Occupational silica exposure and lung cancer risk: a review of epidemiological studies 1996–2005

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Background: In 1997, a Monograph from the International Agency for Research on Cancer (IARC) classified occupational exposure to crystalline silica as carcinogenic to humans. Large amounts of epidemiological data have been published subsequently.

Methods: We conducted a systematic review of epidemiological investigations on silica exposure and lung cancer risk published after the IARC Monograph, including 28 cohort, 15 case–control and two proportionate mortality ratio (PMR) studies. These were identified in the available literature.

Results: The pooled RR of lung cancer, calculated using random effects models, from all cohort studies considering occupational exposure to silica was 1.34. The RRs were 1.69 in cohort studies of silicotics only, 1.25 in studies where silicosis status was undefined and 1.19 among non silicotic subjects. The pooled RR was 1.41 for all case–control studies. The RRs were 3.27 in case–control studies of silicotics only, 1.41 in studies where silicosis status was undefined and 0.97 among non silicotic subjects. The RR was 1.24 for PMR studies.

Conclusions. In this re-analysis, the association with lung cancer was consistent for silicotics, but the data were limited for non silicotic subjects and not easily explained for undefined silicosis status workers. This leaves open the issue of dose–risk relation and pathogenic mechanisms and supports the conclusion that the carcinogenic role of silica per se in absence of silicosis is still unclear.

Key words: case–control studies, cohort studies, lung neoplasms, silica, silicosis, systematic review

introduction

Occupational exposure to silica occurs in a large number of industries and settings, such as mines, stone quarries and granite production, ceramic and pottery industries, steel production, and many others.

In 1987 and 1997, the International Agency for Research on Cancer (IARC) published two Monographs that evaluated the relation between silica exposure and human cancer [1, 2]. The 1987 Monograph concluded that there was sufficient evidence for carcinogenicity of crystalline silica in experimental animals but limited evidence in humans (Group 2A). The 1997 Monograph, basing on both animal and epidemiological data, classified crystalline silica inhaled in the form of quartz or cristobalite from occupational sources as carcinogenic to humans (Group 1).

However, the IARC Working Group noted that carcinogenicity was not found in all industrial circumstances studied [2], and a long debate followed the publication of the Monograph [3–7].

As about 50 studies have been published since 1996 on the relation between occupational silica exposure and lung cancer, we conducted a systematic review to provide summarizing data of investigations in the last decade. Included were studies published between 1996 (excluding those previously reviewed in the IARC Monograph) and July 2005, identified through Medline and by searching papers quoted as references in these studies. Pooled relative risks (RR) were calculated according to study design, and using both fixed and random effect models. Results of the latter were presented in the figures, though the overall estimates for fixed effect models were also given.

cohort studies

The main findings from cohort studies that investigated the relation between silica exposure and lung cancer are summarized in Table S1 (available as supplementary data online).

In a study of phosphate industry workers that were followed-up from 1949 to the end of 1992, a slight increase in the risk of lung cancer in white (standardized mortality ratio, SMR = 1.19, 95% confidence interval (CI), 1.07–1.32) and...
non-white men (SMR = 1.13, 95% CI, 0.92–1.37) was found when comparing with national rates [8]. When mortality from lung cancer was compared with local county rates, however, the corresponding SMRs were 0.98 and 0.94. According to subsequent levels of silica exposure in the cohort, as compared to the lowest level, the RRs were 1.58, 1.81 and 1.05 in white and 1.44, 1.22 and 0.68 in non-white males. Also, total dust exposure was unrelated to lung cancer risk in both groups in analyses of internal mortality.

A cohort study of mortality was conducted in Poland between 1970 and 1991 on 11 224 males who were diagnosed with pneumoconiosis [9, 10]. Most subjects included in the cohort had worked in coal mines (63%), while the others had been employed in foundries and metallurgical industry (16%), refractory materials, ceramics and quarries (13%), and underground works such as drift cutting (8%). Mortality in each subcohort was compared with Polish male mortality rates. All causes mortality was significantly increased in all subcategories of workers, largely due to excess deaths from non-malignant respiratory diseases (NMRD). SMRs of lung cancer were 1.04 (95% CI, 0.88–1.22) in coal miners, 1.59 (95% CI, 1.24–2.01) in foundry, 1.02 (95% CI, 0.72–1.40) in ceramics and quarry and 1.30 (95% CI, 0.85–1.90) in underground workers. Thus, only men employed in the metallurgical industry, i.e. the subcohort with the most complex concurrent occupational exposures, had a significantly increased mortality from lung cancer in this cohort study of pneumoconiosits [9].

In another investigation, men hospitalised for silicosis in Sweden (from 1965 to 1983) and Denmark (from 1977 to 1989) were linked to national cancer incidence and mortality registries [11]. Lung cancer incidence in these two cohorts was higher than expected (standardized incidence ratio, SIR = 3.1 in Sweden and 2.9 in Denmark), as compared to national data in the corresponding countries. Forty-one deaths from lung cancer were reported in Sweden (SMR = 2.9, 95% CI, 2.1–3.9), whereas no information on mortality was available from Denmark.

A total of 2342 diatomaceous earth industry workers enrolled in a cohort mortality study in California were considered in three subsequent analyses [12–14]. All subjects were white males, engaged in mining and milling of diatomaceous earth. In the first study, the SMR of lung cancer was 1.29 (95% CI, 1.01–1.61) comparing cohort data with US mortality rates, and 1.44 (95% CI, 1.14–1.80) comparing with local county mortality rates [12]. NMRD mortality was also significantly increased (SMR = 2.01, 95% CI, 1.56–2.55). Further, lung cancer mortality was elevated among subjects at the highest level of cumulative silica exposure (RR = 2.15, 95% CI, 1.08–4.28), with a borderline trend slope (RR = 1.05, 95% CI, 0.99–1.11). After adjustment for smoking, the RR for the highest level of silica exposure decreased to 1.67.

The second study considered the role of silicosis, besides silica exposure, in relation to lung cancer mortality [13]. The analyses were conducted on 1809 men, out of 2342 in the cohort, for whom readable chest radiographs were available. The overall SMRs of lung cancer were 1.19 and 1.57 in workers without (n = 48 deaths) and with (n = 4 deaths) silicosis, respectively. Corresponding SMRs for high cumulative silica exposure were 2.40 (95% CI, 1.24–4.20) and 2.94 (95% CI, 0.80–7.53). Thus, in this cohort the increased risk of lung cancer related to silica exposure was not limited to workers with radiological silicosis, based only on four deaths [13].

The third study was aimed at estimating lung cancer mortality after silica exposure by using various exposure-response models [14]. According to the model that best fitted the data, the linear relative rate model, the RR of lung cancer at mean cumulative silica exposure was 1.6 compared with no exposure. The RR at maximum cumulative exposure was 5.4. Thus, this study supported a linear exposure–response relation between silica exposure and lung cancer mortality.

Among 2933 male workers of a continuous filament fiberglass manufacture from the USA, the SMR of lung cancer were 1.26 (95% CI, 0.92–1.68) as compared to US mortality rates and 1.17 (95% CI, 0.86–1.55) as compared to local mortality rates [15]. Exposures to various occupational agents other than silica (i.e. respirable glass fibers, asbestos, formaldehyde, arsenic, chromium) were reported in the plant, and an effort was made by the authors to investigate them separately in a nested case–control study. Thus, the unadjusted RRs for subsequent levels of exposure to respirable silica were 0.47, 1.07, 0.21 and 0.61, as compared to non-exposed subjects. When the analysis was confined to smokers, the RRs were not materially heterogeneous. Other potential carcinogenic agents considered were also unrelated to lung cancer risk in this study of continuous filament fiberglass workers.

The incidence of lung cancer was investigated using a cohort design among workers of a diatomaceous plant in Iceland [16]. Among 919 men and 423 women, five lung cancer cases were reported during the follow-up period, whereas 4.4 were expected according to sex-specific Icelandic incidence rates (SIR = 1.14). Among subjects with longer duration of employment, there were three lung cancer cases versus 1.3 expected (SIR = 2.34, 95% CI, 0.48–6.85).

Pottery, refractory and sandstone industries workers were analysed in a cohort study conducted in Stoke-on-Trent, UK, including 5115 men [17]. A nested case-referent analysis was also performed, based on 52 lung cancer cases and a total of 247 controls. Silica exposure measurements and smoking data were recorded. Men who had worked previously with asbestos in foundries, in coal mining or had been exposed to other dusts, were excluded from the cohort. There was a marked difference in the number of lung cancers expected deaths by applying England/Wales (35.6) and Stoke-on-Trent (53.1) mortality rates. Observed lung cancer deaths were 68, and the corresponding SMRs were 1.91 (95% CI, 1.48–2.42) and 1.28 (95% CI, 0.99–1.62). In a subcohort analysis, pneumoconiosis was directly related to both cumulative and mean concentration of silica exposure, with no influence of smoking adjustment. On the other side, lung cancer risk was unrelated to cumulative silica exposure (RR = 1.01, 95% CI, 0.85–1.19) and directly associated with mean concentration (RR = 1.67, 95% CI, 1.13–2.47).

A total of 2297 goldminers were examined in a cohort study from Australia [18]. The aim of the study was to assess the relation between measures of silica exposure and subsequent silicosis and lung cancer. Subjects compensated for silicosis were 662 (29%), and 138 deaths from lung cancer and 48 from pneumoconiosis were reported during the follow-up.
period. After adjustment for smoking, the RR slightly increased with a score (1 to 10, based on type of job) for silica exposure (RR = 1.03 for one point increase, 95% CI, 0.999–1.005). Considering the log cumulative exposure, the RR was 1.13 (95% CI, 1.01–1.70), and declined to 1.20 (95% CI, 0.92–1.56) after further adjustment for silicosis. Silicosis was directly associated with lung cancer (RR = 1.59, 95% CI, 1.10–2.28).

A total of 1490 male silicotics were investigated on lung cancer mortality in a cohort study from Hong Kong [19]. Subjects with job histories related to asbestos or polycyclic aromatic hydrocarbons (PAH) exposure were excluded. Thirty-three deaths from lung cancer were observed, whereas 17 were expected on the basis of Hong Kong mortality rates. The SMR increased up to 5.88 (SMR = 1.94, 95% CI, 1.35–2.70). The overall lung cancer risk was significantly above unity (SMR = 1.39), but there were important differences according to the areas considered. Risk was higher for subjects employed in the four Illinois and New Jersey factories (SMR = 2.12), whereas no increased risk emerged among the other four plants combined (SMR = 1.01) [22]. A case–control analysis was undertaken in the same cohort, including 91 lung cancer deaths and 162 matched controls [23]. Information on job histories and smoking habit was obtained, and all the analyses were adjusted for smoking (ever/never). Considering a time-lag of 15 years, the ORs for both lung cancer and silicosis were increased (2.07 and 5.16, respectively) at the highest level of cumulative silica exposure. Results for unlagged exposures were slightly different (RR = 2.58 and 2.13, respectively), but the general indications were unchanged. Lung cancer risk was also directly related with average concentration of silica exposure. A recent update of both cohort and nested case–control studies, with follow-up period extended through year 2000 and exclusion of data from the Canadian plant, confirmed the results [24]. In fact, the SMR of lung cancer after 20 or more years since hire was 1.47 and the OR for the highest level of cumulative silica exposure was 2.66.

Two reports analysed lung cancer risk in another cohort of industrial sand workers [25, 26]. This included 4626 workers (99% males) of 18 plants from 11 states of the US. The follow-up period was from 1960 to 1996. Exposures to potential occupational lung carcinogens other than silica in this cohort were unlikely. Data on smoking habits were available for a subgroup of 404 men. The first report included 109 deaths from lung cancer (SMR = 1.60, 95% CI, 1.31–1.93). No significant exposure-risk trend for cumulative respirable silica was evident in the whole cohort. However, when workers with less than 6 months of employment were excluded, a borderline positive exposure-risk trend emerged (P for trend = 0.06). Nested data for subjects with a detailed working history and at least 6 months of employment were examined. Compared to subjects with low/average silica exposure, subjects with high exposure had a RR of lung cancer of 2.26 (95% CI, 1.17–4.38). Smoking was reported to be more frequent in the cohort than in the general US population, but in a way that was likely to explain only a fraction of the 60% excess lung cancer risk found. In the second report, the authors adjusted the SMR for smoking by applying Monte Carlo sensitivity analysis and Bayesian bias analysis [26]. The adjusted SMRs of lung cancer were 1.43 using both methods (95% limits, 1.15–1.78 and 1.13–1.84, according to the method used, respectively).

Mortality from cancer and other selected causes was studied in an Italian cohort of 1795 miners and millers of non-asbestiform talc [27]. Total mortality was increased (SMR = 1.20), mainly because of excess deaths from oral/oesophageal...
cancers and non-malignant respiratory tract diseases (62 observed deaths from silicosis). No association was found with lung cancer (SMR = 0.94), neither in miners (SMR = 1.07) nor in millers (SMR = 0.69), whereas SMRs of non-malignant respiratory tract diseases were 3.05 in miners and 1.03 in millers. In fact, there was a remarkable difference in the amount of free silica in air dust in mines and mills, due to the high content of quartz in footwall rocks as opposed to the very low content (<2%) of free silica in talc minerals. In spite of such a pattern of exposure, no excess lung cancer was observed in this cohort [27].

Kauppinen et al. [28] analysed data on mortality and incidence from the Finnish cohort included in the IARC Multicentric Study on Cancer Risk among European Asphalt Workers. These workers were potentially exposed to various suspected or known risk factors for lung cancer, such as bitumen fume, PAH, asbestos, diesel exhaust, and silica dust. The SMR of lung cancer was significantly increased for building/ground construction workers (SMR = 1.54), but not for bitumen (SMR = 1.08) and other workers (SMR = 1.47). When exposure to each agent was considered separately, silica dust showed a direct association with lung cancer risk (SMR = 1.45). After adjustment for duration of employment, only the group at highest cumulative silica exposure had an increased RR of 2.26, as compared to non-exposed. Smoking habits were similar to the general Finnish population. Thus, there was some evidence of increased lung cancer risk following silica dust exposure in this cohort, but inference was limited by impossibility to control for other occupational and lifestyle factors.

A Japanese study of whetstone cutters investigated mortality from lung cancer and silico-tuberculosis among 200 male workers [29]. During the observation period, that started in 1955 and ended in 1995, 99 deaths were reported. Six of these, compared with 4.85 expected deaths calculated using the Kyoto Prefecture mortality rates, were due to lung cancer (SMR = 1.24). Five out of six subjects deceased from lung cancer had complication with silicosis.

Two papers that updated results from the Vermont cohort study of granite workers, including data on 5414 subjects, were published in 2004 [30, 31]. Their opposite conclusions well illustrate controversies of the issue. The first paper [30], with follow-up to 1994 (201 deaths for lung cancer), considered the cumulative exposure to respirable free silica. The SMR of lung cancer for all subjects was 1.17 (P < 0.05). Risk increased with cumulative silica exposure, up to a SMR of 1.70 (P < 0.01) at 3.0–5.9 mg-yr/m³, but there was no association (SMR = 1.16) at the highest level of exposure (≥6.0 mg-yr/m³). In consideration of the lack of other occupational confounding exposures in this cohort, the authors concluded that there was an exposure–response association between silica and lung cancer. The second paper [31], with follow-up extended to the end of 1996 (and 211 deaths for lung cancer), separately considered employees before and after 1940 (since dust control measures were adopted in 1940), as well as shed and quarry workers. The SMR of lung cancer for all workers was 1.18 (95% CI, 1.03–1.35). Shed workers were at higher risk (SMR = 1.31) than quarry workers (SMR = 0.74). For subjects employed before and after 1940, the SMRs were 1.26 and 1.13, respectively. Dust exposure measures radically reduced deaths from silicosis in subjects employed thereafter, but had little effect on lung cancer mortality. Further, quarry workers had high quartz dust exposures and increased mortality from silicosis, but no excess risk of lung cancer. Therefore, the authors attributed the overall 18% excess risk of lung cancer to confounding by smoking rather than exposure to quartz dust.

A mortality study from New South Wales considered 1467 men who received compensation for silicosis [32]. The follow-up period was from 1968 to end of January 2000, and information on smoking status (never, ex, current smokers) was available from 1970. The SMR of lung cancer was 2.15 (95% CI, 1.74–2.63). After standardization for smoking status, the SMR was lower but remained highly significant (SMR = 1.90, 95% CI, 1.54–2.33). The authors cautiously underlined that incomplete allowance for smoking and particularly for chronic obstructive pulmonary diseases, besides silica exposure, could explain the excess risk.

Another mortality study was conducted in Italy and included 1291 males employed in the graphite electrode manufacturing, where exposures to silica and graphite dusts, PAH and asbestos have been reported [33]. A high level of silica exposure was supported by the reported excess risk of death from silicosis in this cohort (79 observed versus 1.2 expected deaths), whereas lung cancer risk was not increased (SMR = 0.97, 95% CI, 0.67–1.37). Limits of this study were the absence of data on specific jobs and exposures of each worker and of measurements of silica exposure.

A prospective study in Austria considered 1630 male workers ≥40 years old exposed to dusts and 1630 non-exposed workers matched on selected characteristics, including smoking status at enrolment, over the period 1950–2000 [34]. Among dust exposed workers, 189 men died of lung cancer, as compared to 149 among those non-exposed (RR = 1.42, 95% CI, 1.14–1.76). The RRs of silicosis were high in foundry workers and low in men employed in other metal industries, based on measures of silica exposure in the different workplaces performed in the 1960s. RRs of lung cancer were higher for workers of the brick and stone industry and for glass and pottery workers, whereas RRs of silicosis for these job categories were 0.76 and 0.85, respectively. Further, risk was not significantly increased in silicotics as compared to non-silicotics. The authors concluded that crystalline silica was not the main cause of excess lung cancer risk.

A study conducted in Lithuania analysed both incidence and mortality using data from a cohort of cement production workers [35]. The factory produced Portland cement, which contains hexavalent chromium. There were 2498 subjects who were followed from 1978 to the end of 2000, for a total of 43 490 person-years. There were 36 male (SMR = 1.4, 95% CI, 1.0–1.9) and two female deaths (SMR = 1.4, 95% CI, 0.3–5.5) for lung cancer. As concerns incidence, SIR were slightly higher (1.5 in men and 1.7 in women) and there was no significant trend in risk with increasing levels of cumulative dust exposure, though the SIR were 2.15 (95% CI, 1.74–2.63). After standardization for smoking status, the SMR was lower but remained highly significant (SMR = 1.90, 95% CI, 1.54–2.33). The authors cautiously underlined that incomplete allowance for smoking and particularly for chronic obstructive pulmonary diseases, besides silica exposure, could explain the excess risk.

Female workers employed between 1945 and 1978 in 10 US fiberglass Industries were investigated according to their risk of respiratory system cancers (RSC) [36]. The study included
4008 women, most of whom were exposed to various potential carcinogens. Silica was not the central issue of this study, but rather a co-exposure. In fact, only 12% of women included in this cohort were exposed to silica. Fifty-three cases of RSC were reported, 52 of which were lung cancers. The overall SMR of lung cancer was 1.02 (95% CI, 0.76–1.34), compared with local county mortality rates. Silica exposure was not associated with lung cancer. The corresponding expected values calculated using UK mortality rates were 77.7 and 2.8, thus the SMR were 0.97 (95% CI, 0.96–0.99) for non-exposed subjects, 1.10 (95% CI, 1.06–1.14), 1.17 (95% CI, 1.12–1.21) and 1.31 (95% CI, 1.10–1.55) for levels of silica exposure of ≤0.9, 1.0–9.9 and ≥10.0 mg/m³-years, respectively. When internal comparison was performed, after adjustment for age, period, social class, smoking and asbestos exposure, the RRs of lung cancer for subsequent levels of silica dust exposure were 1.05 (95% CI, 1.00–1.10), 0.97 (95% CI, 0.91–1.03) and 1.42 (95% CI, 1.20–1.70) as compared to non-exposed. Thus, this study found an increased lung cancer risk in subjects occupationally exposed to silica, and suggested a possible threshold effect as the excess risk was mainly attributable to workers with cumulative silica exposure ≥10 mg/m³-years.

**case–control studies**

Table S2 (available as supplementary data online) reports data from case–control studies that investigated the relation between silica exposure and lung cancer.

De Stefani et al. [41] analyzed, in a case–control study from Uruguay, various occupational risk factors for lung cancer. After adjustment for cigarette smoking and other covariates (not including concurrent occupational exposures), they found an odds ratio (OR) of 1.6 (95% CI, 1.1–2.3) for subjects who had ever been exposed to silica dust (n = 125 cases), and of 1.8 (95% CI, 1.2–2.8) for ≥21 years of silica exposure.

Seventy-eight lung cancer cases were matched to 386 controls in a nested case–control study of South African goldminers, with the aim of analyzing the role of occupational risk factors and silicosis [42]. Various regression models were applied, the best of which included smoking and silicosis status (RR = 2.45, 95% CI, 1.2–5.2). In the model including cigarette consumption and cumulative dust exposure, the RRs of lung cancer for increasing levels of dust exposure were 1.83, 1.85 and 3.19. When smoking, cumulative dust exposure and silicosis were considered together, the RR for the highest level of dust exposure declined to 1.93 (95% CI, 0.8–5.0), and the RR for silicosis was 2.10 (95% CI, 1.0–4.6). Thus, silicosis appeared to be more important than dust exposure for lung cancer in this study. Further, cigarette smoking and silicosis showed a strong multiplicative effect (RR = 48.9 for silicotics at highest cigarette consumption). Similar results were previously reported for the combination of smoking and cumulative silica exposure in the same study [43].

Finkelstein [44] re-analysed data from a cohort of workers under surveillance for silicosis in Ontario, by recoding
radiographs according to the ILO 1980 Classification, in a nested case–control study of lung cancer. Particular attention was given to potential confounding by smoking, using computer simulations as only one out of 42 lung cancer cases had never smoked. The RR of lung cancer was 3.27 (95% CI, 1.32–8.2) for subjects with ILO classification ≥1/0 as compared to ≤0/1. Adjustment for cumulative radon exposure increased the risk. The author concluded that, even though small smoking differences could explain the increased lung cancer risk among silicotics, the empirical evidence was against the existence of any such difference.

Non-silicotic workers of the stone, quarrying and ceramic industries were included in a German case–control study of lung cancer [45]. Cases (n = 247) and controls (n = 795) were matched by smoking habit, and their exposure to silica dust and other occupational agents was assessed by industrial hygienists. All RRs were adjusted for time-related factors of silica exposure, and for other occupational exposures. Lung cancer risk was not associated with different measures of silica exposure: the RRs for high versus low level were 1.02 for cumulative, 0.91 for average and 0.85 for peak exposure. When cumulative exposure was divided into quartiles, the RRs were 0.95, 0.92 and 1.04 for subsequent levels of exposure, with compared to the lowest one. Differences in risks between stone/quarry and ceramics workers were negligible.

In a pooled analysis of two German case–control studies, including a total of 3498 male cases and 3541 controls, the relation between occupational exposures to selected agents and lung cancer risk was analysed [46]. The study design permitted to estimate ORs after adjustment for smoking and asbestos exposure. The OR of lung cancer for subjects ever exposed to crystalline silica was 1.41 (95% CI, 1.22–1.62). The RR increased with levels of cumulative silica exposure up to 1.91 (95% CI, 1.39–2.63) for >5 mg/m³. Many of the workers exposed to silica were coal-miners, for whom the OR after >20 years of employment was 2.77 (95% CI, 1.34–5.74).

The relation between silica exposure, silicosis, NMRD and lung cancer risk was examined in a nested case–control study conducted in 29 Chinese mines and potteries, including 316 lung cancer cases and 1356 controls [47, 48]. A first report from this study analyzed potential interactions between NMRD and lung cancer risk according to cumulative silica exposure [47]. In subjects with no history of chronic bronchitis, risk increased with quartiles of cumulative silica exposure (RR = 1.3, 1.6, 1.8 and 1.4 as compared to non-exposed). Lung cancer risk was not associated with silica exposure in those with a history of chronic bronchitis or pulmonary tuberculosis. A second report among the same data investigated the modifying role of silicosis and potential occupational lung carcinogens other than silica on the relation between silica and lung cancer [48]. The RRs of lung cancer were 1.1, 1.5, 1.6 and 1.2 for subsequent quartiles of cumulative silica exposure, compared with non-exposed, after adjustment for age at first exposure and smoking. Exclusion of silicotics and adjustment for radiological classification of pneumoconiosis did not substantially alter these estimates. The RR of lung cancer was 1.5 for silicotics, and the risks were similar at different degrees of silicosis and by radiological evolution (all RRs between 1.3 and 1.5). An increased risk was observed only among silicotics exposed to another occupational lung carcinogen. Among subjects with silica exposure, the risk was somewhat higher for those not exposed to nickel (RR = 1.7), radon-daughters (RR = 1.6) and particularly PAH (RR = 2.4) than for those exposed to these agents (RRs = 1.3, 1.1 and 1.3, respectively).

Occupational risk factors for lung cancer were examined in a nested case–control analysis in the French cohort of employees of the national electricity and gas company (EDF-GDF) [49]. Three hundred and ten cases of lung cancer, diagnosed between 1978 and 1989, were compared with 1225 randomly selected subjects working in the company, and matched by year of birth. The OR of lung cancer for those ever exposed to silica was 1.59 (95% CI, 1.08–2.35). ORs were 1.79, 1.23, 1.18 and 2.37 according to increasing levels of cumulative silica exposure, with a direct trend in risk (trend OR=1.04, 95% CI, 1.01–1.07, for an increase of one level (quartile) of exposure). The authors found a significant increase in risk of lung cancer even though exposures to crystalline silica in this cohort were probably lower than in other industries.

From a cohort of 24 490 iron and steel foundry workers, a nested case–control study including 144 men with lung cancer and 558 controls was performed [50]. As iron and steel foundry workers face various occupational risk exposures for lung cancer, these were considered separately according to the production process. No measurement of exposure to silica or other potential lung carcinogens was available. The highest risks were found in workers of the blast furnace (OR = 2.11, as compared to a group of subjects not employed in metal production) and foundry (OR = 1.91), after adjustment for smoking habit. These production processes could entail exposures to silica, PAH, chromium, nickel and welding fumes.

Pulp and paper workers of a Polish mill were investigated in a study including 79 lung cancer cases and 237 controls, from a cohort of 10 460 subjects [51]. All ORs were adjusted for smoking, while no information was available on silicosis. Exposure to various types of dust was examined. The highest concentrations of silica were found in kaolin (3.2–5.1%) and coal dusts (2.9–4.6%). Even if silica concentrations in dusts were relatively low, very high levels of dust exposure were reported in the factory. For exposure to coal dust, the RR of lung cancer was 0.96, whereas for other inorganic dust the RR was 3.99. For exposure to paper dusts, that had free crystalline silica concentrations of 1.1–1.4%, the RR was 0.79.

An update from a Chinese study of workers of four tin mines was published in 2002 [52]. In a cohort of 7855 subjects, 130 male lung cancer cases were observed between 1972 and 1994. These were matched by age and mine to 627 controls. Information was available on demographic factors, smoking habits, silicosis, cumulative silica dust exposure and, after 1988, measures of other potentially confounding factors including arsenic, PAH and radon exposure. Similar dust concentrations in all the tin mines were reported, whereas arsenic concentration, which was positively related to lung cancer, was high in three mines in Dachang and low in the Limu mine. There was a direct association between cumulative dust, duration of exposure and lung cancer (RRs = 2.8 and 2.3 for the highest categories of exposure, respectively). Silicosis was directly related to lung cancer risk in workers of Dachang but not of Limu tin mines. Although there was some evidence...
that high exposures to dust might raise lung cancer risk, it was likely that arsenic had a more important role than crystalline silica in the increased mortality from lung cancer in this study.

A case–control study was performed in a Japanese region with many refractory bricks and pottery factories [53]. An advantage of this study was that occupation in these settings is unlikely to involve exposures to other lung carcinogens, such as PAH and radon. Lung cancer deaths (n = 184) were compared to three groups of subjects deceased for liver (n = 119), colon (n = 66), and other cancers (n = 132). According to the comparison group used, the age and smoking adjusted ORs of lung cancer ranged between 1.59 and 2.13 for silica exposure and between 2.45 and 2.94 for silicosis.

Exposures to asphalt fumes and respirable crystalline silica were evaluated in relation to lung cancer risk in a case–control study including 39 cases and 133 controls that were employed in asphalt roofing manufacturing and asphalt production [54]. Risk was non-significantly increased for subjects reporting the highest level of cumulative silica exposure (OR = 1.31 or 1.49, according to the method used to estimate the exposure).

An US case–control study used death certificates from the National Occupational Mortality Surveillance system to investigate the relation between exposure to crystalline silica and various diseases, including lung cancer [55]. The matched control group was made of subjects whose death certificate did not mention any of the diseases likely associated with silica exposure. In the 27 states examined for the period 1982–1995, a total of 396 481 death certificates mentioned lung cancer and were matched to 1 964 005 controls. Silica exposure was assessed by industrial hygienists, who assigned each occupation/industry pair reported on death certificates into four exposure categories. As compared to low/no exposure, the mortality RRs were 0.88 (95% CI, 0.87–0.90) for intermediate, 1.13 (95% CI, 1.11–1.15) for high and 1.13 (95% CI, 1.06–1.21) for very high exposure to crystalline silica. Combining the three categories, the OR for ever exposed subjects was 0.99 (95% CI, 0.98–1.00).

The relation between various occupational exposures and lung cancer risk was investigated in a case–control study conducted in New Caledonia [56]. After adjustment for age, ethnicity and smoking, the OR for men exposed to silica was 0.9 (95% CI, 0.5–1.6). There was no evidence of an increasing trend in risk with cumulative silica exposure, as an elevated risk was observed only for the lowest quartile of exposure.

A case–control study of lung cancer, nested in a cohort of 5016 workers of seven aluminium foundries and remelting plants, was conducted in Sweden [57]. Analyses were based on 31 subjects with lung cancer and 233 controls, employed for at least 1 year in the factories considered. As compared to subjects reporting no quartz exposure, the ORs of lung cancer were 1.6 (95% CI, 0.5–4.6) and 2.5 (95% CI, 0.7–9.2) among subjects with cumulative quartz exposures of 0.001–1.0 and >1.0 mg/m³-year, respectively.

**proportionate mortality ratio (PMR) studies**

Table S3 (available as supplementary data online) reports data from two PMR studies that investigated the relation between silica exposure and lung cancer.

The first PMR study was conducted in 24 of the US and analyzed death certificate data for 1984–1993, according to occupations or industries related to silica exposure [58]. The PMRs of all respiratory system cancers were 1.11 (95% CI, 0.82–1.46) and 1.15 (95% CI, 1.13–1.17) for women and men with probable silica exposure, respectively.

The second PMR study, including about 84 000 members of the IUBAC association, was conducted in the USA [59]. Among 10 386 deaths that occurred in the period 1986–1991, 1244 were caused by lung cancer. The PMRs of lung cancer were 1.44 (95% CI, 1.36–1.53) for white men and 1.21 (95% CI, 0.92–1.56) for non-white men. Elevated risks were observed in white men also for oesophageal and other respiratory tract cancers and for NMRD, including asbestosis (13 deaths, PMR = 5.54) and silicosis (four deaths, PMR = 3.22), though the latter risk was not significant. Silica and asbestos, besides smoking, were the chief exposures that could explain these excess deaths.

### pooled- and meta-analyses

Three quantitative reviews were conducted between 1996 and 2005 in an effort to summarize the relation between silica exposure and lung cancer risk. In a meta-analysis of two cohort studies that provided quantitative estimates of lung cancer risk in relation to cumulative silica exposure, it was calculated that risk increased by about 16% per mg/m³-year [60], Steenland et al. [61] pooled data of 10 cohort studies, and thus examined a total of 65 980 subjects (67% of those were miners) and 1072 deaths from lung cancer. According to subsequent quintiles of cumulative silica exposure, the RRs of lung cancer were 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).

Therefore, this pooled analysis found an increasing trend in risk with cumulative exposure [61]. A recent meta-analysis of 30 studies found a pooled RR of lung cancer of 1.32 (95% CI, 1.23–1.41) in subjects exposed to crystalline silica [62]. In the same investigation, the pooled RR was 2.37 (95% CI, 1.98–2.84) in silicotics only (based on 16 studies), whereas no increase in risk emerged in non-silicotics (pooled RR = 0.96, 95% CI, 0.81–1.15, based on eight studies). The authors concluded that silica may induce lung cancer indirectly, probably through silicosis [62].

### meta-analysis and discussion

Summary results of the relation between silica exposure and lung cancer risk by silicosis status from cohort, case–control and PMR studies carried out between 1996 and 2005 are shown in figures 1 to 3. Different patterns emerged according to different studies and subcategories. The pooled RR from studies of silicotics only (seven cohort, one case–control) was 1.74 (95% CI 1.37–2.22) suggesting a close relation between silicosis and lung cancer and supporting old theories on the role of pulmonary fibrosis induced by silica.

This is in agreement with the data reported in the IARC Monograph [2] which, without pooling the RRs, showed a high proportion (84%) of RRs above unity and significant for lung cancer from case–control and cohort studies of silicotics.
Figure 1. Relation between silica exposure and risk of lung cancer: cohort studies.1

1Some of the studies in Table S1 are not present here because other data from the same cohort study are reported in Figure 1.
2Incidence
3Pooled data were computed from the RR presented in Table 1.

However, some questions still arise. The first regards the definition of silicosis itself and specifically whether identification of silicotic subjects by compensation lists was further confirmed by radiology and/or autopsy examinations. The second is concerned with the assessment of a relation between severity of silicosis and lung cancer risk. Two of the studies considered in this review [19, 21] concluded that the trend was unclear. Another study on Chinese miners and pottery workers [48] reported no increase in cancer risk with increasing silicosis degree. In that study, however, an increased lung cancer risk was observed only among silicotics exposed to another occupational lung carcinogen. We suggest as a possible explanation that lung function impairment following high degrees of silicosis may act as a competing cause of death as well as chronic obstructive pulmonary disease [21, 32]. Thirdly, the role of co-exposures cannot be ruled out. Some co-exposures are deducible on the basis of common knowledge (e.g. foundry workers in the study from Starzynski et al. [9]), some are stated by the authors (e.g.: potential exposure to radon in the study from Brown et al. [11]), some are controlled for by excluding co-exposed workers (PAH and asbestos in the study from Chan et al. [19]). It is difficult to assess to what extent these points may affect the overall evaluation.

Although the role of silicosis is somewhat difficult to address, a support to the epidemiological evidence as a whole comes from results of experiments in rats, the only species which...

<table>
<thead>
<tr>
<th>Study or sub-category (reference no.)</th>
<th>RR (random)</th>
<th>RR (95% CI)</th>
<th>Year</th>
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<td>[0.98, 1.91]</td>
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<td>[1.35, 2.70]</td>
<td>2000</td>
</tr>
<tr>
<td>Checkoway (13)</td>
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<td>[0.43, 4.03]</td>
<td>1999</td>
</tr>
<tr>
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<td>1996</td>
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<tr>
<td>Starzynski - foundries (9)</td>
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<td>[1.04, 2.01]</td>
<td>1996</td>
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<th>RR (95% CI)</th>
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<td>Cherry (17)</td>
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<td>[1.48, 2.42]</td>
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<td>McDonald (24)</td>
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<td>Ogawa (29)</td>
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<td>2003</td>
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<td>[1.11, 1.17]</td>
<td>2005</td>
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<td>Pukkala - women 2.3 (40)</td>
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<td>[1.12, 1.60]</td>
<td>2005</td>
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<td>Rahnsson 2 (16)</td>
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<td>Steenland (26)</td>
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<td>[1.15, 1.78]</td>
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<td>Subtotal (95% CI), random effects</td>
<td>1.25</td>
<td>[1.18, 1.33]</td>
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<table>
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<th>RR (95% CI)</th>
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<td>Checkoway (13)</td>
<td>1.19</td>
<td>[0.87, 1.57]</td>
<td>1999</td>
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<tr>
<td>Subtotal (95% CI), random effects</td>
<td>1.19</td>
<td>[0.87, 1.57]</td>
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</table>

| Subtotal (95% CI), fixed effects          | 1.34        | [1.25, 1.45] |      |
| Total (95% CI), fixed effects             | 1.19        | [1.16, 1.21] |      |
showed a carcinogenic response to silica. It was recently stated [63] that ‘the close association of epithelial proliferations with adjacent silicotic granulomas indicate the importance of cell–cell interactions between mesenchymal cells (macrophages, monocytes, fibroblasts, mast cells) and the adjacent epithelial cells’, (…) ‘and their cascade of mediators’. The issue of assessing whether silica itself increases lung cancer risk in the absence of silicosis is much more controversial. The pooled RR from cohort studies of exposed workers with undefined silicosis status was 1.25 (95% CI, 1.18–1.33) whereas the RR for silica exposed, non silicotic subjects was based on two studies only – one cohort study (RR = 1.19, 95% CI, 0.87–1.57) [13] and one case–control study (RR = 0.97, 95% CI, 0.68–1.38) [45]. The pooled RRs were 1.41 (95% CI: 1.18–1.67) for case–control and 1.24 (95% CI: 1.05–1.47) for the two PMR studies.

This points to both a moderately increased lung cancer risk and the problem of whether the lower RR for exposed non silicotics or not defined as such is related to dose (i.e.: the higher RR in silicotics is related to higher exposure, not excluding that lower doses not able to induce silicosis are still able to induce cancer, as in the case of asbestos) or it is the expression of the uncertainty of the data.

It is a limitation of a meta-analysis to take the risks from single studies at their face value (i.e. to disregard the possible effect of several factors reported in detail thereafter). Such
factors may affect risk estimates, and can be identified by only a full examination of data reported in tables S1 to S3 (online) and include:

A) The use of national rates versus local rates as reference. In a Checkoway et al. [8] study, local rates produced a lower risk as compared to US rates. Opposite results were obtained in another study of the same author [12]. In a study of Cherry et al. [17] the RR was substantially lower when using Stoke-on-Trent rates as compared to England and Wales rates. Chiazze et al. [15] and McDonald et al. [22, 24] showed similar results when using US or local rates.

B) Controlling for smoking. Adjusted rates were reported in some studies, whereas in some other there was indication that they were not adjusted. In most cohort studies there was no indication on smoking data at all, whereas in case–control studies information was available.

C) Stratified analysis according to silicosis status. This is a very important point since the subcategory ‘undefined silicosis’ represents the largest body of cohort studies. Clear indication that some results were adjusted for silicosis is given only by De Klerk and Musk [18] and by Checkoway et al. [13] when examining dose–response relationship. Among case–control studies, adjustment for silicosis showed a stronger effect together with smoking on RR in a study from Haizdo et al. [42], whereas in the study from Cocco et al. [48] no effect was found for the presence of silicosis on death rates. In the Chen and Chen [52] study the risk declined at silicosis stage III. Checkoway et al. [13] and Ulm et al. [45] provided results for non silicotic workers, thus allowing separate analyses to be carried out.

D) Co-exposures to other established or likely lung carcinogens were reported in several studies. Co-exposures to asbestos, formaldehyde, arsenic and chromium, were reported by Chiazze et al. [15], to PAH by Moulin et al. [20] and Merlo et al. [33], to diesel exhaust, bitumen fume, asbestos by Kauppinen et al. [28], to hexavalent chromium by Smailyte et al. [35], to uranium by Haizdo et al. [42], to PAH, chromium, nickel and welding fumes by Rodriguez et al. [50], to arsenic by Chen and Chen [52], to asphalt fumes by Watkins et al. [54]. Potential co-exposure to asbestos and hexavalent chromium was considered by Finkelstein and Verma [39]. Possible asbestos exposure was suggested by Rice et al. [14]. Another author [34] showed an elevated risk in foundries. The effect of co-exposures depends upon carcinogenic potency, exposure level and the number of workers involved; thus, it cannot be easily controlled for in the data analysis. Only a few studies could adjust for asbestos co-exposure [40, 46, 49].

E) Past exposure assessment. Some studies report a categorical subdivision only (say low, medium and high exposure), others use exposure duration as a surrogate measure of actual exposures. In several studies an effort was made to develop quantitative exposure estimates based on existing data for the past which were used or converted to the current measurement methods (mg/m³ respirable silica dust). This is a crucial point since quantitative data are aimed at better defining the shape of the dose-response relation and eventually at defining ‘safe levels’ of exposure. Even when gravimetric measurement methods were available for the past it is difficult to rely upon, since at concentration of the order of 0.025–0.05 mg/m³ an error of about 50% is associated with such levels. The uncertainty is much higher when exposure estimates are based on statistical models for past exposure level, or when conversion factors are used from particle count to gravimetric dust. This implies that measurements in million particles per cubic foot (mppcf) or particle per cubic centimetre (ppcc) have to be converted to total quantitative dust, then to respirable dust and finally to respirable crystalline silica. Although this procedure was used by Mannetje et al. [64] to provide accurate estimates of exposures for the Steenland et al. [61] pooled analysis, we can only suggest that they should be taken with caution. For example, it is not clear why in the same study surface mine workers were considered as unexposed and were excluded from the SMR analysis. The minimal level of exposure assigned to these workers (0.01 mg/m³) seems to be exceedingly low on the basis of common knowledge (and personal experience of one of the authors).

F) Dose–response relationship. This point needs to be examined in detail since there are inconsistencies across both cohort and case–control studies. Among cohort studies, when categorical or exposure duration subdivisions were used [16, 27, 28, 31, 33] no clear trend was found. When cumulative exposure (mg/m³-y) was used, Checkoway et al. [12] found a borderline trend in slope. The same author reported a significantly elevated RR only for workers with cumulative exposure higher than 5 mg/m³-y. Steenland et al. [25] showed no clear trend in the whole cohort and a slope close to statistical significance (P = 0.06) when excluding workers with less than 6 months employment. No trend at all was found in the Smailyte et al. [35] and Brown and Rushton [38] studies. A clear trend was reported by Pukkala et al. [40] after asbestos exposure adjustment and in the nested case–control study from McDonald et al. [24]. No better evidence is provided by case-control studies. Here, among 10 studies out 12 where dose–response relation was evaluated, only two showed a significant trend, one [46] by using cumulative exposure after asbestos adjustment and the other [49] by using undefined cumulative exposure levels and adjusting for asbestos exposure. All of the others showed no clear trend. As far as non silicotic subjects are concerned, Checkoway et al. [13] results showed no clear trend but a higher SMR at the highest exposure level. The Ulm et al. [45] study also showed no trend in risk. As far as other pooled analysis are concerned [61] the increasing trend in risk with cumulative exposure was considered as a support of silica carcinogenicity, although the author stated that, by comparison, ‘silica appears to be a weaker carcinogen than other lung carcinogens’. This shallow exposure-risk relation is hard to interpret.

G) The authors’ interpretations of their own findings. A few examples may well illustrate the situation. Kauppinen et al. [28] reported that inference which may be gained by the increased risk (RR = 1.45) was limited by impossibility to control for other occupational factors (nor it will be possible in the future for asphalt workers, authors’ note). Chen and Chen [52] stated that arsenic exposure was more important than silica in explaining the increased risk in tin miners (RR = 2.19) and that probably dust particles may act as an arsenic vector. Graham et al. [31] stated that, according to an internal analysis, the overall risk (RR = 1.19) ‘do not support’
silica carcinogenicity. Moshammer and Neuberger [34] concluded that crystalline silica was not the main cause of excess lung cancer risk (RR = 1.42). On the other hand, there are some studies in which the authors try to explain the negative findings on the basis of statistical power or simply do not discuss them [33].

Further insights may be gained by splitting the overall meta-analysis (excluding silicotics) into different occupational settings, assuming more homogeneity of occupational exposures. Therefore, we examined separately (a) miners, (b) sand workers, (c) diatomaceous earth, ceramic, refractory brick workers, (d) other workers included in studies with miscellaneous exposures (Table 1).

Workers included in subsets (c) and (d) show similar risks, though lower confidence limits are around unity (0.99 and 1.02, respectively) in case–control studies and marginally above (1.1) in cohort studies. On the contrary, the pooled RR for miners are slightly higher in case–control studies than in cohort studies; however, the former includes studies [42, 48, 52] which are affected by the factors already reported. The risk estimate among sand workers is limited to two positive studies [22, 24–26] and one negative study [38], which altogether gave a pooled RR of 1.29 (95% CI, 1.03–1.61).

It has long been reported [65] that quartz is a variable entity, its toxicity depending upon surface characteristics related, among other factors, to the age of crystalline silica particles. This cannot be verified on an epidemiological basis, even when considering various subsets of occupational exposures.

On the basis of the meta-analysis which shows a moderately increased risk for workers with undefined silicosis status, no increased risk in non-silicotics (though based on two studies only) and on the evaluation of single studies which underlines the drawbacks and limitations of most of them, the available data leave open the issue as to whether silica per se materially increases lung cancer risk in absence of silicosis.

The silicosis–cancer association is now established, in agreement with other studies and meta-analysis.

**acknowledgements**

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