control study in Montreal, Canada, to explore the possible associations between hundreds of occupational substances and multiple cancer sites, including lung cancer (13). In the late 1990s, we carried out a similar study in the same region, this time focusing on respiratory cancers. These two investigations enabled us to examine the effect of occupational exposures to silica in a wider range of occupational circumstances than in any cohort study. Further, because these were case-control studies with detailed diagnostic information on cases and detailed lifetime smoking histories, it was possible to go further than most previous studies in controlling for smoking and in assessing risks in relation to particular histologic types of lung cancer. The purpose of the present study was to examine the risk of developing lung cancer associated with occupational exposure to silica under these varied conditions.

Materials and Methods

The population of metropolitan Montreal consisted of 2.7 and 3.1 million persons in 1981 and 1996, respectively. Both studies used a case-control design, with eligible subjects restricted to Canadian citizens resident in the study area. Study I, conducted from 1979 to 1986, included males ages 35 to 70 diagnosed with cancer at any of 19 sites, including the lung. Study II, conducted from 1996 to 2001, included men and women ages 35 to 75 diagnosed with a lung malignancy. In both studies, cases were ascertained at the 18 largest hospitals located in the metropolitan area; only incident, histologically confirmed cancers were included. In both studies, population controls were randomly sampled from population-based electoral lists, stratified by sex and age to the distribution of cases. In Quebec, Canada, electoral lists were maintained by means of active enumeration of households until 1994; since then they have been continually updated and are thought to represent nearly complete listings of Canadian citizens residing in the province. Results are presented here for males only, because the prevalence of occupational exposure to crystalline silica among females was very low in our study population. Additional details of subject ascertainment and data collection have been presented previously (16-18).

In study I, 1,082 lung cancer cases and 740 eligible population controls were identified, and attempts were made

to interview them. Of these, 857 (79%) cases and 533 (72%) controls completed the interview. As study I included cancers at several different sites, an additional control group for the lung cancer series comprised patients with non-lung cancers. We refer to these 1,349 subjects as "cancer controls." Sampling of these cancer controls was carried out to ensure that none of the 19 cancer sites that comprised the cancer controls would constitute >20% of the total. In study II, 860 eligible male cases and 1,294 eligible male controls were identified, and 738 (86%) and 899 (69%) of these, respectively, agreed to participate and completed the interview. Ethical approval was obtained for both studies from each participating hospital and university. All participating subjects provided informed consent.

Data collection

In study I and study II, over 78% and 76% of participants, respectively, responded for themselves, whereas surrogate respondents (proxies) provided information for the other participants. Interviews were divided into two parts: a structured section requesting information on sociodemographic and lifestyle characteristics, including ethnicity, family income, and smoking history, and a semistructured section eliciting a detailed description of each job held by the subject in his working lifetime. On average, subjects had held 4.2 jobs each. A trained interviewer asked the subject, for each job held, about the company, its products, the nature of the work-site, the subject's main and subsidiary tasks, and any additional information (e.g., equipment maintenance, use of protective equipment, activities of coworkers) that could provide clues about work exposures and their intensity. Occupations were coded according to the Canadian Classification and Dictionary of Occupations (19). For some occupations, supplementary questionnaires were used to assist interviewers with detailed technical probing (20). A team of chemists and industrial hygienists examined each completed questionnaire and translated each job into a list of potential exposures using a checklist of 294 agents that included several substances of interest, such as crystalline silica, arsenic, asbestos, benzo(a)pyrene, chromium VI, diesel emissions, nickel, and PAHs.

In the two studies combined, >28,000 jobs were evaluated. The team of coders spent about 40 person-years on this project, which included helping to develop the methodology, monitoring the quality of the interviewing, conducting background research on exposures in different occupations, coding the individual participants' files, and recoding after the initial complete round of coding was finished. The final exposure codes attributed to a participant were based on consensus among the coders. Coders were blind with regard to the subject's disease status. For each substance considered present in each job, the coders noted three dimensions of information, each on a three-point scale: their degree of confidence that the exposure had actually occurred (possible, probable,

Table 1. Distribution of study subjects according to selected characteristics

Variable	Study I (1979-1986)			Study II (1996-2001)	
	Population controls	Cancer controls	Cases	Population controls	Cases
	<i>n</i> = 533	<i>n</i> = 1,349	<i>n</i> = 857	<i>n</i> = 899	<i>n</i> = 738
Age (%)					
≤55 y	28.0	32.5	27.4	11.9	13.7
56-65 y	45.2	43.7	50.8	28.5	32.8
66-75 y	26.8	23.7	21.8	59.6	53.5
Ancestry (%)					
French	64.2	58.0	69.1	64.4	77.5
Anglo	14.1	16.1	13.5	6.3	4.6
Other	21.8	25.9	17.4	29.3	17.9
Schooling (%)					
≤7 y	30.6	31.9	44.7	35.4	45.2
8-13 y	48.4	48.1	44.9	41.3	41.5
>13 y	21.0	19.9	10.4	23.3	13.3
Median family income (in Canadian dollars)*	26,627	24,761	22,386	35,292	32,932
Smoking status (%)					
Never	19.7	17.3	1.5	17.7	2.4
Ever	80.3	82.7	98.5	82.3	97.6
Pack-years [†]	49.9	52.3	74.3	40.7	74.5
Proxy respondent (%)	12.6	19.2	29.4	9.9	40.0

*Mean of census tract median family income.

[†]Mean pack-years among ever smokers, based on 20 cigarettes/pack.

definite), the frequency of exposure in a normal work-week (<5%, 5-30%, >30% of the time), and the relative level of concentration of the agent (low, medium, high). Concentration levels were established with reference to certain benchmark occupations in which the substance is found. Specifically, we identified some hypothetical workplace situations *a priori* that would correspond to low, medium, and high exposure for each substance, and the experts rated each real job against these benchmarks. For crystalline silica, the following occupations were used as benchmarks: mining or brickworks as low concentration, foundries or concrete work and masonry as medium concentration, and sandblasting or pottery works as high concentration. Unfortunately, it proved impossible to reliably estimate absolute concentration values corresponding to the relative levels coded. Nonexposure was interpreted as exposure up to the level that can be found in the general environment. The exposure assessment was based not only on the worker's occupation and industry, but also on individual characteristics of the workplace and tasks as reported by the subject; an illustrative example is in the appendix of Parent et al. (21).

Statistical analysis

The main purpose was to estimate the relative risk of lung cancer in relation to silica exposure. Unconditional logistic regression (22) was used to estimate odds ratios (OR)

between silica and lung cancer and the corresponding 95% confidence intervals (95% CI).

For each job in which the subject was exposed to silica, we had the duration in years and a set of ordinal values for confidence, frequency, and concentration. If a subject was exposed in two or more jobs, then lifetime values of confidence, frequency, and concentration were calculated by taking averages, weighted by the durations of the various jobs in which exposure occurred. The combination of duration, confidence, frequency, and concentration was used to categorize the lifetime exposure into categories as follows: unexposed, exposed at nonsubstantial level, and exposed at substantial level. Because of latency considerations, exposures occurring within 5 years of diagnosis or interview were excluded. To be classified as exposed at the substantial level, a subject had to have been exposed at confidence of probable or definite, concentration and frequency of medium or high, and for duration >5 years. All other exposed subjects were then classified in the non-substantial category. We consider this nonsubstantial/substantial dichotomy to be a simple proxy for cumulative exposure. The reference group for analyses consisted of those subjects who were never exposed to silica.

To control for possible confounding, we included in the regression models the following variables: age, ancestry, education level, natural logarithm of median family income of census tract of residence, type of respondent (self, surrogate), smoking history, and exposure to some

known occupational lung carcinogens, namely, asbestos, benzo(a)pyrene, chromium VI compounds, and diesel emissions. These occupational covariates were selected for inclusion because they are on the IARC group 1 list of lung carcinogens (23) and because they had >3% prevalence of exposure in this population. Some other lung carcinogens were available in our database but were not included because of low exposure prevalence (arsenic) or because of high correlation with one of the covariates that were included (nickel compounds, PAHs). A smoker was defined as someone who had smoked ≥ 100 cigarettes in his lifetime; a former smoker was defined as someone who stopped smoking at ≥ 2 years before the interview. Following the recommendations of Leffondré et al. and Racht et al. (24, 25), smoking history was represented by three variables: a binary variable indicating whether the person was ever a regular smoker, a variable for the number of years since quitting, and a variable for the cumulative amount smoked, as measured by pack-years.

The availability of two studies and two control groups in study I provided various opportunities. We first carried out analyses of the study I data by comparing the cases separately with population controls and with cancer controls, and we separately analyzed study II. To maximize precision of estimates, we also conducted analyses pooling the study I and study II samples, both cases and controls. Our prior belief was that the two control groups in study I were equally valid. Consequently, to avoid giving greater weight to the more numerous cancer controls, we randomly subsampled among those controls a number (533) exactly equal to the number of population controls, thereby providing an estimate of risk from study I that was equally weighted to the two control groups. We then pooled the two studies, using this set of 1,066 (2×533) subjects as the control series for study I. When combining the two studies in a single model, we included an indicator of study, to avoid any confounding that could derive from different case/control ratios in the two studies. We thus present risk estimates separately in four study populations: study I using population controls, study I using cancer controls, study II using population controls, and study I plus study II pooled, as described above. In

addition, for the pooled study, we calculated the population attributable risk percent and estimates of its 95% CI, using a combination of the method of Natarajan et al. (26) and exact methods for confidence intervals of binomial proportions (27).

We conducted a number of additional analyses. The associations between silica and the most prevalent histologic types of lung cancer, namely, squamous cell, adenocarcinoma, and small cell, were evaluated. To establish whether risks related to silica exposure are localized in certain industries, we identified the sectors where silica exposure was most prevalent in our study population, and carried out analyses of subjects stratified according to the industry and silica exposure status. Finally, because of the importance of smoking in lung cancer etiology, we explored the joint effects of silica and smoking by means of stratified analyses.

Results

Table 1 shows the distribution of subjects according to selected sociodemographic characteristics. In both studies, cases were more often of French ancestry, had fewer years of formal education, had lower mean family income, and were more likely to have had a proxy responding for them than did controls. The proportion of ever smokers and the intensity of smoking were higher among cases than among controls. All the covariates in Table 1 were adjusted for in the subsequent risk analyses.

Table 2 shows the lifetime prevalence of occupational exposure to crystalline silica. Overall, 725 (16.6%) of subjects were exposed at the nonsubstantial level and 270 (6.2%) at the substantial level. In study I, the prevalence of exposure was almost identical between population controls and cancer controls, reinforcing the reasonableness of combining them in pooled analyses. Similarly, cases and controls of study I had a prevalence of exposure nearly identical to that of the cases and controls of study II, supporting the pooling of studies I and II. In both studies, the proportions of subjects exposed were slightly higher among cases than controls.

Although silica exposure was allocated to workers in many occupations and industries, the largest number of

Table 2. Distribution of subjects according to their lifetime occupational exposure to crystalline silica

Exposure	Study I (1979-1986)			Study II (1996-2001)	
	Population controls n (%)	Cancer controls n (%)	Cases n (%)	Population controls n (%)	Cases n (%)
Unexposed	422 (79.2)	1,055 (78.2)	623 (72.7)	721 (80.2)	560 (75.9)
Nonsubstantial exposure*	82 (15.4)	212 (15.7)	152 (17.7)	140 (15.6)	139 (18.8)
Substantial exposure*	29 (5.4)	82 (6.1)	82 (9.6)	38 (4.2)	39 (5.3)

*Distinction between substantial and nonsubstantial is based on estimated concentration, frequency, duration, and latency of exposure, as described in text.

Table 3. Risk of lung cancer among males associated with occupational exposure to crystalline silica

	Study I					
	Cases versus population controls			Cases versus other cancer controls		
	Ca/Co	OR ₀ *	OR ₁ (95% CI) [†]	Ca/Co	OR ₀ *	OR ₁ (95% CI) [†]
Unexposed	623/422	1	1	623/1,055	1	1
Any level of exposure	234/111	1.43	1.28 (0.93-1.75)	234/294	1.33	1.24 (0.99-1.56)
Non-substantial exposure	152/82	1.26	1.11 (0.78-1.59)	152/212	1.20	1.12 (0.86-1.45)
Substantial exposure	82/29	1.92	1.77 (1.05-2.98)	82/82	1.67	1.56 (1.09-2.25)

Abbreviation: Ca/Co, cases/controls.

*OR₀ is adjusted only for age and, in the pooled study, for initial source study.

[†]OR₁ is adjusted for several covariates determined *a priori*, including age; ethnicity; proxy respondent; education level; natural logarithm of median postal code region income; cigarette ever smoking; natural logarithm of cigarette-years; years since quitting smoking; occupational exposure to respirable asbestos, benzo(a)pyrene, chromium VI, and diesel emissions; and, for pooled study, original study (i.e., study I or II). Other covariates such as occupational exposure to respirable arsenic, nickel, and polyaromatic hydrocarbons were examined but not retained because they did not contribute meaningfully to the model.

exposed jobs (close to half of all exposed jobs) was among the construction trades. Other occupations with notable numbers of jobs involving silica exposure included mining and quarrying, metal foundry working, metal processing and manufacturing, and mechanics and repairmen. In terms of exposure intensity, occupations related to the processing of ore, clay, glass, and stone (including core making, casting, smelting, crushing, forming, and grinding) were assigned the highest exposures. Construction trade occupations were generally associated with low to medium exposure. Over calendar time, there were decreases in both estimated prevalence of exposure to silica (from 3.9% of all jobs held during the 1950s to 0.5% of all jobs held during the 1980s) and estimated concentration levels of those exposed (the proportion of jobs assigned low exposure increased from 48% to 75% over that period).

Table 3 presents four sets of ORs for lung cancer, representing the two comparisons of study I (population controls and cancer controls), the one comparison of study II, and the pooled set of results from both studies. In all, three levels of exposure to respirable silica were compared with nonexposure: any, nonsubstantial, and substantial exposure. Overall, ORs for each level of exposure were remarkably consistent between study I and study II. Substantial exposure was associated with lung cancer in all analyses, and this association was statistically significant in both analyses of study I and in the pooled analysis. All analyses suggested an exposure-response relationship, with substantial exposure ORs being higher than nonsubstantial exposure ORs, although there was considerable overlap of confidence intervals due to the small numbers.

Assuming that the elevated risk observed among subjects considered substantially exposed represents a real excess and given the pooled OR for substantial ex-

posure of 1.67 and the pooled lifetime prevalence of substantial exposure among cases of 7.6%, the population attributable risk of lung cancer for substantial silica exposure in our sample was approximately 3% (95% CI, 0.8-5.4). If it were to be confirmed that any exposure to silica (i.e., substantial and nonsubstantial in our terminology) carries some excess risk and given the pooled OR for any exposure of 1.31 and the lifetime prevalence of any exposure among cases of 25.8%, we estimate that the population attributable risk of lung cancer for any silica exposure would be approximately 6% (95% CI, 1.2-11.0).

Table 4 presents ORs for the main histologic types of lung cancer based on the pooled sample from both studies. The ORs for squamous cell carcinoma were markedly and significantly greater than unity, those for small cell carcinoma were moderately and nonsignificantly elevated, and those for adenocarcinoma were slightly and nonsignificantly elevated. All ORs were higher at substantial exposure than at nonsubstantial.

Table 5 presents the joint effects of smoking and silica based on the pooled sample from both studies. Odds ratios for none, any, nonsubstantial, and substantial exposure to respirable silica were calculated across four strata of smoking: never smoking, ever smoking but <400 cigarette-years (i.e., 20 pack-years), from 400 to <1,000 cigarette-years, and ≥1,000 cigarette-years. There was an increasing risk of lung cancer with increasing silica exposure in each stratum of smoking. Although the ORs for substantial silica exposure were not statistically significant in the 0 and the >0 to <400 cigarette-years smoking strata, their point estimates were elevated and dose related, suggesting that their lack of statistical significance might have been due to small numbers in these strata. If we use the ORs in the first row (i.e., among subjects unexposed to silica) and in the first column (i.e.,

Table 3. Risk of lung cancer among males associated with occupational exposure to crystalline silica (Cont'd)

Ca/Co	Study II		Pooled study		
	OR ₀ *	OR ₁ (95% CI) [†]	Ca/Co	OR ₀ *	OR ₁ (95% CI) [†]
560/721	1	1	1,183/1,565	1	1
178/178	1.30	1.28 (0.95-1.74)	412/400	1.37	1.31 (1.08-1.59)
139/140	1.28	1.23 (0.88-1.70)	291/302	1.28	1.20 (0.97-1.49)
39/38	1.35	1.53 (0.88-2.67)	121/98	1.64	1.67 (1.21-2.31)

among nonsmokers) as reference points for estimating ORs within the body of the table, using first an additive model and then a multiplicative model, the observed point estimates of the ORs are generally between the predictions of the additive and multiplicative models, perhaps closer to the latter in the cells with highest observed numbers. However, the OR estimates are quite imprecise and we cannot conclusively rule out subadditive or supramultiplicative models of joint effects.

Because the most prevalent industry among workers exposed to silica in our study was the construction industry, it is natural to wonder whether the increased risk we observed was simply a reflection of a generalized excess risk among construction workers. To address this hypothesis, we stratified the study subjects by industry (construction versus other) and by exposure to silica. Table 6 shows that the excess risk due to silica was not specific to the construction industry, and construction workers not exposed to silica did not show an excess risk of lung cancer.

Discussion

Although evidence has gradually accumulated indicating that workers highly exposed to silica may be at excess risk of lung cancer (2-4), this hypothesis has not attained the widespread acceptance that some others have, such as those dealing with asbestos and cancer. It is a more

recent hypothesis with fewer studies to back it up, but because silica is such a widespread exposure (2), it is an important one to establish firmly and to characterize. Whereas cohort studies typically focus on study populations with particularly high exposure levels of the agent under investigation, population-based case-control studies cover the entire range of exposure circumstances. The bulk of previous evidence on silica and cancer comes from cohorts of brick, diatomaceous earth, pottery, sand, and stone workers drawn from occupations in which exposure is generally high because of generation of dust with high silica content. For example, diatomaceous earth work involves extraction from open-pit mines, crushing, and calcining (4), and industrial sand production involves mining, crushing, screening, and sizing, as well as milling to a fine powder known as silica flour (28). Similarly, granite and pottery work entail substantial exposure to dust (29, 30). When such workers appeared in our study, our exposure experts assigned them medium to high concentration levels of exposure on our ordinal three-point scale, depending on the particulars of their job descriptions. By contrast, the great majority of silica-exposed workers in our study were given low concentration. A population-based case-control study also allows for the integration of entire job histories, rather than focusing only on the worker's employment with one employer, and it allows for the collection of more detailed hospital record medical diagnostic information than that typically found on death

Table 4. Risk of specific histologic types of lung cancer among males associated with occupational exposure to crystalline silica, studies I and II pooled

Exposure	Squamous cell		Small cell		Adenocarcinoma	
	Ca/Co	OR (95% CI)*	Ca/Co	OR (95% CI)*	Ca/Co	OR (95% CI)*
Unexposed	434/1,565	1	213/1,565	1	324/1,565	1
Any level of exposure	186/400	1.49 (1.17-1.90)	73/400	1.37 (0.97-1.92)	84/400	1.07 (0.79-1.46)
Nonsubstantial exposure	132/302	1.41 (1.08-1.84)	54/302	1.31 (0.90-1.90)	63/302	1.03 (0.74-1.45)
Substantial exposure	54/98	1.77 (1.18-2.65)	19/98	1.57 (0.87-2.82)	21/98	1.22 (0.71-2.09)

*Adjusted for several covariates determined *a priori*, including original study (i.e., study I or II), age, ethnicity, proxy respondent, education level, natural logarithm of median postal code region income, cigarette ever smoking, natural logarithm of cigarette-years since quitting smoking, and occupational exposure to respirable asbestos, benzo(a)pyrene, chromium VI, and diesel emissions.

Table 5. Joint effects of smoking and substantial silica exposure on risk of lung cancer, studies I and II pooled

Exposure	Smoking level			
	0 cigarette-years		>0 to <400 cigarette-years	
	Ca/Co	OR (95% CI)*	Ca/Co	OR (95% CI)*
Unexposed	24/298	1	43/238	2.19 (1.28-3.76)
Any level of exposure	7/65	1.28 (0.52-3.17)	14/50	3.20 (1.51-6.77)
Nonsubstantial exposure	4/50	0.98 (0.32-3.00)	11/38	3.09 (1.36-7.00)
Substantial exposure	3/15	2.25 (0.59-8.56)	3/12	3.67 (0.95-14.14)

*Adjusted for several covariates determined *a priori*, including original study (i.e., study I or II), age, ethnicity, proxy respondent, education level, natural logarithm of median postal code region income, and occupational exposure to respirable asbestos, benzo(a)pyrene, chromium VI, and diesel emissions.

certificates. Finally, whereas it is notoriously difficult to control for smoking in cohort studies, a case-control study allows for ascertainment of a complete history of cigarette smoking. For all these reasons, the conduct of case-control studies is an important complement to cohort studies.

Our study had strengths and weaknesses. Two thirds of the study population were of French ancestry. Compared with the typically diverse North American populations, this considerably diminishes the risk of confounding by genetic and environmental factors related to ethnicity. All cancer cases were incident and histologically confirmed. Response rates were quite high, over 80% for case groups and 70% for population control groups. Although the participation proportions were lower among controls than among cases, our proportions were as high as or higher than those in most recent studies (31), thus diminishing the likelihood of selection bias. We had extensive information on potential confounders, covering sociodemographic and lifestyle factors including smoking history, as well as other occupational exposures such as asbestos, benzo(a)pyrene, chromium VI, and diesel emissions. By contrast with most occupational cohort studies we had information on the worker's complete lifetime work history, not just the history with one of his employers. The assessment and control of smoking history is an obvious concern. For the parameterization of smoking history, we used an approach based on a risk model derived from our study subjects (24, 25). Although this is an optimal approach, it is conceivable that some degree of residual confounding remains.

There were quite high proportions of proxy response, but it was reassuring that prevalence of exposure was similar between proxy and self-respondent subjects, and that the overall results were similar when we excluded proxies from the analyses (data not shown). Occupational exposure was attributed to subjects on the basis of their detailed lifetime job history reported at the interview. We considered the specific tasks they carried

out and their use of protective gear. We have previously shown that the subjects' reports of occupational history were valid (32). Our team of chemists and industrial hygienists attributed exposure to the subjects using a method for which reasonable reliability (33, 34) and validity (35) have been shown in our own study population and using our own study personnel. However, as our exposure assessment protocol was based on expert opinion rather than direct measurement or biomarkers, it inevitably entailed some degree of measurement error. Because this work was done blindly with respect to disease status, we assume that any misclassification of the exposure variables under consideration would have occurred at random with respect to the outcome and thus would lead to an attenuation of estimates of association. Our assessment of exposure frequency and concentration was semiquantitative, based on descriptions provided by the subjects and established by expert chemists and industrial hygienists. Although errors in exposure assessment for silica would likely lead to attenuation of risk estimates, errors in exposure assessment for occupational confounders or failure to include true occupational confounders could lead to bias in any direction. We cannot be certain that the associations observed are not attributable to some other concomitant exposures in the same environments as silica, but the variety of those environments in our study population mitigates against this possibility.

The results of the two studies were remarkably consistent, in spite of the time interval between them. Workers exposed to any silica had about a 30% increased risk of lung cancer and those exposed to substantial levels had about a 70% increase, both of which were statistically significant. The population attributable risk percent for substantial exposure to silica was approximately 3%, and if it were to be confirmed that any exposure (i.e., substantial and nonsubstantial) carries some excess risk, we estimate that the population attributable risk would be approximately 6%.

Table 5. Joint effects of smoking and substantial silica exposure on risk of lung cancer, studies I and II pooled (Cont'd)

		Smoking level	
		≥400 to <1,000 cigarette-years	≥1,000 cigarette-years
Ca/Co	OR (95% CI)*	Ca/Co	OR (95% CI)*
278/467	6.91 (4.40-10.85)	816/553	16.90 (10.87-26.28)
74/125	6.76 (4.01-11.40)	313/160	23.20 (14.41-37.36)
51/96	5.98 (3.44-10.40)	222/118	22.00 (13.46-35.96)
23/29	9.49 (4.68-19.24)	91/42	26.93 (15.16-47.84)

We confirmed that the association observed was unlikely to be attributable to errors engendered by the inclusion of proxy respondents or to a generalized excess risk of lung cancer among construction industry workers for which silica might just be a marker. In our data, silica was more strongly associated with small cell and squamous cell tumors than with adenocarcinoma. This pattern is compatible with the possibility of residual confounding, because squamous and small cell tumors have the strongest relationships with cigarette smoking. However, this pattern is also compatible with the possibility that silica is causally related to the same histologic types of lung cancer as smoking. We carried out a detailed adjustment for the various smoking dimensions in the multivariate analyses, and when stratifying by level of smoking, we found excess risks due to silica in each smoking stratum. Because of small numbers and the consequent imprecision of estimates, it was not possible to ascertain with confidence the nature of the joint effects of silica and smoking, although the point estimates were generally between additive and multiplicative.

In addition to consistency with epidemiologic evidence (3, 4, 8), our results are also consistent with a wide range of basic science evidence supporting the carcinogenicity of inhaled crystalline silica. Silica can cause chromosomal

aberrations and transformation *in vitro* in mammalian cells (36). It has been found to be carcinogenic in rats, but not mice, guinea pigs, or hamsters (37). Endocytosis of single silica nanoparticles into human lung cancer cells has been seen on microscopy (38). Silica lyses macrophages that ingest it, causing release of lysozymes and other toxic substances, thereby leading to inflammation, collagen deposition, fibrosis, and, possibly, tumor formation. Its toxicity to alveolar macrophages may be through reactive oxygen species or through cytokine release and apoptosis (1, 39). Silica also induces a reduction in mRNA expression of glyoxalases, which remove methylglyoxal, a potent cell proliferation inhibitor and apoptosis inducer, and thereby can increase methylglyoxal (40). Finally, asbestos and silica are sensed by the Nalp3 inflammasome, which leads to interleukin 1 β secretion, triggered by reactive oxygen species that are generated upon particle phagocytosis (41).

We conclude that the carcinogenicity of inhaled crystalline silica was observed in a population that experienced a wide variety of occupational exposure circumstances, with exposure levels probably lower than those evaluated in past cohort studies. The main cell types affected are squamous and small cell tumors. Joint effects between silica and smoking were between additive and multiplicative, possibly closer to the latter. In our sample,

Table 6. Risk of lung cancer by exposure to construction industry and occupational exposure to silica

Any exposure to construction industry	Any occupational exposure to silica	Ca/Co	OR (95% CI)*
No	No	1,030/1,335	1
No	Yes	155/165	1.20 (0.91-1.59)
Yes	No	153/230	0.70 (0.54-0.91)
Yes	Yes	257/235	1.25 (0.99-1.58)

*Adjusted for several covariates determined *a priori*, including original study (i.e., study I or II), age, ethnicity, proxy respondent, education level, natural logarithm of median postal code region income, cigarette ever smoking, natural logarithm of cigarette-years, years since quitting smoking, and occupational exposure to respirable asbestos, benzo(a)pyrene, chromium VI, and diesel emissions.

approximately 3% of all lung cancers were attributable to substantial silica exposure.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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