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Quantitative relationship between silica exposure and lung cancer mortality in German uranium miners, 1946–2003

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BACKGROUND: In 1996 and 2009, the International Agency for Research on Cancer classified silica as carcinogenic to humans. The exposure–response relationship between silica and lung cancer risk, however, is still debated. Data from the German uranium miner cohort study were used to further investigate this relationship.

METHODS: The cohort includes 58 677 workers with individual information on occupational exposure to crystalline silica in $mg\,m^{-3}$-years and the potential confounders radon and arsenic based on a detailed job-exposure matrix. In the follow-up period 1946–2003, 2995 miners died from lung cancer. Internal Poisson regression with stratification by age and calendar year was used to estimate the excess relative risk (ERR) per dust-year. Several models including linear, linear quadratic and spline functions were applied. Detailed adjustment for cumulative radon and arsenic exposure was performed.

RESULTS: A piecewise linear spline function with a knot at $10\,mg\,m^{-3}$-years provided the best model fit. After full adjustment for radon and arsenic no increase in risk $<10\,mg\,m^{-3}$-years was observed. Fixing the parameter estimate of the ERR in this range at 0 provided the best model fit with an ERR of 0.061 (95% confidence interval: 0.039, 0.083) $>10\,mg\,m^{-3}$-years.

CONCLUSION: The study confirms a positive exposure–response relationship between silica and lung cancer, particularly for high exposures.

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In 1996, the International Agency for Research on Cancer (IARC) classified crystalline silica, inhaled in the form of quartz from occupational sources, as carcinogenic to humans (group 1) with the lung as target organ (IARC, 1997). However, IARC noted a lack of extensive exposure–response data from epidemiological studies, differences in exposure metrics between the studies as well as inconsistencies in the exposure–response relationship across the studies. Since then, a number of individual studies (Ulm *et al*; 1999; Rice *et al*, 2001; Pukkala *et al*, 2005; Chen *et al*, 2007; Mundt *et al*, 2011; Vacek *et al*, 2011) on the relationship between occupational inhaled crystalline silica and lung cancer risk have been published, in addition to a series of meta- or pooled analyses (Brüske-Hohlfeld *et al*, 2000; Steenland *et al*, 2001; Kurihara and Wada, 2004; Lacasse *et al*, 2009; Erren *et al*, 2011) and reviews (Soutar *et al*, 2000; Pelucchi *et al*, 2006; Brown, 2009). In 2012 the IARC reconfirmed the classification of silica (IARC, 2012). However, there is still a debate on the shape of the exposure–response relationship, especially in the low exposure range.

The two most recent and currently largest analyses addressing the shape of the relationship between cumulative silica exposure and lung cancer are a pooled analysis of 10 cohort studies by Steenland *et al* (2001) and a meta-analysis of 4 cohort and 6 case–control studies by Lacasse *et al* (2009). The meta-analysis showed a statistically significant increased risk $>1.8\,mg\,m^{-3}$-years with a plateau $>6\,mg\,m^{-3}$-years. The interpretation of these findings is limited by differences in the quality of silica exposure assessment reported in the original studies and heterogeneity across studies (Lacasse *et al*, 2009). The pooled analysis by Steenland *et al* (2001) included 65 980 workers and 1079 lung cancer deaths over several industrial settings. There was a considerable heterogeneity between the various studies. An increase in risk with the natural logarithm of cumulative silica concentration was observed.

The German uranium miner cohort (Wismut cohort) study has a comparable size (nearly 60 000 members) to the pooled analysis (Steenland *et al*, 2001); it includes a large number of lung cancer deaths ($n=2995$) and provides a long follow-up with almost 2 million person-years. Individual information on occupational exposure to crystalline silica is available, which allows a detailed investigation of the shape of the dose–response relationship with particular focus on the low-dose range in a single study. Individual information on other known occupational carcinogens such as exposure to radon and arsenic dust is available and can be accounted for in the risk analyses. In addition, there is some information about smoking from a nested case–control study on lung cancer in the Wismut cohort (Schnelzer *et al*, 2010), which allows the evaluation of potential confounding by smoking. The aim of the present analyses is to investigate the shape of the exposure–response relationship between crystalline silica exposure and lung cancer mortality and the combined effect of silica and radon.

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MATERIALS AND METHODS

Cohort definition and mortality follow-up

The Wismut cohort has been described in detail (Grosche *et al*, 2006; Kreuzer *et al*, 2008, 2010a, b; Walsh *et al*, 2010a, b). In brief, the cohort includes 58 987 males employed for at least 180 days between 1946 and 1989, selected as a random sample stratified by date of first employment, place of work and area of mining. Every cohort member contributes to the time at risk starting at the date of employment plus 180 days and ending at the earliest of date of death, date of loss to follow-up or the end of the follow-up period (31 December 2003). Information on the vital status of individuals was obtained from local registration offices, whereas death certificates were obtained from the responsible Public Health Administrations and the pathology archive of the Wismut company.

Information on exposure to dust and radiation

The silica and respirable fine dust content in the Wismut mines varied between time periods and mining regions and also between different mines within a given district, and even between regions within a specific mine (Dahmann *et al*, 2008). In the early period (1946–1954) the situation in mines was aggravated by poor industrial hygiene (i.e., dry drilling) and also by extremely low ventilation rates, i.e., air velocities $<0.1\,\mathrm{m\,s^{-1}}$ (Bauer, 1997; Dahmann *et al*, 2008). Thus, the dust exposures for the Wismut miners show high shift concentration averages for crystalline silica of well $>2\,\mathrm{mg\,m^{-3}}$ in many mines in the early times. After 1955 the situation improved continuously with the introduction of wet drilling and increasing mine ventilation rates up to about $0.3\,\mathrm{m\,s^{-1}}$. This resulted in a decrease of dust concentrations by >97% (Bauer, 1997; Dahmann *et al*, 2008) as illustrated in Figure 1.

From 1960, systematic measurements of silica and fine dust concentrations performed by the Wismut company were available. Major efforts were undertaken to retrospectively quantify exposures to silica and fine dust before 1960, including reconstruction of historical workplaces and simulating ventilation conditions (Bauer, 1997; Dahmann *et al*, 2008). Using these estimates and measurements, a detailed job-exposure matrix (JEM) was developed (HVBG and BBG, 2005). This JEM provides annual exposure values for each calendar year, each place of work and job type (>900 different jobs and several mining facilities). Annual and cumulative exposures are given in units of dust-years that are $1\,\mathrm{mg\,m^{-3}}$ silica dust or fine dust over a time period of 220 shifts of 8 h. Differences in the number of shifts and daily working hours in the different calendar years were accounted for. Figure 1 shows the mean annual exposure values for silica dust in the cohort. Silica dust is a proportion of the total measured respirable fine dust and therefore highly correlated with fine dust exposure ($r>0.95$). Consequently, the variable respirable fine dust is excluded from all risk analyses.

Arsenic exposure occurred only in mines located in Saxony (Dahmann *et al*, 2008). The arsenic content in the deposit and data on dust exposure were used as proxy variables to estimate the arsenic exposure within the JEM because only a few measurements of arsenic levels in air were available. The cumulative exposure to arsenic dust is quantified in dust-years, where 1 dust-year equals an exposure of $1\,\mu\mathrm{g\,m^{-3}}$ over 220 shifts of 8 h (HVBG and BBG, 2005).

Information on exposures to ionising radiation is based on a separate JEM similar to that for dust. This JEM includes information on exposure to radon and its progeny in working level month (WLM), external gamma radiation in mSv and long-lived radionuclides in $\mathrm{kBq\,h\,m^{-3}}$ (HVBG and BBG, 2005; Lehmann *et al*, 1998). Estimates for radon exposure were based on systematic measurements in the air from 1955 onwards, and on detailed expert rating in the years before (HVBG and BBG, 2005). A WL is defined as 1.3×10^3 MeV of potential alpha energy per litre of air. One WLM corresponds to exposure to 1 WL during 1 month, i.e., 170 working hours. The annual very high mean exposure values for radon and its progeny in the early years decreased after 1955 due to the introduction of ventilation measures (see Figure 1). Exposures to external gamma and long-lived radionuclides are not considered in the risk analyses due to negligible doses to the lung compared with the radon progeny.

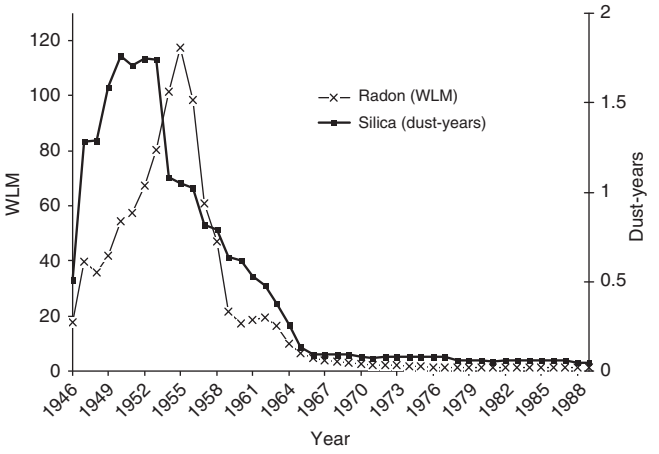

Figure 1 Mean annual exposure to silica dust in $\mathrm{mg\,m^{-3}}$-years and radon and its progeny in WLM among exposed cohort members with respect to silica ($n=58\,677$) and radon ($n=50\,468$).

Statistical methods

Several RR models based on internal Poisson regression have been applied here to investigate the shape of the relationship between cumulative silica dust exposure and lung cancer mortality risk and its interaction with radon. The confidence intervals (CIs) were of the Wald-type at the 95% level. Age was stratified in 5-year groups and individual calendar year in 58 categories. Analogously to previous analyses on lung cancer (Grosche *et al*, 2006; Walsh *et al*, 2010a, b) a 5-year lag was used in calculating the cumulative exposures to allow for a latent period between exposure and death. Lag times of 0, 10 and 15 years were also considered. Information on silica and arsenic dust was missing for 310 individuals of the cohort. Therefore, these individuals were excluded from all analyses leaving 58 677 miners out of 58 987 and 2995 out of 3016 lung cancer deaths. All models were fitted with the AMFIT module of the EPICURE software (Preston *et al*, 1998).

Main models for risk of lung cancer and silica In a first step, the RR of lung cancer death was estimated by a simple model with silica dust in categories. The following *a priori* defined cut-points were used for cumulative silica dust in $\mathrm{mg\,m^{-3}}$-years (0–0.5, 0.5–2, 2–5, 5–10, 10–20, 20–30 and 30+). In a second step, several excess relative risk (ERR) models with baseline stratification by age and calendar year were used. If $r(a, y, \mathrm{sil}, \mathrm{rn}, \mathrm{ars})$ is the specific lung cancer mortality rate for age, a; year, y; silica, sil; radon, rn; arsenic, ars; and $r_0(a,y)=r(a,y,0,0,0)$ is the baseline disease rate for non-exposed individuals, then

$$r(a, y, \mathrm{sil}, \mathrm{rn}, \mathrm{ars}) = r_0(a, y)\cdot\{1+\mathrm{ERR}(\mathrm{sil}, \mathrm{rn}, \mathrm{ars})\}.$$

Here, *ERR* is the excess RR for which several different functions of sil were tested:

Epidemiology

1. A linear function $ERR\ (\mathrm{sil}) = \beta \cdot \mathrm{sil}$, where sil is the total cumulative exposure to silica dust in mg m^{-3}-years.
2. A piecewise linear spline function with one knot.

$$\mathrm{ERR}\,(\mathrm{sil}) = \begin{cases} \beta_1 \cdot \mathrm{sil} & \mathrm{sil} \leqslant \mathrm{sil_k} \\ \beta_1 \cdot \mathrm{sil} + \beta_2 \cdot (\mathrm{sil} - \mathrm{sil_k}) & \mathrm{sil} > \mathrm{sil_k} \end{cases}$$

Different locations of the knots $\mathrm{sil_k} \in \{5, 7, 8, 9, 10, 11, 12, 15\}$ in mg m^{-3}-years were tested. A model in which β_1 was fixed at zero was also fitted.

3. Quadratic as well as linear–quadratic functions of cumulative silica exposure.

To adjust for potential confounding in the models above, the cumulative radon and arsenic exposures were first included as continuous variables in a linear way. Previous analyses on the relationship between lung cancer and cumulative radon exposure in the Wismut cohort provided evidence for a model that is linear in radon exposure with the exponential effect modifiers age at median exposure (or attained age), time since median exposure and radon exposure rate (Walsh *et al*, 2010a, b). Therefore, these three exponential effect modifiers of radon exposure were then additionally included to achieve better adjustment for the major confounder radon. The preferred models were identified by applying model techniques for nested models, i.e., the likelihood ratio test (see Walsh, 2007 for an explanation). Adjustment for confounders was performed in an additive and in a multiplicative way. As the additive model provided a better fit, only these results are shown.

Effect modification Effect modification by age, time and exposure rate was present in the radon-induced lung cancer risk. These factors may also modify the effect of the silica-induced lung cancer risk. Therefore, all possible combinations of effect modification on silica and radon were tested. The effect modifiers were calculated in analogy to the calculations for radon (Walsh *et al*, 2010b). The aim was to obtain the best suited and most parsimonious model to describe the combined effect of silica and radon.

Quantification of the combined effect of silica and radon In a first step, the combined effect of silica dust and radon on the risk of lung cancer death was described by simple categorical analyses with combinations of radon (<50, 50–1000 and >1000 WLM) and silica dust (<10, 10–20, 20–30 and $30+$ mg m^{-3}-years) without consideration of arsenic and risk effect modifiers. To gain more insight into the form (additive or multiplicative) of the interaction between silica and radon, a geometric mixture model that is piecewise linear in silica (with a knot at 10 mg m^{-3}-years) and linear in radon with effect modifiers for silica and radon and adjustment for arsenic, as described above, was fitted: $1 + \mathrm{ERR_{mix}} = (1 + \mathrm{ERR_{mult}})^{\lambda}\ (1 + \mathrm{ERR_{add}})^{1-\lambda}$

The mixing parameter λ ($0 \leqslant \lambda \leqslant 1$) was first set to 0.0 (additive) and was then enhanced up to 1.0 (multiplicative) in 0.1-length steps.

RESULTS

Among the 58 677 cohort members, 20 748 died overall between 1946 and 2003 while 2995 died from lung cancer. The cause of death was available for 93.6% of the miners. In all, 4.7% were lost to follow-up. The cohort members contributed 1 984 687 person-years with an average follow-up period of 34 years, and the mean duration of employment was 14 years. All cohort members were exposed to silica dust at some time, because silica occurred not only underground but also in appreciably lower concentrations at the surface (Table 1).

In Table 2 the risk of lung cancer death in relation to cumulative silica dust exposure is given. A positive trend could be observed.

Table 1 Exposures of the Wismut cohort, 1946–2003

Cumulative exposure to	Exposed (%)	Mean	Median	Max	s.d.
Silica (mg m^{-3}-years)	100	5.9	1.8	56	8.0
Radon (WLM)	86	280	33	3224	445
Arsenic (μg m^{-3}-years)	31	121	67	1417	145

Abbreviation: WLM = working level months.

Without adjustment for radon and arsenic a statistically significant increased RR, compared with the reference category of 0–0.5 mg m^{-3}-years was present in all categories except for the category 0.5–2 mg m^{-3}-years (see also Figure 2A). After adjustment for the major confounder radon, all estimates decreased markedly, but remained statistically significant in the exposure categories 10–20, 20–30 and 30–56 mg m^{-3}-years. Additional adjustment for cumulative arsenic exposure led to a significant improvement of the model fit quality, but only to a small decrease of the RR (Table 2). More detailed adjustment for radon including the effect modifiers age at median exposure, time since median exposure and radon exposure rate, led to a further decrease of the silica-induced risk, showing a statistically significant increased risk only in the categories 20–30 and 30–56 mg m^{-3}-years.

As the categorical analyses indicated a non-linear exposure response relationship (Figure 2A), two-line spline models with different knots were applied and compared by model selection procedures (Walsh, 2007). Models with silica dust as linear spline with one knot at 7, 8, 9 and 10 mg m^{-3}-years yielded in statistically better fits compared with the pure linear model. After adjustment for radon and arsenic a spline model with a knot at 10 mg m^{-3}-years provided the best fit. Table 3 provides information on the risk estimates for the model parameters β_1 and β_2 and the corresponding RRs at 5 and 15 mg m^{-3}-years based on the spline model, with a knot at 10 mg m^{-3}-years. Without adjustment for radon and arsenic, the RR was 1.34 (95% CI: 1.20; 1.47) at 5 mg m^{-3}-years and 2.44 (95% CI: 1.96; 2.61) at 15 mg m^{-3}-years compared with 0 dust-years. The RRs decreased after simple adjustment for radon and arsenic. After more detailed adjustment for radon, i.e., inclusion of the three exponential effect modifiers the silica risk estimates further decreased to 0.97 (95% CI: 0.86; 1.08) at 5 mg m^{-3}-years and 1.24 (95% CI: 0.98; 1.49) at 15 mg m^{-3}-years, but yielded significant RRs for cumulative exposures >16 mg m^{-3}-years (Figure 2B). As β_1 decreased to -0.006 (-0.028; 0.015) after full adjustment, a model in which β_1 was fixed at zero was fitted additionally. The preferred model was achieved after detailed adjustment for the confounder radon (with effect modifiers) and arsenic and β_1 fixed at zero between 0 and 10 mg m^{-3}-years. Quadratic and linear quadratic models of cumulative silica exposure did not result in an improvement in goodness of fit.

The best suited and most parsimonious model, to describe both effects of silica and radon and their corresponding time- and dose-rate-related effect modifiers, was piece-wise linear in cumulative silica dust with one knot at 10 mg m^{-3}-years, with the initial slope fixed at 0 below 10 mg m^{-3}-years including attained age as exponential effect modifier. Table 3 shows that the preferred model had a deviance of 30 592.5 and one parameter less than the model with the optimised initial slope (deviance = 30 592.3). It was linear in radon with exponential effect modifiers that depend on time since median exposure and radon-exposure rate. The silica-induced lung cancer risk decreases with increasing attained age (Table 3).

In Table 4 the results of the categorical analyses on the combined effect of radon and silica are shown. There was an increase of the RR of silica (see increase in columns), and an increase of the RR of radon (see rows). The risk in the highest silica and radon exposure category (>30 mg m^{-3}-years and

Table 2 Risk of death from lung cancer by cumulative silica dust exposure in mg m^{-3}-years by categories, 1946–2003

Silica dust in mg m^{-3}-years	Mean	Person-years	# of cases	RR 95% CI unadjusted	RR 95% CI adjusted for radon	RR 95% CI adjusted for radon, arsenic	RR 95% CI adjusted for radon, arsenic with effect modifiers
0–0.5	0.1	681 780	137	1.00 Reference	1.00 Reference	1.00 Reference	1.00 Reference
0.5–2	1	394 559	283	1.12 (0.89–1.35)	1.09 (0.86–1.31)	1.08 (0.86–1.31)	0.95 (0.77–1.12)
2–5	3	274 523	356	1.26 (1.00–1.51)	1.15 (0.91–1.38)	1.13 (0.89–1.37)	0.96 (0.78–1.13)
5–10	7	238 032	430	1.38 (1.10–1.66)	1.07 (0.83–1.30)	1.05 (0.81–1.28)	0.86 (0.67–1.04)
10–20	14	264 140	936	2.45 (1.98–2.92)	1.53 (1.19–1.88)	1.47 (1.13–1.81)	1.14 (0.87–1.40)
20–30	24	108 502	664	3.76 (3.02–4.49)	2.19 (1.64–2.75)	2.05 (1.51–2.60)	1.51 (1.08–1.94)
30–56	34	23 151	189	4.71 (3.62–5.80)	2.91 (1.96–3.83)	2.79 (1.87–3.70)	2.02 (1.28–2.75)
Total	5.9	1 984 687	2995				

Abbreviations: Adj. = adjusted; CI = confidence interval; RR = relative risk. RR, baseline stratified on age in 5-year groups and individual calendar year in 58 categories. RR adj. for radon (last-but-two column), for radon and arsenic (next-to-last column) and for radon with exponential inclusion of the effect modifiers age at median exposure, time since median exposure and radon exposure rate and arsenic (last column) as continuous variables in an additive way.

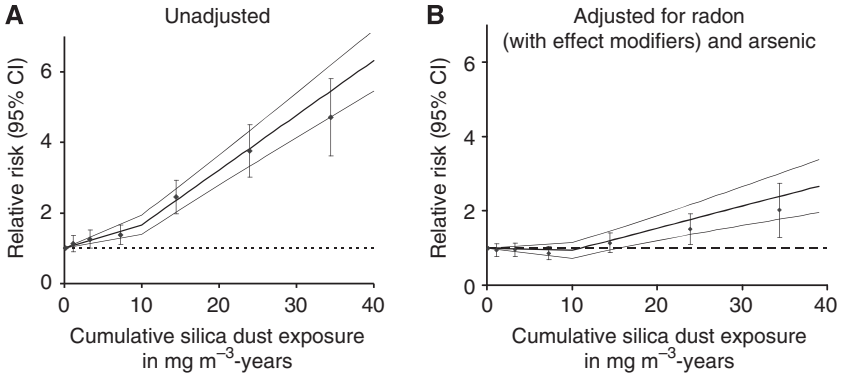

Figure 2 RR of death from lung cancer ($n = 2995$) in relation to cumulative silica dust without adjustment (**A**) and with additive adjustment for radon (with the effect modifiers age at median exposure, time since median exposure and radon exposure rate) and arsenic (**B**). Categorical analysis (0–0.5, 0.5–2, 2–5, 5–10, 10–20, 20–30 and 30+) and linear spline model (bold line) with 95% confidence limits (fine lines).

>1000 WLM) is 4.6-fold (95% CI: 3.7–5.4) higher compared with the risk in the reference category (<10 mg m^{-3}-years and <50 WLM). With the geometric mixture model, the form of the interaction between silica and radon was further investigated. The purely additive model provided a statistically significant better fit compared with the multiplicative model. These results indicate that the effects of silica and radon exposure are more likely to be additive rather than multiplicative.

DISCUSSION

The analysis of the Wismut uranium miner cohort study showed a statistically significant positive exposure–response relationship between silica and lung cancer for high cumulative silica exposures. Analyses on the combined effects of radon and silica provided evidence for a more additive rather than multiplicative relationship of both effects.

In contrast to other studies, beside silica a strong second risk factor – radon – was present in the cohort. Both variables correlate over time ($r = 0.79$) with high exposures in the very early years and low exposures later (Figure 1). Thus, the major challenge in the statistical analyses was to fully account for this strong confounder. The large size of the cohort and the detailed information on both risk factors enabled this adjustment. Owing to the relatively high correlation of radon and dust over time and the fact that radon is a stronger risk factor than silica, it cannot be ruled out that adjustment for radon including the three effect modifiers may have led to some over adjustment. Therefore, a small increase in risk even in the range <10 mg m^{-3}-years cannot be ruled out.

Arsenic exposure was high in the early years and decreased later, however, the correlation with silica was low ($r = 0.46$), and arsenic itself a weak risk factor. The decrease in the silica-induced lung cancer risk was small after adjustment for arsenic. Restriction of the cohort data to individuals without any arsenic exposure ($n = 40\,753$) showed a very similar exposure–response pattern (RR at 15 mg m^{-3}-years = 1.35; 95% CI: 1.17–1.53) compared with the non-restricted data (RR = 1.31; 95% CI: 1.20–1.42) for the fully adjusted model.

The preferred model indicated that attained age modifies the silica-induced risk. With increasing attained age, the risk for silica-induced lung cancer decreases. Again, owing to the high timely correlation of both factors and the fact that radon is a stronger risk factor, it cannot be resolved whether there could be other modifying factors for the silica-induced lung cancer risk.

Limitations

A possible limitation of this study could be misclassification of the silica exposure in the early years from 1946 to 1960 when no measurements for silica were available. A very detailed expert assessment had been performed with simulated, remodelled historical exposure settings using historic equipments, model calculations and expert rating (Dahmann *et al*, 2008). Thus, misclassification, if present, should be small.

A further limitation is the lack of individual information on the potential confounder smoking. In a nested case–control study on lung cancer some information on smoking based on data from the medical archives or from relatives was obtained for 439 cases and 550 controls (Schnelzer *et al*, 2010). No statistically significant

Table 3 Risk of lung cancer death by cumulative silica exposure in a linear spline model with one knot at 10 mg m^{-3}-years, 1946–2003

Model	β_1[a] 95% CI	β_2[b] 95% CI	Deviance	RR[c] 95% CI 5 mg m^{-3}-years	RR 95% CI 15 mg m^{-3}-years
Unadjusted	0.067 (0.039; 0.094)	0.088 (0.058; 0.119)	30 768.1	1.34 (1.20; 1.47)	2.44 (1.96; 2.61)
Adjusted for radon [d]	0.015 (−0.008; 0.038)	0.072 (0.042; 0.102)	30 692.1	1.08 (0.96; 1.19)	1.59 (1.09; 2.08)
Adjusted for radon and arsenic [e]	0.012 (−0.011; 0.035)	0.068 (0.038; 0.098)	30 688.2	1.06 (0.95; 1.18)	1.52 (1.24; 1.79)
Adjusted for radon (with exponential	−0.006 (−0.028; 0.015)	0.066 (0.038; 0.094)	30 604.2	0.97 (0.86; 1.08)	1.24 (0.98; 1.49)
effect modifiers [f]) and arsenic	0.000 (fixed[g])	0.061 (0.039; 0.083)	30 604.5	1.00 (fixed)	1.31 (1.20; 1.42)
0-year lag	0.000 (fixed)	0.061 (0.039; 0.083)		1.00 (fixed)	1.31 (1.20;1.42)
10-year lag	0.000 (fixed)	0.060 (0.037; 0.082)	not comparable	1.00 (fixed)	1.30 (1.19; 1.41)
15-year lag	0.000 (fixed)	0.062 (0.039; 0.085)		1.00 (fixed)	1.31 (1.20; 1.43)
Silica with exponential effect modifier	0.000 (fixed)	0.073 (0.046; 0.100)	30 592.5	1.00 (fixed)	1.37 (1.23; 1.50)
attained age (centred at 64 years)	0.002 (−0.014; 0.018)	0.073 (0.043; 0.100)	30 592.3	1.01 (0.93; 1.09)	1.39 (1.16; 1.63)
adjusted for radon (with exponential modifiers [h]) and arsenic					
50 years attained age	0.007 (−0.040; 0.057)	0.223 (0.142; 0.322)	30 592.3	1.04 (0.80; 1.29)	2.21 (1.43; 3.02)
60 years	0.003 (−0.019; 0.025)	0.105 (0.066; 0.134)	30 592.3	1.15 (0.90; 1.13)	1.55 (1.30; 1.84)
70 years	0.001 (0.008; 0.011)	0.045 (0.021; 0.068)	30 592.3	1.01 (0.96; 1.06)	1.24 (1.07; 1.39)
80 years	0.001 (−0.004; 0.005)	0.020 (0.004; 0.035)	30 592.3	1.00 (0.98; 1.03)	1.11 (1.02; 1.20)

Abbreviations: CI = confidence interval; ERR = excess relative risk. [a,b]β_1 and β_2 describe the ERR in the following way, $sil_k = 10$:

$$\mathrm{ERR}(\mathrm{sil}) = \begin{cases} \beta_1 \cdot \mathrm{sil} & \mathrm{sil} \leqslant \mathrm{sil}_k \\ \beta_1 \cdot \mathrm{sil} + \beta_2 \cdot (\mathrm{sil} - \mathrm{sil}_k) & \mathrm{sil} > \mathrm{sil}_k \end{cases}$$

[c]Relative risk with 95% CI for a cumulative exposure of 5 mg m^{-3}-years compared with 0. [d]Adjusted for cumulative radon exposure in a linear way. [e]Adjusted for cumulative radon and arsenic exposure in a linear way. [f]Exponential effect modifiers age at median exposure, time since median exposure and radon exposure rate. [g]Parameter β_1 is fixed at 0. [h]Exponential effect modifiers, time since median exposure and radon exposure rate.

Table 4 Combined effect of cumulative exposure to silica and radon on the risk of death from lung cancer, Wismut cohort, 1946–2003

	Radon						
	<50 WLM		50–1000 WLM		>1000 WLM		
Silica dust mg m^{-3}-years	*n*	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)	Total
< 10	609	1.0 Reference	585	1.52 (1.34–1.69)	12	1.95 (0.83–3.07)	1206
10–20	54	1.10 (0.79–1.41)	663	2.45 (2.17–2.73)	219	3.11 (2.62–3.61)	936
20–30	6	1.33 (0.26–2.41)	238	3.11 (2.63–3.60)	420	4.29 (3.64–4.74)	664
30+	0	—	42	4.75 (3.25–6.25)	147	4.56 (3.72–5.41)	189
Total	669		1528		798		2995

Abbreviations: CI = confidence interval; RR = relative risk; WLM = working level month.

trend in the proportion of smokers with increasing silica exposure for both lung cancer cases and controls was observed (two-sided test for trend: $P = 0.31$ for cases, $P = 0.52$ for controls; Figure 3). Pukkala *et al* (2005) observed no increased risk of lung cancer in their preferred model in the category 1.0–9.9 mg m^{-3}-years (RR = 0.97; 95% CI: 0.91–1.03) compared with 0 mg m^{-3}-years and a statistically significant risk >10 mg m^{-3}-years (RR = 1.42; 95% CI: 1.20–1.70) after adjustment for smoking on aggregate level. This is similar to results given in Table 2 and therefore possibly further evidence that smoking is not a major confounder in this study. However, residual confounding by smoking cannot be fully excluded, because data on duration and amount of smoking are incomplete.

Silicosis is debated as possible effect modifier of the silica-induced lung cancer risk (Hnizdo *et al*, 1997; Ulm *et al*, 1999; Soutar *et al*, 2000; Pelucchi *et al*, 2006; Taeger *et al*, 2008; Brown, 2009; Erren *et al*, 2011) and the carcinogenic role of silica in the absence of silicosis is still debated. There is consistent evidence of an increased lung cancer risk among silicotics, whereas studies restricted to non-silicotics or those with 'unknown silicotic status' mainly show no increased risk of lung cancer. Many studies, however, suffer from insufficient information on silicosis status (e.g., Steenland *et al*, 2001; Attfield and Costello, 2004; Lacasse *et al*, 2009) or missing quantitative data on silica exposure. In the Wismut cohort selective data on silicosis are available. For a total of 3645 cohort members silicosis was noted on the death

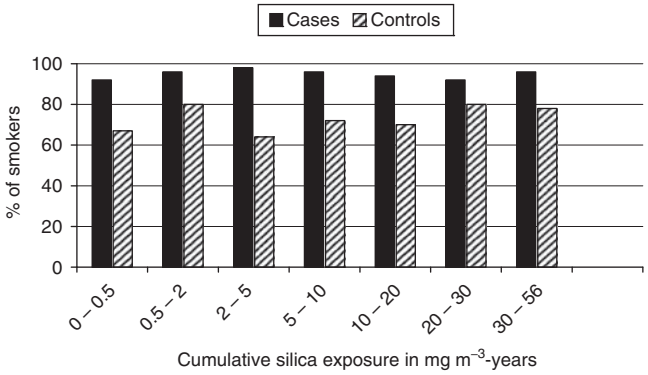

Figure 3 Percentages of smokers within cases ($n = 439$) and controls ($n = 550$) from a nested case–control study (Schnelzer *et al*, 2010) on lung cancer among the Wismut miners. A smoker is defined as a person who ever smoked in the last 20 years before death (for cases) or the reference case's death (for controls).

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Table 5 Risk of death from lung cancer by cumulative silica dust exposure in mg m^{-3}-years by categories after exclusion of known silicotics, 1946–2003

	Cohort excluding known silicotics				'Known' silicotics	
Silica dust in mg m^{-3}-years	**Person-years**	**# of lung cancer deaths**	**RR 95%CI adjusted for radon and arsenic**	**RR 95%CI adjusted for radon and arsenic with effect modifiers**	**Person-years**	**# of lung cancer deaths**
0–0.5	665 199	137	1.00 Reference	1.00 Reference	16 497	0
0.5–2	390 539	276	1.12 (0.86–1.31)	0.98 (0.79–1.18)	4019	7
2–5	267 161	333	1.12 (0.88–1.36)	0.97 (0.78–1.17)	7361	23
5–10	223 766	379	1.06 (0.82–1.30)	0.88 (0.69–1.07)	14 146	51
10–20	219 248	675	1.44 (1.10–1.78)	1.16 (0.89–1.43)	44 600	261
20–30	66 313	308	1.64 (1.13–2.15)	1.31 (0.92–1.70)	41 874	356
30–56	11 864	68	1.87 (0.98–2.77)	1.31 (0.63–1.99)	11 192	121
Total	1 844 090	2176			139 692	819

Abbreviations: CI = confidence interval; RR = relative risk. RR adjusted for radon and arsenic (forth column) and for radon with exponential inclusion of the effect modifiers age at median exposure, time since median exposure and radon exposure rate and arsenic (fifth column) as continuous variables in an additive way

certificates, the autopsy protocols or the protocols of the medical archive of the Wismut company. It is unclear how valid this information is. For the remaining 55 032 cohort members, the silicosis status is unknown. Categorical risk analyses excluding the 3645, known' silicotics (Table 5) show elevated RR's in the silica exposure categories >10 mg m^{-3}-years after full adjustment. The corresponding estimate for the parameter β_2 (>10 mg m^{-3}-years) was 0.034 (95% CI: 0.013; 0.055), which is appreciably lower compared with that in the full data set ($\beta_2 = 0.061$; 95% CI: 0.039; 0.083). It is unclear whether this excess is real or due to residual confounding (misclassified non-silicotics). Moreover, the statistical power is reduced, because the majority of highly radon- and silica-exposed cohort members were excluded as silicotics.

Comparison with other epidemiological studies

The increase in risk with increasing exposure in this study is consistent with other studies (Checkoway *et al*, 1997; Brüske-Hohlfeld *et al*, 2000; Rice *et al*, 2001; Steenland *et al*, 2001; Pukkala *et al*, 2005; Lacasse *et al*, 2009). On the other hand, a few single studies concluded that there was no evidence that crystalline silica acts as a risk factor for lung cancer (Steenland and Brown, 1995; Ulm *et al*, 1999; Graham *et al*, 2004; Chen *et al*, 2007; Mundt *et al*, 2011; Vacek *et al*, 2011). Exposures in some of these studies (Graham *et al*, 2004; Vacek *et al*, 2011) or parts of the study (Chen *et al*, 2007) have been quite low or subjects with silicosis had been omitted (Ulm *et al*, 1999).

Steenland *et al* (2001) pooled 10 cohort studies from a variety of industries and countries. The pooled study included 65 980 workers and 1079 lung cancer deaths. The logarithm of cumulative exposure with a 15-year lag showed a statistically significant positive trend with lung cancer risk. Categorical analyses by quintiles of cumulative silica exposure resulted in odds ratios of 1.0, 1.0 (95% CI, 0.85–1.3), 1.3 (95% CI, 1.1–1.7), 1.5 (95% CI, 1.2–1.9) and 1.6 (95% CI, 1.3–2.1) for cumulative silica exposure of <0.4, 0.4–2.0, 2.0–5.4, 5.4–12.8 and >12.8 mg m^{-3}-years, respectively. The risks for high exposures are approximately comparable to the present results, however, slightly shifted with a RR in this study of 1.51 (95% CI: 1.08–1.94) in the category 20–30 mg m^{-3}-years. The odds ratios of the lower exposure categories are appreciably higher compared with the fully adjusted risks presented here, but the CIs overlap in both studies. No adjustment for smoking and other confounders was made. Furthermore, there was a considerable heterogeneity between the various studies in this pooled analysis.

The meta-analysis of Lacasse *et al* (2009) included four cohort studies and six case–control studies having quantitative measurements of crystalline silica exposure and adjustment for smoking. An increase in risk of lung cancer was observed with increasing cumulative silica exposure. Differences in the quality of silica exposure assessment of the original studies and significant heterogeneity across the studies limit its interpretation.

In conclusion, results indicate an elevated lung cancer risk at higher cumulative silica exposures. No increase in risk in the range <10 mg m^{-3}-years was found, but a small increase cannot be ruled out. It is unclear whether these results can be applied to other industrial settings than uranium mining. In this study, even in the absence of known silicotics some increase in the silica-induced lung cancer risk was observed, however, this result has to be treated with caution due to possibly incomplete data on silicotics. Overall, the findings of this study support the evaluation of the IARC to classify silica as carcinogenic to humans with the lung as target organ (1997, 2012). The extension of the follow-up period to the end of 2008 will allow more detailed analyses of the low exposure range with alternative models.

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