Silica dust and lung cancer in the German stone, quarrying, and ceramics industries: results of a case-control study

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Abstract

***Background*—A work force based case-control study of lung cancer was performed in non-silicotic subjects exposed to crystalline silica to investigate the association between silica dust and lung cancer excluding the influence of silicosis.**

***Methods*—Two hundred and forty seven patients with lung cancer and 795 control subjects were enrolled, all of whom had been employed in the German stone, quarrying, or ceramics industries. Smoking was used as a matching criterion. Exposure to silica was quantified by measurements, if available, or otherwise by industrial hygienists. Several indices (peak, average and cumulative exposure) were used to analyse the relationship between the level of exposure and risk of lung cancer as odds ratios (OR).**

***Results*—The risk of lung cancer is associated with the year of and age at first exposure to silica, duration of exposure, and latency. All odds ratios were adjusted for these factors. Considering the peak exposure, the OR for workers exposed to high levels ($\geqslant$0.15 mg/m^3 respirable silica dust which is the current occupational threshold value for Germany) compared with those exposed to low levels (<0.15 mg/m^3) was 0.85 (95% CI 0.58 to 1.25). For the time weighted average exposure the OR was 0.91 (95% CI 0.57 to 1.46). The OR for the cumulative exposure was 1.02 (95% CI 0.67 to 1.55). No increase in risk was evident with increasing exposure.**

***Conclusions*—This study shows no association between exposure to crystalline silica and lung cancer. The exclusion of subjects with silicosis may have led to dilution with respect to the level of exposure and therefore reduced the power to detect a small risk. Alternatively, the risk of getting lung cancer may be restricted to subjects with silicosis and is not directly linked to silica dust.**
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Keywords: silica dust; lung cancer; stone and quarry industry; ceramics industry

The association between crystalline silica and lung cancer is the subject of extensive discussion and in recent years several studies from various countries have been published. Crystalline silica was recently considered by a working group of the International Agency for Research on Cancer (IARC) which re-evaluated earlier classification.[1] All the data available up to that time were considered and, as a result, crystalline silica was classified into group 1 which means it is considered to be carcinogenic to humans. In the overall evaluation, however, it was noted that carcinogenicity was not detected in all industrial circumstances and that it may depend on the characteristics of silica or on external factors.

The regulatory agencies in various countries responsible for the classification of health hazards in work places are currently concerned with the implementation of the decision of the IARC to their systems to protect workers. In order to investigate the carcinogenic potential of crystalline silica, work forces exposed to silica dust with little or no contamination from known carcinogenic compounds are of particular interest. The two main areas are the quarrying and ceramics industries.

The IARC defined nine cohort studies which provided the least confounded examinations of an association between crystalline silica and lung cancer: three studies from the stone and quarrying industries, five from the ceramics, pottery and related industries, and one from gold miners in the USA. The risk of lung cancer in the three cohorts from the stone and quarrying industries (Danish stone workers,[2] granite workers from Vermont,[3] and US crushed stone industry workers[4]) varied between 1.05 and 1.19 compared with the general population and up to 1.93 compared with the local population. In subgroups, however, higher relative risks were reported. The risk of lung cancer in the five studies from the ceramics industries (one from the UK,[5] two from China,[6 7] one from Italy,[8] and one from the USA[9–11]) varied from 0.58 to 1.51.

Another population of interest because of their high exposure are workers compensated for silicosis. Studies with silicosis show an approximately twofold increased risk for developing lung cancer compared with the general population.[12]

The decision of the IARC was also based on the increasing risk gradients in relation to dose observed in one of these studies.[11] However, there are also studies showing no dose-response relationship.[13] The IARC concluded that bias or confounding cannot explain the observed association.

The major problem in evaluating the carcinogenic risk of silica dust is the role of silicosis. In all subgroups with an increased relative risk the proportion of workers compensated for silicosis is also higher. If workers with silicosis are excluded from the analysis, the increased risk of lung cancer is no longer present. In a detailed analysis of a study of South African gold miners[14] silicosis was the factor other than smoking with the greatest impact on the risk of lung cancer. The fit of the logistic model could not be improved by including data on the level of exposure or the duration of exposure. A similar result was reported in Australian gold miners.[15] When silicosis was ignored the log cumulative exposure was significantly related to the incidence of lung cancer, but this became non-significant once the onset of silicosis was taken into account. In one study of German slate quarry workers[16] the standardised mortality ratio (SMR) for lung cancer in the cohort including subjects with silicosis was 1.83 while in the cohort of non-silicotic subjects it was 0.91. In a study of workers from a refractory plant in China[7] the mortality risk for lung cancer was compared with that in workers in rolling steel mills. The relative risk for lung cancer was 1.11 for non-silicotic subjects (n = 30) and 2.10 for subjects with silicosis (n = 35).

For practical purposes it would be of interest to know whether silica dust itself can induce lung cancer or only via silicosis. Smoking is the major factor affecting this association. In many studies all or nearly all cases of lung cancer have been smokers. In the absence of lung fibrosis the evidence of an association between silica and lung cancer must be considered scanty and inconsistent, but still biologically plausible.[17]

The present study was performed to gain more insight into the association between silica dust and lung cancer, taking into account the problem of silicosis and smoking. Cases and controls compensated for silicosis have been excluded from the study and, in order to reduce the influence of possible occupational confounders, special industries were selected—namely, the stone, quarrying, and ceramics industries. The aim of the study is to investigate whether there is an association between the exposure to silica dust and lung cancer, excluding the influence of silicosis and adjusting for the effect of smoking.

Methods

DESIGN OF THE STUDY

Most of the studies published so far are cohort studies. To analyse a possible dose-response relationship the level of the exposure has to be ascertained for all members of the cohort. The assessment of dust exposure is expensive and cumbersome. Occasionally a cohort study has also been analysed in the form of a nested case-control study.[18] Within this design all cases and a group of controls are selected, often matched by some risk factors such as age, sex, and smoking. Because a much smaller fraction of the cohort is used, there is a saving of time and resources for recording the relevant data. We therefore decided to perform a case-control study.

Quarries and the ceramic factories are concentrated in certain areas of Germany. For this study one area was selected where both industries are located, the northern part of Bavaria.

IDENTIFICATION OF CASES

The goal was to ascertain all cases of lung cancer diagnosed between 1980 and 1994. Several sources were used to identify cases: the general and specific disease insurance institutes, the files of the hospitals of the industrial accident insurance institutes, and the files of these institutes themselves. Germany lacks a nationwide cancer registry but, if a worker is diagnosed with lung cancer, it should be noted in at least one of these sources. The year 1980 was selected as the start date because the insurance institutes introduced computerised systems in that year. All diagnoses were confirmed by histopathological examination. Cases compensated for silicosis were excluded from the study.

SELECTION OF CONTROLS

All controls had been occupationally exposed to silica dust and were matched for sex, age, smoking habits, area of residence, and type of industry.

In the ceramics industry over 95% of all workers are registered in a file for preventive check ups in order to detect silicosis. The controls for this industry were selected from this file, excluding workers with lung cancer. Unfortunately, in the quarrying industry no such file exists; the prevention file contains only workers with a higher exposure and thus with an increased risk of developing silicosis. Another sampling frame was therefore used which contains all workers with an accident regardless of whether it happened during work or on the way to or from work. Controls with silicosis were excluded and in each industry the cases and controls were "frequency matched" by sex, year of birth, and smoking habit.

RECORDING OF EXPOSURE

The complete occupational history of the professional life of all cases and controls was ascertained. For time periods with a possible exposure to silica dust all the relevant information for assessing the level of exposure was considered by an industrial hygienist. For each interval with a difference in the exposure caused by change in type of occupation, plant or technical equipment, the calendar period, level of exposure, and other occupational exposures were recorded. If there were no dust measurements available the level of exposure was assessed by industrial hygienists who were well acquainted with the situation at the work places. The hygienists did not know whether the person was a case with lung cancer or a control.

For statistical analyses several indices of silica exposure are suggested.[19] Typical surrogates of dose are duration of exposure, peak exposure intensity, and cumulative and time weighted average exposure. In this study all these indices have been used.

Each exposure index was reclassified into two groups according to low and high exposure. The current threshold limit value (called

MAK in Germany) of 0.15 mg/m^3 was used as a cut off point. In a further analysis the different exposure indices were also classified into four categories in order to investigate a possible dose-response relationship similar to other studies.[13]

IDENTIFICATION OF SUBJECTS WITH SILICOSIS

The preventive medical check ups are routinely performed every three years unless there are medical indications for an earlier investigation. The radiographs are classified according to the ILO. A requirement for compensation is a radiological category equal to or greater than 1/1 and reduced lung function. Subjects with silicosis were excluded from both groups in the study.

SMOKING

For the selection of controls by frequency matching, information about smoking (past or current) was obtained from the corresponding files if recorded and the current status was also ascertained by personal interview. The number of cigarettes smoked per day and the date of cessation in ex-smokers was also obtained.

OTHER OCCUPATIONAL EXPOSURES

Besides exposure to silica dust, data on other occupational factors such as asbestos, polycyclic aromatic hydrocarbons, radon, diesel exhausts, welding fumes, or heavy metals were also recorded by the industrial hygienists.

STATISTICAL ANALYSIS

The data are presented as medians and ranges (for continuous variables) or as numbers and percentages (for categorical variables). Since the relative risk cannot be determined directly in case-control studies it was estimated by the odds ratio (OR) with 95% confidence limits. Logistic regression[20] was used to adjust for covariates. The analysis was performed separately for the two industries and for both together. A significance level of $\alpha = 5\%$ was applied.

Results

Table 1 shows the characteristics of the 247 cases and 795 controls enrolled in the study. From the stone and quarrying industry there were 133 cases and 231 controls, all of whom were men. From the ceramics industry 114 cases and 564 controls were enrolled, of whom 97.5% were men. The year of birth was used as a matching criterion so the distribution of this factor was nearly identical in both groups. The cases were about two years younger than the controls at onset of exposure and they started their exposure about three years earlier. The time since first exposure was about 40 years in both groups and the duration of exposure was shorter in the cases (median 30 years) than in the controls (median 33 years).

Table 1 Description of cases and controls (n=1042)

	Cases (n = 247)			*Controls (n = 795)*		
	Median	*Min*	*Max*	*Median*	*Min*	*Max*
Year of birth	1928	1901	1958	1929	1907	1959
Age at first exposure (years)	22	11	61	24	13	60
Years since first exposure	40	7	69	41	5	68
Duration of exposure (years)	30	3	54	33	2	53
Year of first exposure	1950	1922	1983	1953	1922	1990

Table 2 Smoking history of cases and controls

	Cases (n = 247)	*Controls (n = 795)*
Non-smokers	7 (2.8%)	25 (3.1%)
Current smokers	136 (55.1%)	342 (43.0%)
≤10 cig/day	24 (17.6%)	116 (33.9%)
>10 cig/day	112 (82.4%)	226 (66.1%)
Ex-smokers	99 (40.1%)	424 (53.3%)
Missing information	5 (2.0%)	4 (0.5%)
Time since cessation (years)		
median (min-max)	4 (1–44)	14 (1–51)

Table 3 Other occupational exposures

	Cases (n = 247)	*Controls (n = 795)*
With other exposures	72 (29.2%)	239 (30.1%)
Diesel exhaust	32 (13.0%)	73 (9.2%)
Asbestos	26 (10.5%)	87 (10.9%)
Other fibres	1 (0.4%)	11 (1.4%)
Polycylic aromatic hydrocarbons	8 (3.2%)	36 (4.5%)
Welding fumes	19 (7.7%)	72 (9.1%)
Heavy metal	4 (1.6%)	20 (2.5%)
Radon	4 (1.6%)	5 (0.6%)

The high percentage of current and ex-smokers among the cases of lung cancer (95.2%, table 2) is comparable to other statistics.[21] Smoking was used as a matching criterion so the percentage of current and ex-smokers among the cases and controls was similar. When the smokers were considered more closely a significant difference was seen between the cases and controls with respect to the number of cigarettes smoked and the time since cessation of smoking (82.4% heavy current smokers (>10 cigarettes/day) among the cases compared with 66.1% among the controls; time between cessation of smoking and end of observation was about four years for the cases and 14 years for the controls).

Other occupational exposures besides silica dust were present in about 30% of the cases and controls (72 cases and 239 controls). The products other than quartz to which they were exposed are shown in table 3. The greatest difference is with respect to diesel exhausts (13.0% of cases exposed compared with 9.2% controls). Diesel exhausts occurred mainly in the stone and quarry industry (24 of 32 cases, 29 of 73 controls).

The distribution of the silica exposures is shown in table 4. The time weighted average exposure shows no difference between the cases and the controls with respect to the median level (0.08 vs 0.07 mg/m^3). However, some of the cases were more heavily exposed than the controls (90% percentile among cases of 0.32 mg/m^3 compared with 0.19 mg/m^3 among controls). The change in the average exposure over time can be seen in the lower part of table 4 which shows that the median level in the sample from the stone and quarrying industry fell from 0.24 mg/m^3 for those hired before 1940 to 0.05 mg/m^3 for those hired after 1980. A similar trend but at a lower level of exposure can be seen in the ceramics industry. The cumulative exposure shows only a slight difference between cases and controls (median 2.97 vs 2.88 mg/m^3 • years). This difference reflects the longer duration of exposure among the controls as shown in table 1. About 50% of all workers had a peak exposure above 0.15 mg/m^3 (53.4% cases, 45.7% controls).

The result of the logistic regression for the three measures of exposure adjusted for the covariates age at onset of exposure, year of first exposure, duration of exposure, latency and the various other occupational factors is given in table 5. The odds ratios for the three indices (comparing "high" to "low" exposure) for both industries separately and together are all around 1.0. None of the values is statistically significant.

If the average exposure is considered the OR in the whole sample is 0.91 (95% CI 0.57 to 1.46) with a slight difference between the two industries (stone and quarrying industry OR = 0.81; ceramics industry OR = 1.03). If the peak exposure is considered the OR for both industries together is slightly below 1.0 (OR 0.85, 95% CI 0.58 to 1.25) with an OR of 1.25 for the stone and quarrying industry and 0.75 for the ceramics industry. For the cumulative exposure the OR for the whole sample is 1.02 (95% CI 0.67 to 1.55) with only a small difference between the two industries (0.86 and 1.05).

To investigate the dose-response relationship the whole sample was divided into four groups of equal size. The results are shown in table 6. When the time weighted average exposure is compared with the lowest category the odds ratios for the three levels of exposure are 0.95, 0.92 and 1.04. No significant trend was observed (p = 0.69). All odds ratios were adjusted for the age at onset of exposure, duration of exposure, latency, year of first exposure, and additional exposures. The same analysis was also performed with the cumulative exposure with a similar result (p = 0.87).

Table 4 Distribution of exposure intensity (n = 1042)

Time weighted average exposure (mg/m^3):							
	Min	*10%*	*25%*	*50%*	*75%*	*90%*	*Max*
Cases	0.01	0.02	0.03	0.08	0.15	0.32	0.83
Controls	0.01	0.02	0.04	0.07	0.12	0.19	0.88
Median of time weighted average exposure (mg/m^3) in relation to the year of first exposure:							
	<1940	*1940–50*	*1950–60*	*1960–70*	*1970–80*	*≥1980*	
Stone/quarry industry (n = 364)	0.24	0.12	0.09	0.06	0.05	0.05	
Ceramics industry (n = 678)	0.07	0.07	0.07	0.05	0.04	0.04	
Cumulative exposure (mg/m^3 • years):							
	Min	*10%*	*25%*	*50%*	*75%*	*90%*	*Max*
Cases (n = 247)	0.12	0.68	1.53	2.97	5.31	11.81	25.92
Controls (n = 795)	0.12	0.84	1.56	2.88	4.50	7.33	28.08
Peak exposure:							
				≤0.15 mg/m^3		*>0.15 mg/m^3*	
Cases (n = 247)				115 (46.6%)		132 (53.4%)	
Controls (n = 795)				436 (53.8%)		359 (45.7%)	

*Table 5 Odds ratios with 95% confidence intervals for the different measures of exposure**

Type of exposure	*Stone and quarry*	*Ceramics*	*Both industries*
Time weighted	0.81 (0.37 to 1.77)	1.03 (0.49 to 2.16)	0.91 (0.57 to 1.46)
Cumulative	0.86 (0.38 to 1.95)	1.05 (0.59 to 1.86)	1.02 (0.67 to 1.55)
Peak	1.25 (0.58 to 2.69)	0.75 (0.46 to 1.24)	0.85 (0.58 to 1.25)

*Adjusted for age at onset of exposure, year of first exposure, duration of exposure, latency, and additional exposures in the work place.
Each index is divided into two levels (low and high): time weighted and peak exposure, low ≤0.15 mg/m^3; cumulative exposure, low ≤2.88 mg/m^3 • years.

*Table 6 Relative risk for lung cancer by time weighted average and cumulative exposure**

Exposure	*Cases*	*Controls*	*OR*(95% CI)*
Cumulative exposure (mg/m^3 • years)			
<1.56	63	195	1.00
1.56–2.88	54	197	0.95 (0.48 to 1.53)
2.89–4.68	52	212	0.92 (0.44 to 1.61)
>4.68	78	191	1.04 (0.53 to 1.89)
Σ	247	795	
p for trend = 0.69			
Time weighted average exposure (mg/m^3)			
<0.04	64	194	1.0
0.04–0.07	45	207	0.74 (0.42 to 1.27)
0.08–0.11	62	209	0.96 (0.56 to 1.71)
≥0.12	76	185	0.82 (0.47 to 1.44)
Σ	247	795	
p for trend = 0.87			

*Adjusted for the same factors as listed in table 5.

Discussion

The aim of this study was to investigate the association between exposure to silica dust and the risk of developing lung cancer after eliminating the effect of silicosis. The study was performed as a case-control study and only workers exposed to silica dust were enrolled. The exposures of all cases and controls were assessed very extensively. All occupations involving a change in the exposure were recorded as accurately as possible and all technical changes and safety regulations were taken into account. For each worker in the study each occupation and change in occupation was recorded to quantify the level of exposure independent of the status. Experienced industrial hygienists classified each occupation of both cases and controls independent of the status.

Analysis of the various measures of the level of exposure (peak, time weighted average, and cumulative exposure) resulted in odds ratios between 0.85 and 1.02, none of which showed a statistically significant increase. The analysis of a dose-response relationship based on the time weighted average and the cumulative exposure also showed no significant trend.

In a case-control study the possibility of a bias must always be considered. Because of the lack of a nationwide cancer registry other sources had to be used to identify cases with lung cancer. All cases with lung cancer have to be treated so at least the disease insurance institutes will be informed for the reimbursement. The period between 1980 and 1994 was defined because the insurance institutes changed to a computerised system in 1980. If a worker had been diagnosed with lung cancer it would have been noted in one of the corresponding files so we believe that we had data on all or nearly all of the cases.

The controls were selected differently as there is no file available in which all workers ever exposed in the related industries are recorded. In the ceramics industry the file for preventive medical examinations covers over 95% of all workers so selection bias in this industry, if present, must be very small. In the stone and quarrying industry the file for preventive medical check ups contains only workers with a higher exposure and therefore an increased risk of developing silicosis. This group of workers cannot be considered representative of the total work force. The only other source available is the file for accidents, regardless of whether they happened during work or on the way to or from work. Whether the workers included in this file are a selected group can be assessed in two ways. Firstly, the result for this subsample is similar to that in the ceramics industry where selection bias was minimal. Secondly, the level of exposure is comparable to that in other studies investigating similar occupations. In the two studies from the USA[3 4] the cumulative exposures reported were similar or even lower. In 1929 dust levels of 0.6 mg/m^3 were reported which were reduced to 0.1 mg/m^3 in 1955.[3] In the crushed stone industry geometric means of 0.04–0.06 mg/m^3 are recorded.[4] Although a bias in selecting these controls cannot be completely ruled out, it seems unlikely.

To investigate the association between silica dust and lung cancer only workers without silicosis were included in the study. The preventive medical check ups are routinely performed every three years except where there are medical reasons to perform them otherwise. In all cases extensive radiographs are taken and signs of silicosis noted. It is possible that among the control subjects some with silicosis have not been recognised. This seems unlikely, but the effect would be a shift towards higher exposures in the control group and therefore to reduced relative risks.

It is assumed that in both types of industries selected (stone, quarrying, and ceramics industries) the frequency and influence of additional occupational factors correlated with lung cancer is small. Nevertheless, some of the cases and controls had additional exposures, mostly during occupations elsewhere. Only diesel exhausts turned out to have a borderline association with lung cancer. The finding that duration of exposure to silica dust was shorter among the cases has been reported in other studies.[22]

Of the data in the literature investigating the risk of lung cancer in subjects without silicosis, only two studies from related industries were found and in both the relative risks were around 1.0 (0.91[16] and 1.11[7]). These two cohort studies support the findings obtained in this case-control study, although the limits of the 95% confidence interval are wide enough to be consistent with a 50% increase in risk. In order to reduce that range, larger samples are required.

In summary, the risk of an association between crystalline silica and lung cancer in the absence of silicosis, if present, seems to be very small. Two reasons make the interpretation difficult. Firstly, smoking data are not available for all subjects in many studies and smoking is still the dominant risk factor in lung cancer. Secondly, the power of the studies available is too low. By excluding subjects with silicosis, workers with an increased exposure are excluded. This means that the distribution of observed exposure data is not identical to that for the total work force. There is a shift towards lower exposures although, even among those without silicosis, high exposures can be found.

The IARC has very recently classified silica dust into group 1 (carcinogenic to humans). For the ceramics and the stone and quarrying industries it still seems unclear to what extent silica dust itself contributes to that risk. From a practical point of view it is recommended that, to avoid silicosis, exposure to silica dust should be restricted.

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