Respirable Crystalline Silica Exposure, Smoking, and Lung Cancer Subtype Risks: A Pooled Analysis of Case–control Studies

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ABSTRACT

Rationale and objectives: Respirable crystalline silica is a lung carcinogen with millions of exposed workers globally. We aimed to address current knowledge gaps in lung cancer risks associated with low levels of occupational silica exposure and the joint effects of smoking and silica exposure on lung cancer risks.

Methods: Subjects from 14 case-control studies from Europe and Canada with detailed smoking and occupational histories were pooled. A quantitative job-exposure matrix was used to estimate silica exposure by occupation, time period, and geographical region. Logistic regression models were used to estimate exposure-disease associations and the joint effects of silica exposure and smoking on risk of lung cancer. Stratified analyses by smoking history and cancer subtypes were also performed.

Measurements and main results: Our study included 16,901 cases and 20,965 controls. Lung cancer odds ratios ranged from 1.15 (95% CI 1.04, 1.27) to 1.45 (95% CI 1.31, 1.60) for groups with the lowest and highest cumulative exposure, respectively. Increasing cumulative silica exposure was associated (p-trend<0.01) with increasing lung cancer risks in non-silicotics, and in current, former, and never smokers. Increasing exposure was also associated (p-trend≤0.01) with increasing risks of lung adenocarcinoma, squamous cell carcinoma, and small cell carcinoma. Super-multiplicative interaction of silica exposure and smoking was observed on overall lung cancer risks; super-additive effects were observed in risks of lung cancer and all three included subtypes.

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Conclusions: Silica exposure is associated with lung cancer at low exposure levels. Exposure-response relationship was robust and present regardless of smoking, silicosis status, and cancer subtype.

(Abstract word count: 250)

INTRODUCTION

Occupational exposure to respirable crystalline silica (silica hereafter) occurs in tens of millions of workers globally in a wide range of industries, including construction, mining, quarrying, as well as manufacturing of bricks, ceramics, and metal products [1,2]. Silica is classified as a human lung carcinogen by the International Agency for Research on Cancer (IARC), US National Institute for Occupational Safety and Health (NIOSH), and the US National Toxicology Program (NTP) [3 – 5]. A pooled analysis of 1,072 lung cancer cases from 10 industry-based studies showed that the risk of cancer increased monotonically with increases in cumulative silica exposure [6]. Additional evidence of an exposure-response relationship between silica and lung cancer were observed in different industrial-cohorts [7,8] as well as in case-control studies in different countries [9 – 11].

Despite the strong epidemiologic evidence of an exposure-response relationship between silica and lung cancer, questions still remain regarding certain aspects of the carcinogenicity of silica, including: the role of cigarette smoking as a potential confounder and effect modifier [12]; whether an exposure threshold exists for silica-related lung cancer [13]; whether silicosis is a prerequisite for developing silica-related lung cancer [14,15]; the effect of silica exposure on risks of different histological subtypes of lung cancer [9,10]; and the joint effect of exposure to silica and smoking on risk of lung cancer and its subtypes [7,9].

In the current study we present findings from a pooled analysis of lung cancer case-control studies from Europe and Canada, the SYNERGY project [16]. Occupational exposure to quartz silica was estimated via a quantitative general population job exposure matrix (SYN-JEM) [17]. The aims of our work were to assess: 1) the risks of lung cancer in relation to various indices of occupational silica exposure by cancer subtype, smoking status, and silicosis status; 2) the interaction of silica exposure and smoking on the risk of lung cancer risk and its major subtypes on the additive and multiplicative scale; and 3) the excess lifetime risks of lung cancer associated with different levels of occupational silica exposure.

METHODS

Study population

The SYNERGY project is a pooled analysis of 14 population-/hospital-based lung cancer case-control studies in 13 European countries and Canada (Supplementary Table E1, available online). Detailed description of the population was presented elsewhere [16]. Lifetime occupational and smoking histories were available for all subjects. Self-reports of physician-diagnosed silicosis were collected in the AUT-Munich, EAGLE, HdA, and INCO studies by in person or next-of kin interview (full silicosis questions available in Supplementary Table E1). Ethical approvals for the SYNERGY project were obtained from all participating countries as well as the IARC institutional review board. More information about the project is available at http://synergy.iarc.fr.

Exposure assessment

The elaborated SYN-JEM and the underlying models for exposure to quartz silica have been described in detail elsewhere [17 – 19]. Briefly, 23,640 historical personal respirable quartz measurements were combined with exposure ratings from a general population JEM, the DOM-JEM [20]. Quantitative quartz silica exposures estimates (in mg/m^3) representing annual average exposure levels were derived for each job title, region, and year combination. Silica concentrations before 1960 were assumed to be the same as those in 1960. JEM linkage to the population was performed via the International Standard Classification of Occupations (version 1968, or ISCO-68) [21]. Cumulative exposure (in mg/m^3-year) was calculated as the sum of the products of modeled exposure intensities and years of employment for all jobs over a subject's entire working history.

Statistical analysis

The overall analysis protocol for silica is similar to those previously applied to characterize lung cancer risks for exposure to diesel engine exhaust and asbestos in the SYNERGY study [16,22]. Odds ratios (OR) and 95% confidence intervals (CI) for lung cancer associated with various categorical indices of occupational silica exposure were calculated using unconditional logistic regression models. Trend analysis p-values were obtained by including the various indices of exposure as continuous variables in models for all subjects and for exposed subjects only. In our main categorical models, lung cancer risks were calculated for the following silica exposure metrics: ever/never exposure, duration of exposure (1-9; 10–19; 20–29; >29 years), time since last exposure (<5; 5–9; 10–19; 20–29; 30–39; >39 years), and cumulative exposure (quartiles of exposure distribution among controls: >0–0.39; 0.4–1.09; 1.1–2.39; ≥2.4 mg/m^3-year). Adjustments were made for age group (<45; 45–49; 50–54; 55–59; 60–64; 65–69; 70–74; >74 years), sex, study, smoking (log(cigarette pack-years+1)), smoking cessation since interview/diagnosis (current smokers; >0-7; 8-15; 16-25; >25 years; never smokers), and ever employment in "List A jobs." List A jobs are occupations with known occupational lung cancer risks (e.g. welders, long distance truck drivers, boiler operators) and their inclusion in the model served as an adjustment for exposures to other occupational lung carcinogens. The list was first published in 1982, then updated in 1995 and 2000 to include exposures reviewed by IARC up to volume 75 of the Monographs [23,24]. We defined smokers as subjects who smoked >1 cigarettes per day for >1 years; pack-year was calculated as the sum of the products of smoking duration in years and average smoking of 20-cigarette packs per day.

Various silica cumulative exposure lag-times (0; 5; 10; 15; 20 years) were applied in the main models, but only results with zero lag are presented because models with no lag had the best model fit according to minimized Akaike information criterion values. Stratified analyses for cancer risks associated with cumulative exposure categories were also calculated for subjects with different major cancer subtypes, without reported silicosis, and with different smoking habits.

For analyses of silica exposure as a continuous variable, both untransformed and natural log-transformed cumulative exposure were used. For the model with log-transformed exposure, non-exposed subjects were assigned two-thirds of the lowest cumulative exposure value among the exposed group (0.0036 mg/m^3-year). To further explore the shape of the exposure-response relationship, we performed thin-plate regression spline analyses as implemented in the R package *mgcv*, with relative maximum likelihood selected as the method for smoothing parameter estimation and total number of basis functions limited to 3. The 95% CI around the splines were based on simulations from posterior distributions of model coefficients with random draws from a multivariate normal distribution parameterized by the estimated mean vector and covariance matrix of the model coefficients. All splines were truncated at the 99th percentile to focus on results that were the most relevant and best supported by our exposure data.

Multiplicative interactions between silica exposure and smoking on risks of overall lung cancer and major cancer subtypes were assessed using p-values from the cross-product interaction terms between silica exposure and smoking in the logistic models. For additive interactions, relative excess risks due to interaction (RERI) were calculated using ORs from the adjusted logistic models as defined by Rothman and Greenland [25] and implemented in the R package *epi.interaction*.

Excess lifetime risks (ELR) of lung cancer at age 80 associated with 45 years of occupational silica exposure at various concentrations were calculated according to life table methods described by Vermeulen and colleagues [26] with all cause and lung cancer mortality rates from the European Union in 2008 as the referent [27]. Silica exposure levels for our ELR calculations were selected based on: the current recommended 8-hour threshold limit value by the American Conference of Governmental Industrial Hygienists (ACGIH) at 0.025 mg/m^3 [28]; the recently updated 0.05 mg/m^3 permissible exposure limit from US OSHA [29]; and the exposure limit of 0.1 mg/m^3 in the latest EU directive (2019/130) on the protection of workers from carcinogens [30].

Statistical analyses were conducted using SAS (version 9.3, SAS Institute, Cary, NC) and R (version 3.5).

RESULTS

After excluding participants with incomplete information on covariates (804 cases; 848 controls), 16,901 lung cancer cases (4,752 adenocarcinomas; 6,503 squamous cell carcinomas; 2,730 small cell carcinomas; 2,822 other/unspecified lung cancers; 94 not available) and 20,965 controls remained for our main analyses (Table 1). Silicosis status was available in 50% of the study population (n=18,931), among which 108 cases of silicosis were reported. Occupations with the highest modeled silica exposure concentrations in SYN-JEM were chimney bricklayers, stone cutters/carvers, and hand monument carvers; the most frequently reported exposed job titles among the control subjects in our population were farm helpers, general farmers, and construction bricklayers (more occupations in these categories are available in Supplementary Table E2).

Increased overall lung cancer risks were observed for silica-exposed versus non-exposed subjects across three occupational exposure metrics, including ever exposure (OR = 1.30; 95% CI 1.23, 1.38), longer exposure duration (longest category: >29 years; OR =1.48; 95% CI 1.34, 1.63) and higher cumulative exposure (highest category: >2.4 mg/m^3-year; OR = 1.45; 95% CI 1.31, 1.60) (Table 2). Elevated lung cancer risk increases were found for groups with the lowest exposure duration and cumulative exposure; ORs were 1.22 (95% CI 1.12, 1.31) and 1.15 (95% CI 1.04, 1.27) for subjects with exposure duration of 1-9 years and cumulative exposure <0.4 mg/m^3-year, respectively. Increasing cancer risk trends were also associated (p-trends<0.01) with both increasing exposure duration and increasing cumulative exposure. Lung cancer risks for those who were more recently exposed also tended to be higher than for those who were last exposed a longer time ago, but confidence in this risk trend is lower (p-trend = 0.10 among exposed subjects). Results for analyses restricted to subjects who did not report silicosis were similar to those from the main analyses (Table 3).

Increasing risks of all three included lung cancer subtypes were observed with increasing silica cumulative exposure (Table 4). We observed elevated risks of squamous cell carcinoma for all cumulative exposure groups, including the lowest (OR = 1.22; 95% CI 1.06, 1.39). Clear increased risks of small cell carcinoma were found for groups with cumulative exposures ≥0.4 mg/m^3-year, with an OR of 1.70 (95% CI 1.43, 2.02) for the highest exposed group. Adenocarcinoma risks were generally lower than those observed in small cell and squamous cell carcinomas; adenocarcinoma OR for the highest exposed group was 1.17 (95% CI 1.00, 1.37).

The continuous model with untransformed exposure showed that every 1 mg/m^3-year increase in cumulative silica exposure increased lung cancer risk by a factor of 1.06 (95% CI 1.04, 1.08). In the model with log-transformed exposure, lung cancer risk increased by a factor of 1.05 (95% CI 1.04, 1.06) for every unit increase in log cumulative exposure. Nonparametric spline analysis showed monotonic increases in risks of overall lung cancer and its subtypes for both untransformed and log-transformed silica cumulative exposure (Figure 1). Individual splines for overall lung cancer and all subtypes with corresponding 95% CI are available in Supplementary Figure 1 and 2.

Stratified analyses showed that regardless of smoking status, increasing cumulative silica exposure were associated (p-trends for all subjects<0.01) with increasing lung cancer risks (Table 5). Risks of lung cancer for different silica exposure groups were similar for former and current smokers, with ORs of 1.47 (95% CI 1.27, 1.70) and 1.39 (95% CI 1.20, 1.62) for the highest exposed group, respectively. For never-smokers, the OR point estimates for all silica cumulative exposure categories were above 1, with the highest exposed group having an OR of 1.40 (95% CI 1.03, 1.86).

Interactions beyond the additive model between smoking and occupational silica exposure were observed for overall lung cancer (RERI = 2.34; 95% CI = 1.85, 2.83), adenocarcinoma (RERI = 0.70; 95% CI = 0.26, 1.15), squamous cell carcinoma (RERI = 4.86; 95% CI = 3.63, 6.09), and small cell carcinoma (RERI = 5.13; 95% CI = 3.03, 7.23) (Tables 6 and 7). Super-multiplicative joint effect of smoking and silica exposure was observed on overall lung cancer risk ($p<0.01$). OR point estimates also suggest super-multiplicative interactions for risks of adenocarcinoma and squamous cell carcinoma, though these effect estimates were associated with higher uncertainties ($p=0.17$ and $p=0.23$, respectively) due to smaller sample sizes.

Lung cancer ELRs were 0.22%, 0.45%, and 0.96% for workers exposed to 0.025, 0.05, and 0.1 mg/m^3 of silica, respectively.

DISCUSSION

In a large international pooled case-control study with more than 16,000 lung cancer cases, we found increases in lung cancer risks associated with continuous silica cumulative exposure as well as different categorical exposure metrics, including ever exposure, longer exposure duration, and higher cumulative exposure.

Positive associations between occupational silica exposure and lung cancer have been reported mainly in industrial cohorts. In a pooled analysis of 10 silica-exposed industrial cohorts, Steenland and colleagues reported a lung cancer risk increase of 1.07 for every unit increase in log-transformed cumulative silica exposure in mg/m^3-year with zero lag [6]. The corresponding risk increase reported by Liu and colleagues in a cohort of 34,018 workers in China was 1.06 [7]. These estimates were very similar to the result from our analysis with log-cumulative exposure (OR 1.05). Results from our corresponding spline analyses were consistent with the exposure-response relationships observed in the linear cumulative exposure logistic models – monotonic risk increases were observed for lung cancer and its subtypes.

Our results showed that silica is associated with lung cancer at very low cumulative exposures with no apparent threshold at concentrations investigated. ORs were 1.15 and 1.33 for our two lowest exposed groups, which had median cumulative exposures of 0.22 and 0.73 mg/m^3-year, respectively. Few other studies quantified lung cancer risks at levels near or below 1 mg/m^3-year. A meta-analysis with data from 19 studies calculated a pooled risk estimate of 1.19 (95% CI 1.01, 1.39) for workers with a median cumulative exposure of 0.42 mg/m^3-year [31]. Liu and colleagues reported an OR point estimate of 1.12 (1.26 with 25 year lag) for Chinese workers in the lowest exposed group with median exposure of 0.56 mg/m^3-year [7]. However, results by Sogl and co-workers, who assessed silica exposure in German uranium mines using a measurement-based JEM, observed no lung cancer effects below cumulative silica exposures of 10 mg/m^3-years [8].

For some carcinogens and related cancers, there is good evidence that disease relative risks after cessation of exposure are below unity when compared to groups with continued exposure (e.g. cigarette smoking[32,33]). We tested whether such a pattern was present in our population using time-since-exposure categories. We observed results suggesting that higher lung cancer risks were associated with more recent silica exposure. To our knowledge, this is the only study that included this metric for silica exposure and more evidence is needed to support this finding.

Whether silicosis is a prerequisite for silica-related lung cancer had been a topic of debate, primarily because results from earlier studies failed to support a consistent association between silica and lung cancer after excluding subjects with silicosis [14,15]. A number of more recent studies set up analyses specifically to address this issue and reported evidence of a positive relationship between silica exposure and lung cancer without clinical silicosis [7,8,10,31,34,35]. Results from our restricted analysis of subjects without silicosis similarly support a direct association between silica and lung cancer. Although underreporting of silicosis due to self-reports by the index subject or proxy was possible in our study, the effects observed were unlikely to be caused solely by the misclassification of silicosis due to the rarity of the condition in the general population.

Our findings suggest that lung squamous cell and small cell carcinomas are more strongly associated with silica exposure than lung adenocarcinoma. Research on lung cancer subtypes related specifically to silica exposure is rare. Two other large case-control studies in Europe and Canada similarly reported increased risks for all three major subtypes in relation to silica exposure, with the strongest association observed in squamous cell carcinoma [9,11]. A large case-control study in Italy found elevated risk only for squamous cell and small cell carcinomas but not for adenocarcinoma [10]. Most subjects in the three aforementioned studies, however, were also included in the current study and represented approximately 35% of our total participants.

Increases in overall lung cancer risk with increasing cumulative exposure were found regardless of smoking status. Our findings are in accordance with those from Liu and colleagues, where never smokers with cumulative silica exposure >1.12 mg/m^3-year had a lung cancer HR of 1.60 (95% CI 1.01, 2.55) [7]. Ours is the first study to report an exposure-response between cumulative exposure to silica and lung cancer among never smokers. Super-additive interactions of silica exposure and cigarette smoking were observed for overall lung cancer as well as all three major subtypes. Super-multiplicative interaction was also observed for all lung cancers combined. One other study reported a super-additive joint effect of silica exposure and smoking on lung cancer [7] and one reported no evidence for a joint effect beyond the multiplicative model [9].

Our study population comprised a large number of cases exposed to silica (n=4,923) and allowed for stratification and interaction analyses for different cancer subtypes and risk factors. Despite having a large study population, our power to investigate silica exposure-related cancer risks in women were limited. This is because the number of exposed cases in women (n=274) was much smaller than those in men (n=4,649). Analyses restricted to females showed imprecise results with OR point estimates that were generally greater than one (Supplementary Table E3a). Male-specific results are also available in Supplementary Table E3b.

We performed quantitative exposure assessment specific for exposure to quartz silica, which allowed for quantification of exposure-disease risks and exploration of the shape of the exposure-response curves in a population-based case-control setting. However, our estimates of silica exposure may be affected by exposure misclassification and less accurate than some industrial-cohort based studies, particularly those with detailed work history and extensive historical silica measurements. This misclassification was likely to be non-differential with respect to case status and would result in a bias of risk estimates toward the null. Due to sparse measurement data for years prior to 1960 in our JEM, we assumed in backward extrapolation that silica exposure did not further increase in years prior to 1960. In a previous publication we have explored different time trend assumptions in our exposure model [19]. Naturally, the assigned silica exposures in the population (and the slope of the exposure-response) would vary if different time-trend assumptions were made, but these changes have little effect on the exposure status and ranking of cumulative exposure among our study population. When we restricted our categorical exposure model to include only subjects who started work after 1960 (Supplementary Table E4.2), the silica lung cancer exposure-response in general and more specifically elevated lung cancer risks associated with lower categories of cumulative silica exposure were still observed.

Our study included more complete information on individual covariates than most industry-based studies, which allowed for the control of important potential confounders such as smoking and exposures to other occupational lung carcinogens in our models. As an alternative to adjusting for co-exposures to other lung carcinogens with ever employment in List A jobs, we performed a sensitivity analysis controlling for DOM-JEM assessed ever exposure to diesel engine exhaust, hexavalent chromium, asbestos, and polycyclic aromatic hydrocarbons in our categorical exposure model. Results of this analysis (Supplementary Table E4.4) were very similar compared to our main results. The associations we observed between silica and lung cancer were also robust in other sensitivity analyses with different subgroups (Supplementary Methods, Results, and Tables E4.1-4.5).

Current definitions of "tolerable" ELR due to occupational exposure to carcinogens vary by jurisdiction, ranging from the 0.4% in the Netherlands and Germany to 0.1% generally accepted by the US OSHA [36 – 38]. According to our calculations lifetime occupational silica exposure at 0.05 and 0.1 mg/m^3 would result in respective lung cancer ELRs of 0.45% and 0.96%, which clearly exceed this range of "tolerable" risks. Lifetime silica exposure at 0.025 mg/m^3 would result in approximately 2 lung cancers in 1,000 workers, which falls below the Dutch/German limit of 0.4% but above the US limit of 0.1%. Other studies have estimated similar lung cancer ELRs at low levels of silica exposure, with one study estimating an ELR of 0.23-0.48% for workers exposed to 0.07 mg/m^3 of silica and another estimating an ELR of 0.2-0.3% for workers with an exposure level of 0.01 mg/m^3 [6,7]. The ELR findings from other studies and ours suggest that lower occupational silica exposure limits may be considered in order to protect exposed workers from excess lung cancer risks. Lastly, because our exposure assessment was specific for quartz silica and did not include other forms of silica, our ELR may not reflect risks from exposures to other forms of crystalline silica such as cristobalite and tridymite. However, since quartz is by far the most common form of crystalline silica, exposure prevalence and disease burden associated with other crystalline silica polymorphs are likely to be much smaller than those associated with quartz exposure [39].

In summary, in a large pooled analysis of lung cancer case-control studies, we observed a positive association and exposure-response relationship between occupational silica exposure and lung cancer. The exposure-disease association was consistent regardless of tobacco smoking history or silicosis status. Silica-exposed workers had higher risks for all investigated lung cancer subtypes; risks were higher for squamous cell and small cell carcinomas than for adenocarcinoma. Our findings support efforts to further reduce occupational exposure to silica for the protection of exposed workers against risks of developing lung cancer.

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FIGURE LEGEND:

Figure 1 Title: Spline analyses results on exposure-response relationships between lung cancer and 1A) cumulative exposure; 1B) natural log-transformed cumulative exposure.

Figure 1 Abbreviation: mg/m^3-years = milligram per cubic metre years

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TABLES

Table 1. Selected study population characteristics by lung cancer status and silica exposure

		Ever exposed to silica				Never exposed to silica			
Characteristic	**Category**	**Cases**	**%**	**Controls**	**%**	**Cases**	**%**	**Controls**	**%**
Sex	Male	4649	94.4	4140	92.2	8956	74.8	12311	74.7
	Female	274	5.6	348	7.8	3022	25.2	4166	25.3
Age group	<45 years	142	2.9	194	4.3	573	4.8	1177	7.1
	45-64 years	2503	50.8	2055	45.8	6260	52.3	8299	50.4
	>64 years	2278	46.3	2239	49.9	5145	43.0	7001	42.5
Smoking status	Never smoker	248	5.0	1253	27.9	1121	9.4	5900	35.8
	Former smoker	1736	35.3	2010	44.8	3696	30.9	6210	37.7
	Current smoker	2939	59.7	1225	27.3	7161	59.8	4367	26.5
Smoking pack years	Never smoker	248	5.0	1253	27.9	1121	9.4	5900	35.8
	<10	227	4.6	683	15.2	582	4.9	2386	14.5
	10-19	475	9.6	598	13.3	1127	9.4	2264	13.7
	>19	3973	80.7	1954	43.5	9148	76.4	5927	36.0
Years-since-quitting-smoking	Never smoker	248	5.0	1253	27.9	1121	9.4	5900	35.8
	>0-7 years	638	13.0	317	7.1	1388	11.6	1105	6.7
	8-15 years	494	10.0	461	10.3	1037	8.7	1437	8.7
	16-25 years	379	7.7	590	13.1	792	6.6	1756	10.7
	>25 years	225	4.6	642	14.3	479	4.0	1912	11.6
	Current smoker	2939	59.7	1225	27.3	7161	59.8	4367	26.5
'List A' job	Ever employment	829	16.8	597	13.3	958	8.0	767	4.7
	Never employment	4094	83.2	3891	86.7	10905	92.0	15563	95.3
Silicosis	Reported silicosis	57	1.2	33	0.7	13	0.1	5	0
	No reported silicosis	2882	58.5	2311	51.5	6091	50.9	7539	45.8
	Unknown	1984	40.3	2144	47.8	5874	49.0	8933	54.2
Lung cancer subtype	Adenocarcinoma	1069	21.7	-		3683	30.7	-	
	Small cell carcinoma	869	17.7	-		1861	15.5	-	
	Squamous cell carcinoma	2251	45.7	-		4252	35.5	-	
	Other/unspecified	711	14.4	-		2111	17.6	-	
	Not available	23	0.5	-		71	0.6	-	

Table 2. Lung cancer odds ratios (OR) associated with various indices of occupational silica exposure

Occupational silica exposure	Exposure category	Cases	%	Controls	%	OR*	95% CI
Reference group	Non-exposed	11978	70.9	16477	78.6	1.0	Referent
Ever exposure	Ever	4923	29.1	4488	21.4	1.30	1.23–1.38
Duration (years)	1–9	2035	12.0	1936	9.2	1.22	1.12–1.31
	10–19	926	5.5	905	4.3	1.20	1.08–1.34
	20–29	635	3.8	519	2.5	1.45	1.26–1.66
	>29	1327	7.9	1128	5.5	1.48	1.34–1.63
	Test for trend, p-value					*<0.01*	
	Excl. never exposed					*<0.01*	
Cumulative exposure (mg/m^3-years)	>0–0.39	1113	6.6	1128	5.4	1.15	1.04–1.27
	0.4–1.09	1221	7.2	1120	5.3	1.33	1.21–1.47
	1.1–2.39	1231	7.3	1122	5.4	1.29	1.17–1.42
	≥2.4	1358	8.0	1118	5.3	1.45	1.31–1.60
	Test for trend, p-value					*<0.01*	
	Excl. never exposed					*<0.01*	
Time since last exposure (years)†	<5	934	5.5	815	3.9	1.43	1.18–1.73
	5–9	462	2.7	351	1.7	1.43	1.15–1.77
	10–19	679	4.0	569	2.7	1.36	1.13–1.63
	20–29	617	3.7	536	2.6	1.26	1.08–1.47
	30–39	931	5.5	812	3.9	1.30	1.15–1.47
	>39	1300	7.7	1405	6.7	1.09	0.99–1.20
	Test for trend, p-value						
	*Excl. never exposed**					*0.10*	

*OR adjusted for study, age group, sex, smoking (pack-years, time-since-quitting smoking), and List A jobs

†OR in "time since last exposure" is additionally adjusted for duration (continuous) of silica exposure. Trend test limited to exposed subjects.

Table 3. Lung cancer odds ratios (OR) associated with cumulative occupational silica exposure in subjects without silicosis

Cumulative silica exposure (mg/m^3-years)	**Cases**	**OR***	**95% CI**
Never	6091	1.0	Referent
>0–0.39	665	1.22	1.07–1.40
0.4–1.09	720	1.50	1.31–1.71
1.1–2.39	757	1.48	1.30–1.69
≥2.4	740	1.42	1.25–1.63
Test for trend, p-value		*<0.01*	
Excl. never exposed		*<0.01*	

*OR adjusted for study, age group, sex, smoking (pack-years, time-since-quitting smoking), and List A jobs

Table 4. Lung cancer major subtype risks (OR*) associated with cumulative occupational silica exposure

Cumulative exposure (mg/m^3-years)	**Adenocarcinoma**			**Squamous cell carcinoma**			**Small cell carcinoma**		
	Cases	OR*	95% CI	Cases	OR*	95% CI	Cases	OR*	95% CI
Never	3683	1.0	Referent	4252	1.0	Referent	1861	1.0	Referent
>0–0.39	283	1.14	0.98–1.33	455	1.22	1.06–1.39	194	1.07	0.89–1.28
0.4–1.09	282	1.18	1.02–1.37	557	1.51	1.33–1.71	204	1.41	1.17–1.68
1.1–2.39	240	1.03	0.88–1.20	593	1.46	1.29–1.65	229	1.48	1.25–1.76
≥2.4	264	1.17	1.00–1.37	646	1.55	1.37–1.76	242	1.70	1.43–2.02
Test for trend, p-value		*0.01*			*<0.01*			*<0.01*	
Excl. never exposed		*0.02*			*<0.01*			*<0.01*	

*OR adjusted for study, age group, sex, smoking (pack-years, time-since-quitting smoking), and List A jobs

Table 5. Lung cancer risks (OR) associated with cumulative occupational silica exposure by smoking status

Cumulative exposure	**Never smokers**			**Former smokers**			**Current smokers**		
(mg/m^3-years)	Cases	OR*	95% CI	Cases	OR†	95% CI	Cases	OR‡	95% CI
Never	1121	1.0	Referent	3696	1.0	Referent	7161	1.0	Referent
>0–0.39	60	1.17	0.85–1.57	366	1.07	0.92–1.25	687	1.19	1.03–1.39
0.4–1.09	59	1.07	0.78–1.43	433	1.37	1.18–1.59	729	1.33	1.15–1.55
1.1–2.39	60	1.02	0.75–1.36	441	1.35	1.16–1.57	730	1.29	1.11–1.50
≥2.4	69	1.40	1.03–1.86	496	1.47	1.27–1.70	793	1.39	1.20–1.62
Test for trend, p-value		*<0.01*			*<0.01*			*<0.01*	
Excl. never exposed		*0.02*			*<0.01*			*0.07*	

*OR adjusted for sex, study, age group and "List A" jobs

†OR adjusted for sex, study, age group, "List A" jobs, pack-years, and time-since-quitting smoking

‡OR adjusted for sex, study, age group, "List A" jobs, and pack-years

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Table 6: Interactions between occupational silica exposure and smoking for all lung cancers

Exposure status	**All lung cancers**			
	Controls	Cases	OR*	95%CI
Never Smoker & Never silica	5900	1121	1.0	Referent
Never Smoker & Ever silica	1253	248	1.02	0.87–1.19
Ever Smoker & Never silica	10577	10857	6.37	5.91–6.87
Ever Smoker & Ever silica	3235	4675	8.72	8.0–9.52
p-value multiplicative interaction			*<0.01*	
RERI			*2.34*	*1.85–2.83*

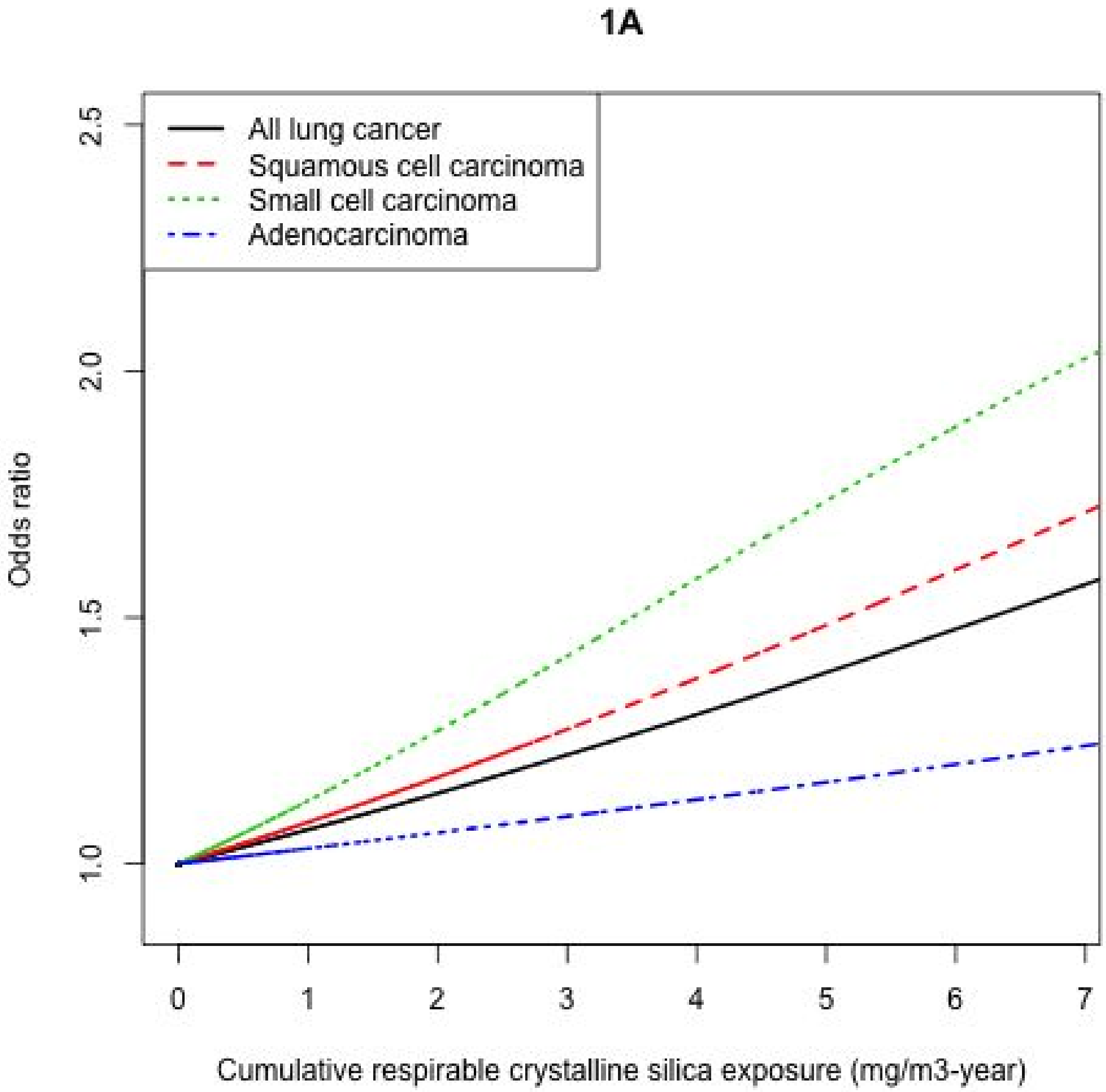
*OR adjusted for sex, study, age group and "List A" jobs

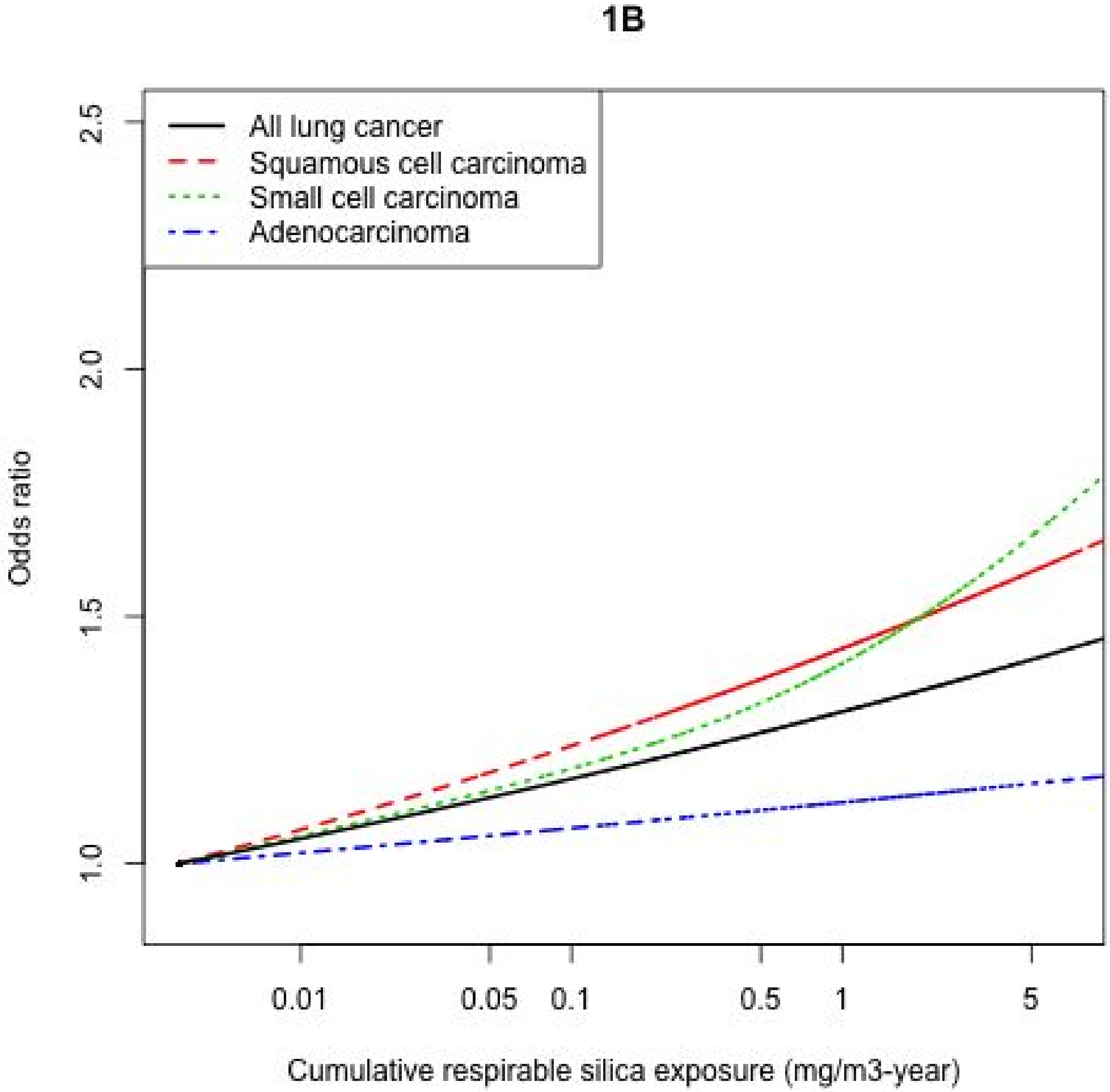
Table 7: Interactions between occupational silica exposure and smoking for major lung cancer subtypes

Exposure status	**Adenocarcinoma**			**Squamous cell carcinoma**			**Small cell carcinoma**		
	Cases	OR*	95%CI	Cases	OR*	95%CI	Cases	OR*	95%CI
Never Smoker & Never silica	589	1.0	Referent	195	1.0	Referent	82	1.0	Referent
Never Smoker & Ever silica	111	1.01	0.81–1.24	62	1.22	0.90–1.62	29	1.49	0.96–2.27
Ever Smoker & Never silica	3094	3.90	3.52–4.32	4057	11.0	9.47–12.8	1779	13.6	10.9–17.3
Ever Smoker & Ever silica	958	4.61	4.06–5.23	2189	16.1	13.7–18.9	840	19.2	15.3–24.7
p-value multiplicative interaction		*0.17*			*0.23*			*0.80*	
RERI		*0.70*	*0.26–1.15*		*4.86*	*3.63–6.09*		*5.13*	*3.03–7.23*

*OR adjusted for sex, study, age group and "List A" jobs

FIGURES


1A
All lung cancer
Squamous cell carcinoma
Small cell carcinoma
Adenocarcinoma
Odds ratio
1.0
1.5
2.0
2.5
0
1
2
3
4
5
6
7
Cumulative respirable crystalline silica exposure (mg/m3-year)



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Respirable Crystalline Silica Exposure, Smoking, and Lung Cancer Subtype Risks: A Pooled Analysis of Case–control Studies

Online Data Supplement

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Supplementary Methods

Sensitivity analysis

To assess if risks associated with categorical silica cumulative exposure differed between studies that used population versus hospital controls, stratified analyses by type of control were performed. Restricted risk analyses were also performed on workers who held blue-collar jobs and who started work after 1960 to assess if risks differed for workers with lower socio-economic status and for workers who worked in more recent periods when exposure estimates are more reliable, respectively. Because workers in mining and agriculture may have different silica exposure patterns compared to other occupations, additional restricted analyses were performed on the study population without subjects who were ever employed in mining or agriculture. As an alternative control for potential confounding exposures to other occupational lung carcinogens, we constructed our main categorical cumulative exposure model without adjustment for List A jobs and with additional adjustment for ever exposure to asbestos, diesel exhaust, hexavalent chromium, and polycyclic aromatic hydrocarbons as assessed by the DOM-JEM. Additionally, study-specific ORs with adjustments identical to the main models were calculated to assess heterogeneity between studies. Extent of heterogeneity between OR estimates from different studies was assessed using the p-value of the Cochran's Q statistic and as a percentage in I^2 [E1].

Supplementary Results

Sensitivity analysis

Associations between cumulative silica exposure and lung cancer were found regardless of the type of controls used (Supplementary Table E4.1), though ORs from studies with hospital controls (4,310 cases; 4,868 controls) were lower and more imprecise compared to those with population controls (12,263 cases; 16,287 controls). Similarly, exposure-response associations were observed when we restricted analyses to blue-collar workers, to workers who started work after 1960, to subjects never employed in mining, and to subjects never employed in agriculture (Supplementary Tables E4.2-4.3). Compared to our main categorical model, slight attenuation of risk estimates was generally observed when we restricted our analyses to blue-collar workers (12,444 cases; 13,111 controls) and to subjects never employed in mining (16,186 cases; 20,508 controls). In contrast, risk estimates were generally higher when we limited our analyses to subjects who started work after 1960 (4,471 cases; 6,478 controls) and who never worked in agriculture (14,462 cases; 18,218 controls). When we adjusted for potential confounding occupational exposures with individual exposures rather than List A jobs, we continue to observe increasing lung cancer risk trend with increasing cumulative exposure, albeit with slightly attenuated ORs across cumulative exposure categories compared to risks observed in our main model (Supplementary Table E4.4).

A moderate amount of heterogeneity (I^2 = 40.8%; Q=31.9, p=0.03) was observed between included studies. Heterogeneity reduced significantly after removal of one study (AUT) from our study population (I^2=5.9%; Q=15.3, p=0.64). The silica-lung cancer exposure-response pattern in the more homogenous subgroup of studies was similar to results of the main analyses, albeit with attenuated ORs for the two highest exposed groups (13,721 cases; 17,716 controls; Supplementary Table E4.5).

Supplementary References

(E1) Higgins, J. P. T.; Thompson, S. G.; Deeks, J. J.; Altman, D. G. Measuring Inconsistency in Meta-Analyses. *BMJ* **2003**, *327* (7414), 557–560.

(E2) Peters, S.; Vermeulen, R.; Portengen, L.; Olsson, A.; Kendzia, B.; Vincent, R.; Savary, B.; Lavoué, J.; Cavallo, D.; Cattaneo, A.; et al. Modelling of Occupational Respirable Crystalline Silica Exposure for Quantitative Exposure Assessment in Community-Based Case-Control Studies. *J. Environ. Monit.* **2011**, *13* (11), 3262–3268. https://doi.org/10.1039/C1EM10628G.

Supplementary Table E1. Description of the studies included in these analyses in the SYNERGY project

			Cases		**Controls**					
Study	**Country**	**Data collection**	**N**	**Response rate (%)**	**N**	**Response rate (%)**	**Quartz exposure**	**Silicosis Self-report**	**Control Source ****	**Interview††**
AUT-Munich	Germany	1990–1995	3180	77	3249	41	1931-1995	Yes†	P	S
CAPUA	Spain	2000–2010	559	91	512	96	1926-2010	No	H	S
EAGLE	Italy	2002–2005	1908	87	2065	72	1932-2005	Yes‡	P	S
HdA	Germany	1988–1993	1004	69	1002	68	1926-1993	Yes§	P	S
ICARE	France	2001–2007	2739	63	3449	77	1937-2007	No	P	S & NOK
INCO	Czech Republic	1999–2002	304	94	452	80	1937-2002	Yesll	H	S
INCO	Hungary	1998–2001	391	90	305	100	1931-1999	Yesll	H	S
INCO	Poland	1998–2002	793	88	835	88	1933-2001	Yesll	P & H	S
INCO	Romania	1998–2002	179	90	225	99	1943-2001	Yesll	H	S
INCO	Russia	1998–2001	599	96	580	90	1938-2000	Yesll	H	S
INCO	Slovakia	1998–2002	345	90	285	84	1937-2002	Yesll	H	S
INCO/LLP	United Kingdom	1998–2005	441	78	916	84	1934-2004	Yesll	P	S
LUCA	France	1989–1992	280	98	282	98	1927-1992	No	H	S
LUCAS	Sweden	1985–1990	1014	87	2307	85	1923-1990	No	P	S & NOK
MONTREAL	Canada	1996–2002	1176	85	1505	69	1936-1999	No	P	S & NOK
MORGEN*	Netherlands	1993–1997	43	N/A	115	N/A	1945-1994	No	P	S
PARIS	France	1988–1992	169	95	227	95	1929-1992	No	H	S
ROME	Italy	1993–1996	326	74	321	63	1926-1995	No	H	S
TORONTO	Canada	1997–2002	365	62	844	71	1929-2002	No	P & H	S
TURIN/VENETO	Italy	1990–1994	1086	79	1489	80	1925-1994	No	P	S
Overall	14 countries	1985–2010	16 901	78%	20 965	69%	1923-2010		H=21%	NOK=7.3%

*Nested case-control study: 45% of invited participants to the original cohort completed the baseline questionnaire.
†: Interview question: Up until two years ago has a doctor ever told you that you have or have had silicosis?
‡: Interview question: More than a year ago did a doctor ever tell you that you had silicosis?
§: Interview question: Up until two years ago has a doctor ever told you that you have or have had silicosis?
ll: Interview question: Have you ever had silicosis (in list with 8 other medical conditions); how old?
**: P = population controls; H = hospital controls
††: S = subject; NOK = Next-of-kin

Supplementary Table E2. The ten jobs with highest modelled silica exposure in SYN-JEM and ten most prevalent exposed jobs among the controls in the SYNERGY population*

ISCO-68†	Job title	GM (mg/m^3) ‡
Highest exposed jobs in SYN-JEM		
9 – 51.25	Bricklayer (chimney)	0.11
8 – 20.90	Stone cutters and carvers	0.10
8 – 20.80	Monument carver (hand)	0.10
7 – 11.70	Sampler (mine)	0.09
9 – 59.45	Demolition worker	0.09
7 – 12.20	Stone splitter	0.08
8 – 20.70	Stone carver (hand)	0.06
8 – 99.40	Clay slip maker	0.05
7 – 11.05	Miner (general)	0.05
8 – 99.30	Clay mixer	0.05
Most prevalent exposed jobs among SYNERGY controls		
6 – 21.10	Farm helper (general)	0.02
6 – 11.10	General farmer	0.02
9 – 51.20	Bricklayer (construction)	0.03
6 – 21.05	Farm worker (general)	0.01
9 – 59.10	House builder (general)	0.04
7 – 11.05	Miner (general)	0.05
6 – 28.20	Motorised farm equipment operator	0.02
9 – 59.90	Other construction workers	0.02
6 – 27.40	Gardener	0.02
9 – 52.10	Reinforced concreter (general)	0.02

*Table adapted from Table 3 in SYN-JEM silica exposure modelling manuscript by Peters and colleagues [E2].

†ISCO-68: International Standard Classification of Occupations, version 1986

‡GM: geometric mean of quartz silica exposure, modelled by SYN-JEM

Supplementary Table E3a. Lung cancer odds ratios (OR) associated with categorical indices of occupational silica exposure in women

Occupational silica exposure	Exposure category	Cases	%	Controls	%	OR*	95% CI
Reference group	Non-exposed	3022	91.7	4166	92.3	1.0	Referent
Ever exposure	Ever	274	8.3	348	7.7	1.11	0.91–1.34
Duration (years)	1–9	170	5.2	183	4.1	1.08	0.84–1.39
	10–19	49	1.5	73	1.6	1.13	0.75–1.69
	20–29	21	0.6	25	0.6	1.40	0.74–2.63
	>29	34	1.0	67	1.5	1.05	0.67–1.63
	Test for trend, p-value					*0.27*	
	Excl. never RCS exposed					*0.25*	
Cumulative exposure	>0–0. 39	108	3.3	102	2.3	1.07	0.77–1.48
(mg/m^3-years)	0.4–1.09	80	2.4	92	2.0	1.24	0.88–1.74
	1.1–2. 39	51	1.5	93	2.1	1.02	0.69–1.47
	≥2.4	35	1.1	61	1.4	1.10	0.69–1.74
	Test for trend, p-value					*0.97*	
	Excl. never RCS exposed					*0.50*	
Time since last exposure (years)†	<5	28	0.8	33	3.9	1.62	0.74–3.59
	5–9	19	0.6	15	1.7	2.00	0.79–5.19
	10–19	22	0.7	42	2.7	0.95	0.46–1.92
	20–29	28	0.8	42	2.6	1.12	0.61–2.05
	30–39	55	1.7	55	3.9	1.46	0.91–2.32
	>39	122	3.7	161	6.7	0.97	0.72–1.30
	Test for trend, p-value						
	*Excl. never RCS exposed**					*0.77*	

*OR adjusted for study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

†OR in "time since last exposure" is additionally adjusted for duration (continuous) of silica exposure. Trend test limited to exposed subjects.

Supplementary Table E3b. Lung cancer odds ratios (OR) associated with categorical indices of occupational silica exposure in men

Occupational silica exposure	Exposure category	Cases	%	Controls	%	OR*	95% CI
Reference group	Non-exposed	8956	65.8	12311	74.8	1.0	Referent
Ever exposure	Ever	4649	34.2	4140	25.2	1.31	1.24–1.39
Duration (years)	1–9	1865	13.7	1753	10.7	1.22	1.13–1.33
	10–19	877	6.4	832	5.1	1.20	1.07–1.34
	20–29	614	4.5	494	3.0	1.44	1.25–1.65
	>29	1293	9.5	1061	6.4	1.51	1.37–1.67
	Test for trend, p-value					*<0.01*	
	Excl. never RCS exposed					*<0.01*	
Cumulative exposure	>0–0.39	1005	7.4	1026	6.2	1.15	1.04–1.28
(mg/m^3-years)	0.4–1.09	1141	8.4	1028	6.2	1.34	1.21–1.48
	1.1–2.39	1180	8.7	1029	6.3	1.31	1.18–1.45
	≥2.4	1323	9.7	1057	6.4	1.45	1.31–1.61
	Test for trend, p-value					*<0.01*	
	Excl. never RCS exposed					*<0.01*	
Time since last exposure (years)†	<5	906	6.7	782	4.8	1.38	1.13–1.69
	5–9	443	3.3	336	2.0	1.37	1.09–1.72
	10–19	657	4.8	527	3.2	1.34	1.11–1.62
	20–29	589	4.3	494	3.0	1.25	1.06–1.47
	30–39	876	6.4	757	4.6	1.28	1.13–1.46
	>39	1178	8.7	1244	7.6	1.10	0.99–1.22
	Test for trend, p-value						
	*Excl. never RCS exposed**					*0.12*	

*OR adjusted for study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

†OR in “time since last exposure” is additionally adjusted for duration (continuous) of silica exposure. Trend test limited to exposed subjects.

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Supplementary Table E4. Sensitivity analyses for the association between silica cumulative exposure categories and lung cancer

Supplementary Table E4.1 Analyses stratified by type of controls

Cumulative exposure	Studies with population controls* (12663 cases/16287 controls)			Studies with hospital controls* (4310 cases/4868 controls)		
mg/m^3-years	Cases/controls	OR†	95%CI	Cases/controls	OR†	95%CI
Unexposed	9136/13099	1.0	Referent	3127/3865	1.0	Referent
>0–0.39	969/964	1.19	1.07–1.33	116/113	1.10	0.82–1.47
0.4–1.09	913/828	1.37	1.23–1.54	222/195	1.24	0.99–1.54
1.1–2.39	899/784	1.42	1.26–1.59	287/258	1.07	0.89–1.31
≥2.4	746/612	1.54	1.36–1.76	558/437	1.29	1.11–1.51
Test for trend, p-value§		*<0.01*			*<0.01*	
Excl. never exposed		*<0.01*			*0.29*	

*Subjects from the INCO Poland and Toronto studies were included in both analyses, since both types of controls were used

†OR is adjusted for sex, study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

Supplementary Table E4.2 Analyses restricted to blue-collar workers and workers who started work after 1960

Cumulative exposure	Restricting the study base to blue-collar workers (12444 cases/13111 controls)			Restricted to workers started after 1960 (4471 cases/6478 controls)		
mg/m^3-years	Cases/controls	OR*	95%CI	Cases/controls	OR*	95%CI
Unexposed	7953/9264	1.0	Referent	3642/5667	1.0	Referent
>0–0.39	1030/992	1.05	0.94 – 1.17	327/352	1.19	0.99–1.44
0.4–1.09	1133/967	1.27	1.15–1.41	235/234	1.34	1.07–1.66
1.1–2.39	1087/895	1.20	1.08–1.34	166/166	1.63	1.24–2.14
≥2.4	1241/993	1.34	1.21–1.49	95/101	1.26	0.90–1.77
Test for trend, p-value§		*<0.01*			*0.01*	
Excl. never exposed		*<0.01*			*0.54*	

*OR is adjusted for sex, study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

Supplementary Table E4.3 Analyses excluding subjects ever-employed in agriculture and mining industries

Cumulative exposure	Subjects never-employed in agriculture (14462 cases/18218 controls)			Subjects never-employed in mining (16186 cases/20508 controls)		
mg/m^3-years	Cases/controls	OR*	95%CI	Cases/controls	OR*	95%CI
Unexposed	11769/16163	1.0	Referent	11973/16467	1.0	Referent
>0–0.39	610/552	1.21	1.06–1.39	1065/1094	1.13	1.02–1.24
0.4–1.09	667/470	1.58	1.38–1.81	1070/1018	1.30	1.18–1.44
1.1–2.39	613/430	1.48	1.28–1.71	1055/1010	1.26	1.14–1.40
≥2.4	803/603	1.52	1.34–1.72	1023/910	1.40	1.26–1.56
Test for trend, p-value§		*<0.01*			*<0.01*	
Excl. never exposed		*0.02*			*<0.01*	

*OR is adjusted for sex, study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

Supplementary Table E4.4 Analyses with alternative adjustment for potential confounding occupational exposures

Cumulative exposure	All subjects		
mg/m^3-years	Cases/controls	OR*	95%CI
Unexposed	11978/16467	1.0	Referent
>0–0.39	1113/1128	1.12	1.01–1.24
0.4–1.09	1221/1120	1.30	1.18–1.44
1.1–2.39	1231/1122	1.25	1.13–1.38
≥2.4	1358/1118	1.39	1.26–1.54
Test for trend, p-value§		*<0.01*	
Excl. never exposed		*<0.01*	

*OR is adjusted for sex, study, age group, smoking (pack-years, time-since-quitting smoking), and ever exposure to asbestos, diesel exhaust, hexavalent chromium, and polycyclic aromatic hydrocarbons

Supplementary Table E4.5 Analyses by more homogenous group of studies (excluding AUT)

Cumulative exposure	All studies except AUT (13721 cases/17716 controls)		
mg/m^3-years	Cases/controls	OR*	95%CI
Unexposed	10224/14279	1.0	Referent
>0–0.39	709/734	1.13	1.00–1.28
0.4–1.09	859/864	1.26	1.13–1.42
1.1–2.39	822/869	1.12	1.00–1.26
≥2.4	1107/970	1.37	1.23–1.52
Test for trend, p-value§		*<0.01*	
Excl. never exposed		*<0.01*	

*OR is adjusted for sex, study, age group, smoking (pack-years, time-since-quitting smoking), and List A jobs

FIGURE LEGEND:

Figure E1 Title: Splines and associated 95% confidence intervals for cumulative silica exposure on risks of 1A) overall lung cancer; 1B) adenocarcinoma; 1C) small cell carcinoma; 1D) squamous cell carcinoma. Bottom bars show frequency of subjects at associated exposure levels.

Figure E1 Abbreviation: mg/m^3-years = milligram per cubic metre years

Figure E2 Title: Splines and associated 95% confidence intervals for log-transformed cumulative silica exposure on risks of 1A) overall lung cancer; 1B) adenocarcinoma; 1C) small cell carcinoma; 1D) squamous cell carcinoma. Bottom bars show frequency of subjects at associated exposure levels.

Figure E2 Abbreviation: mg/m^3-years = milligram per cubic metre years

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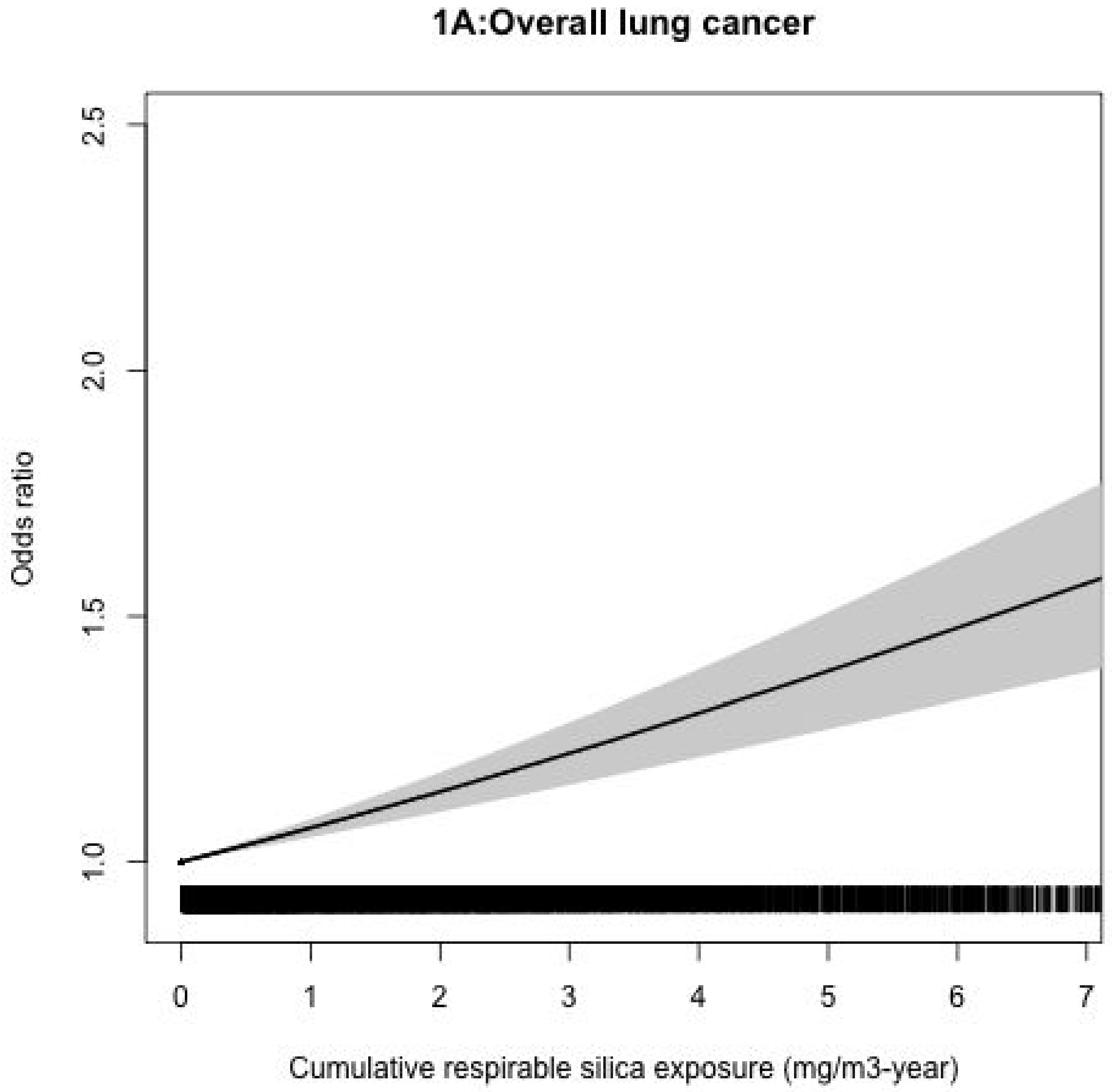
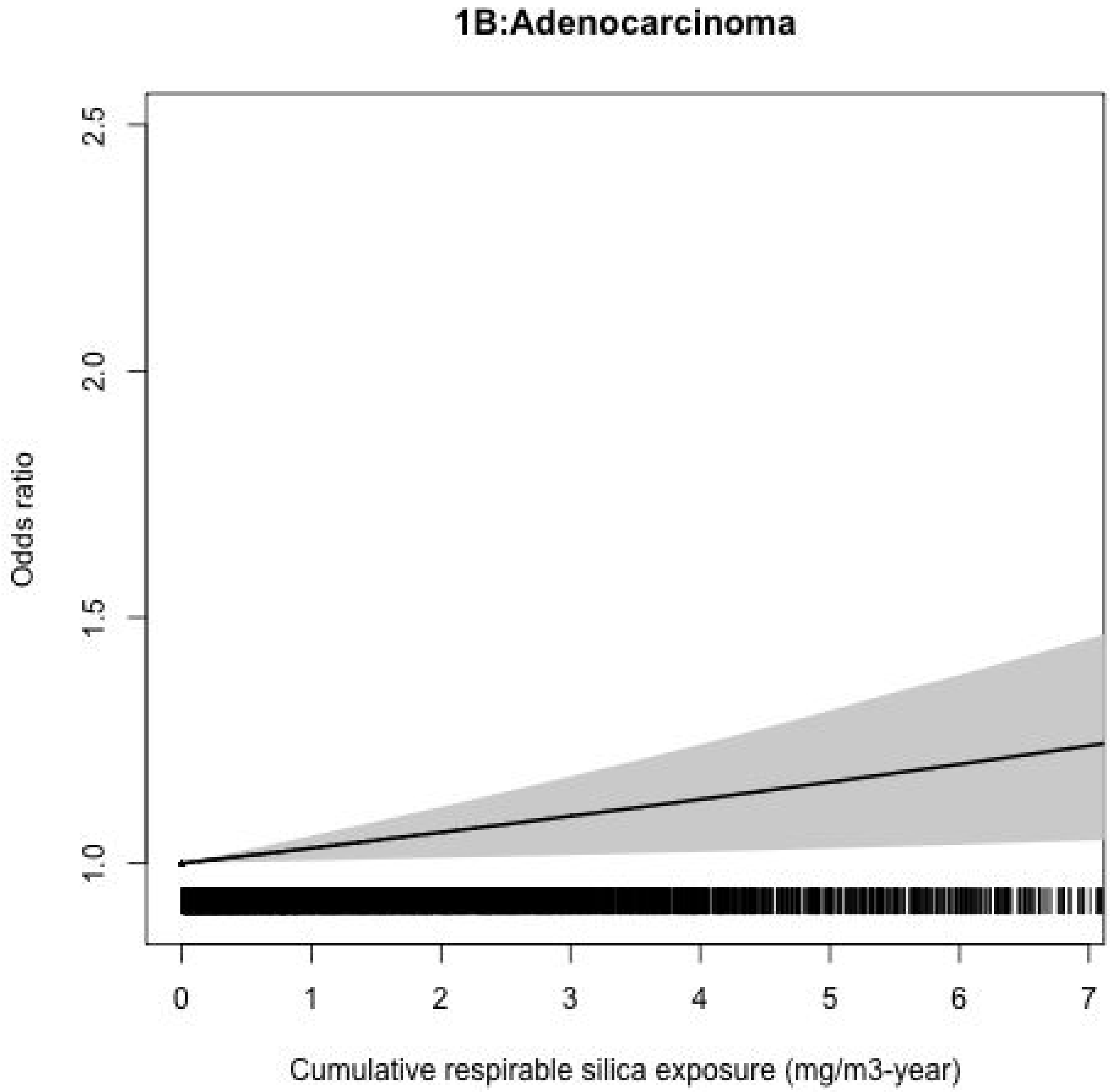
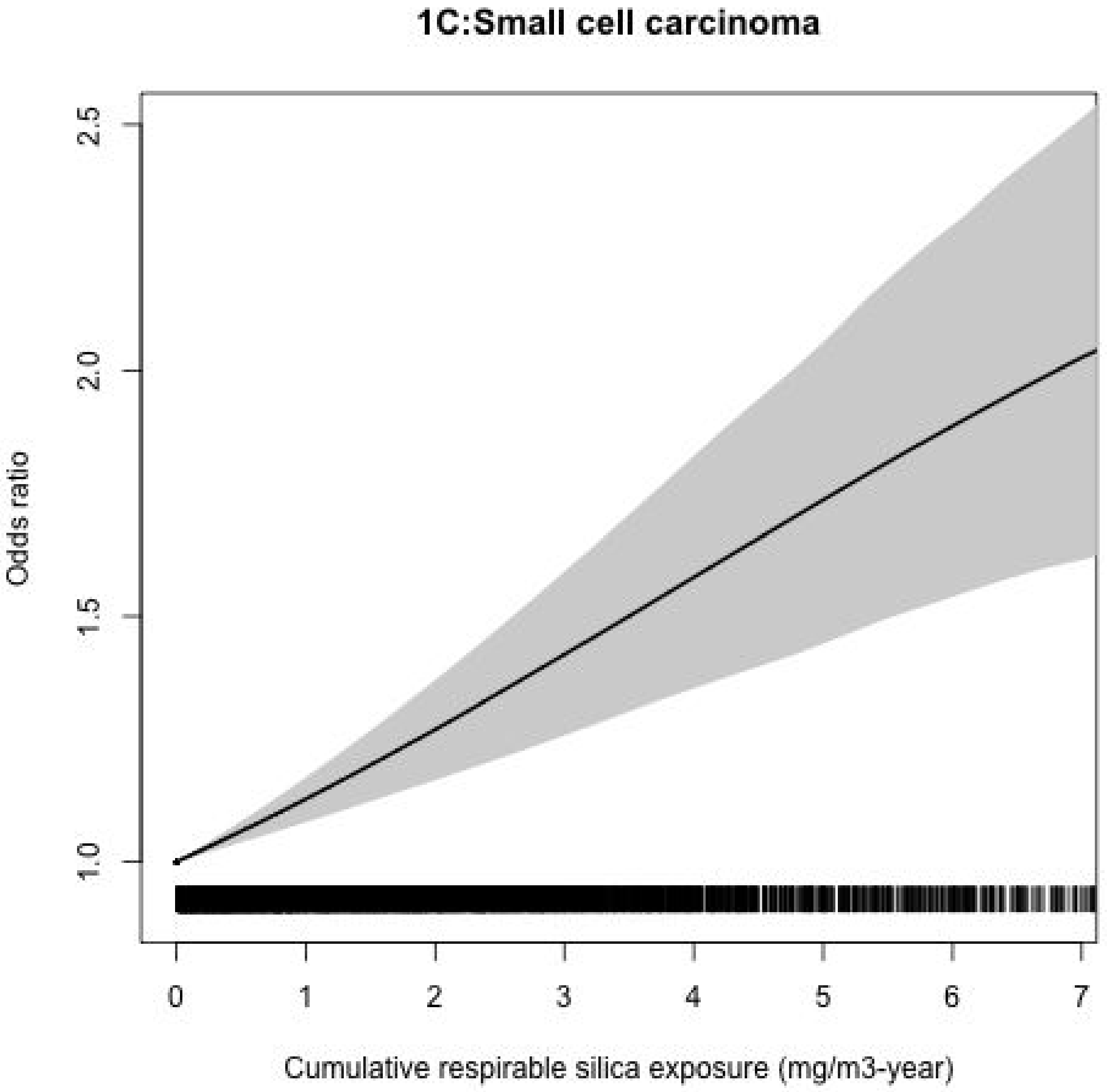
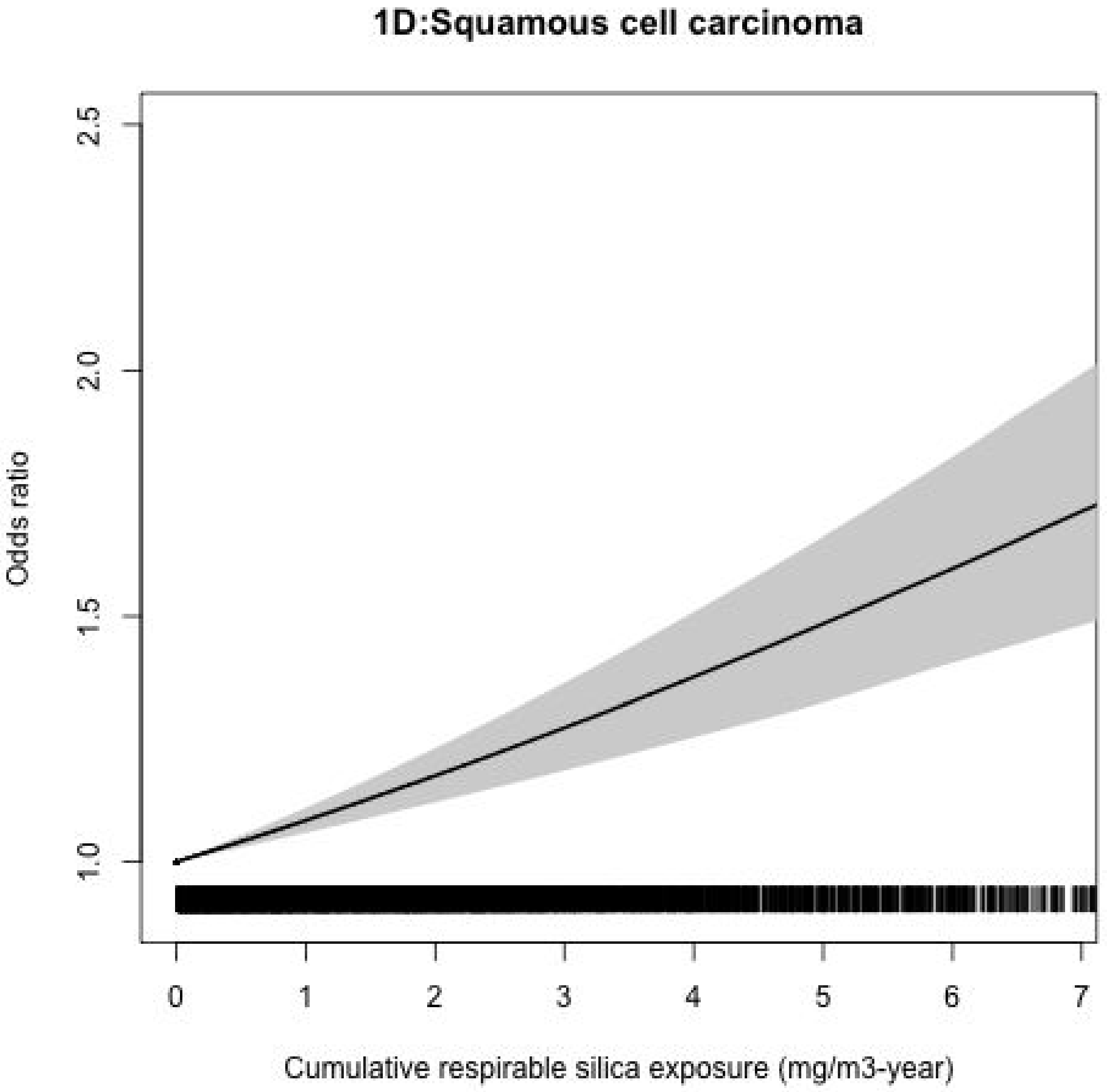
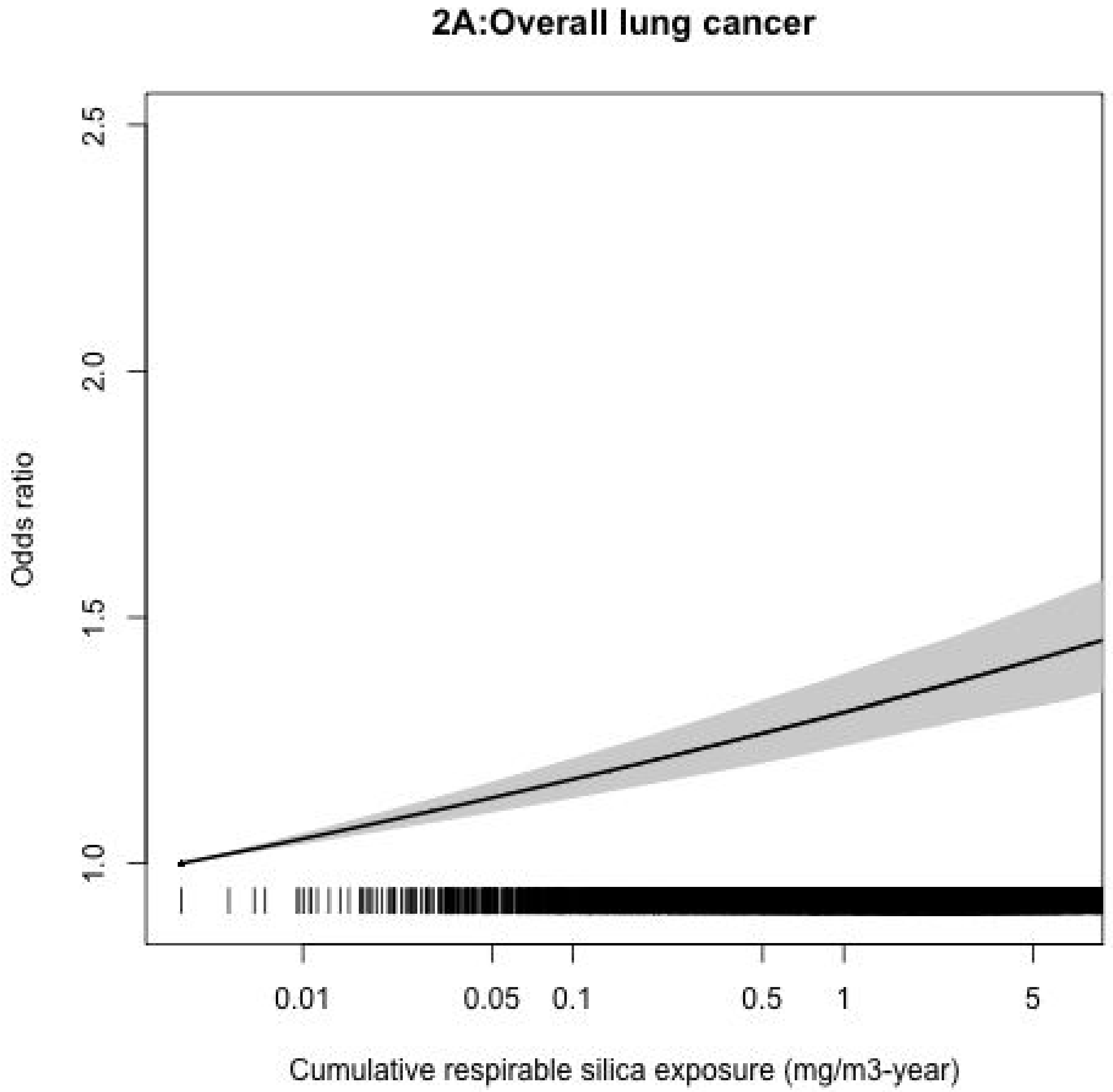

1A:Overall lung cancer
Odds ratio
1.0
1.5
2.0
2.5
0
1
2
3
4
5
6
7
Cumulative respirable silica exposure (mg/m3-year)

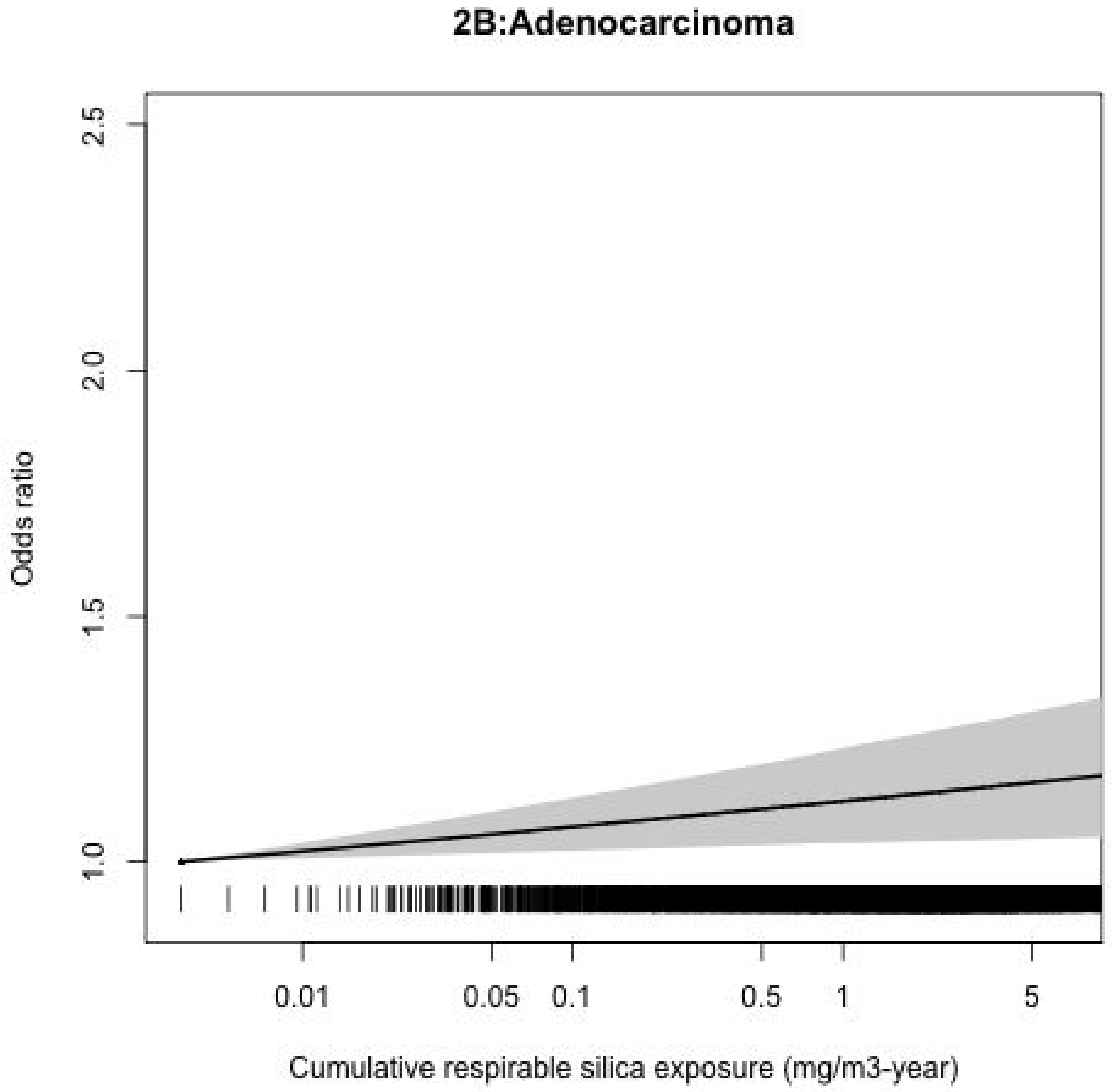

1B:Adenocarcinoma
Odds ratio
1.0
1.5
2.0
2.5
0
1
2
3
4
5
6
7
Cumulative respirable silica exposure (mg/m3-year)

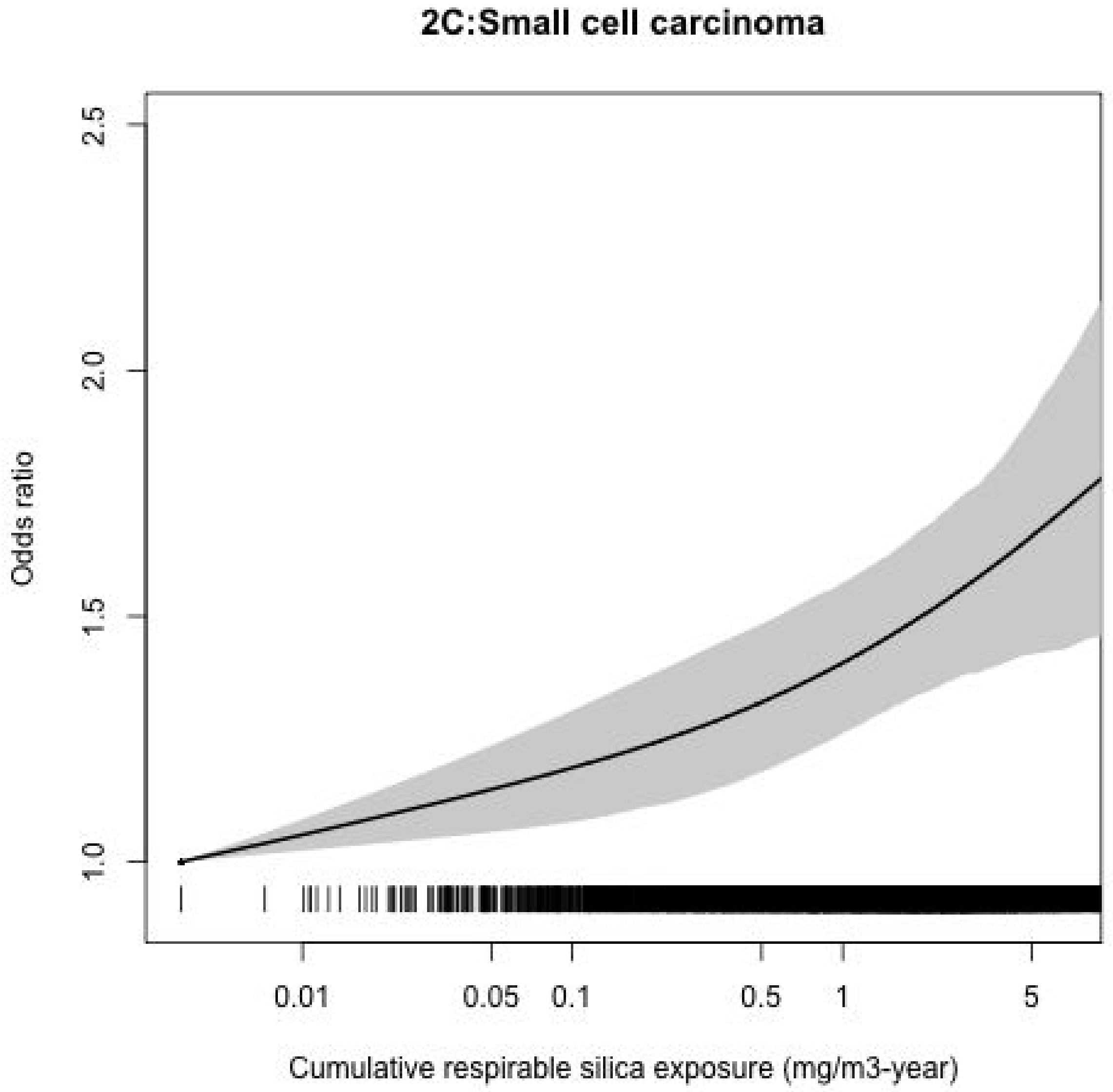

1C:Small cell carcinoma
Odds ratio
1.0
1.5
2.0
2.5
0
1
2
3
4
5
6
7
Cumulative respirable silica exposure (mg/m3-year)


1D:Squamous cell carcinoma
Odds ratio
1.0
1.5
2.0
2.5
0
1
2
3
4
5
6
7
Cumulative respirable silica exposure (mg/m3-year)

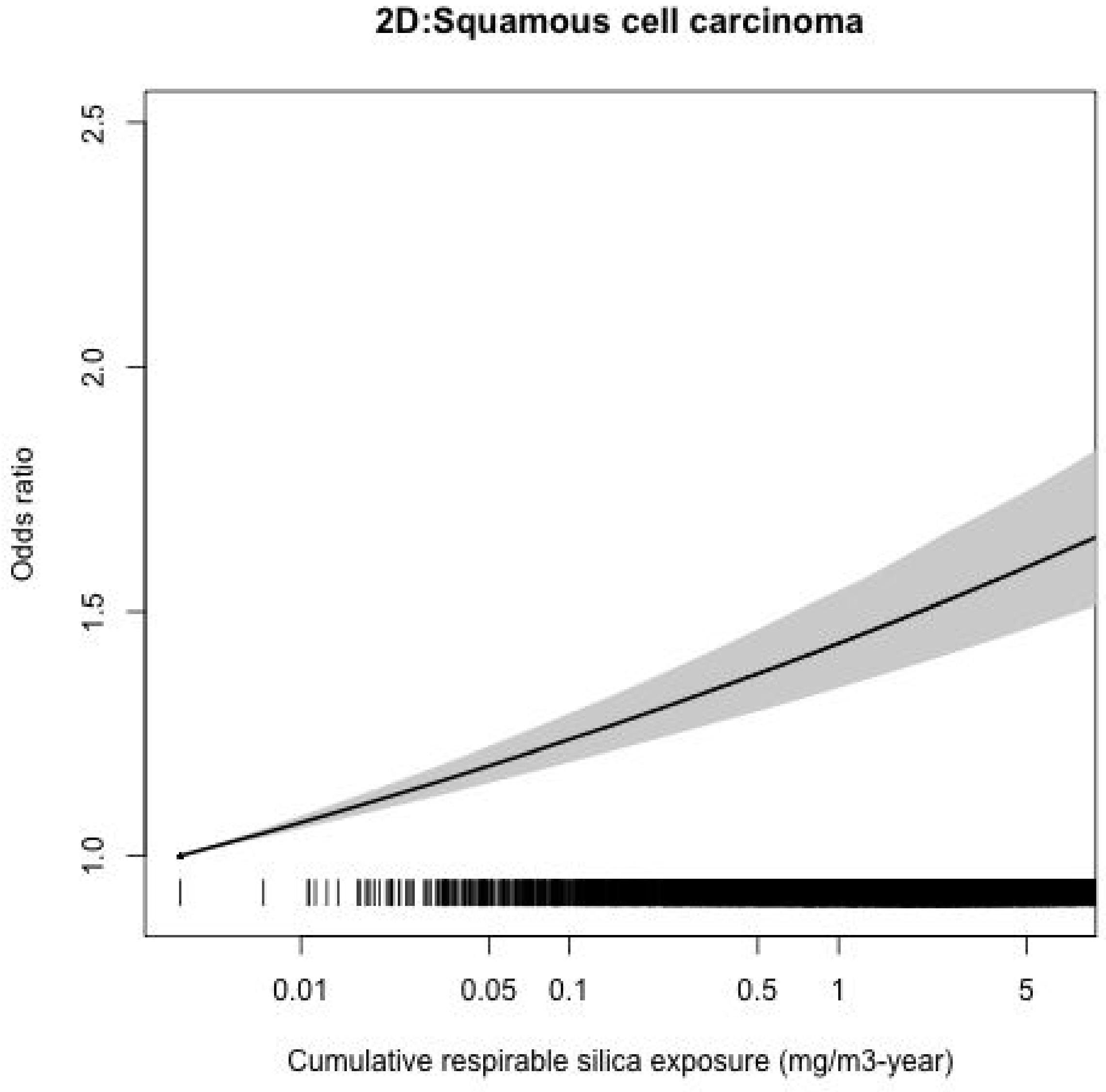


2A:Overall lung cancer


2B:Adenocarcinoma
Odds ratio
2.5
2.0
1.5
1.0
0.01
0.05
0.1
0.5
1
5
Cumulative respirable silica exposure (mg/m3-year)



2C:Small cell carcinoma
Odds ratio
2.5
2.0
1.5
1.0
0.01
0.05
0.1
0.5
1
5
Cumulative respirable silica exposure (mg/m3-year)



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