IN-DEPTH REVIEW

Silica exposure, smoking, silicosis and lung cancer—complex interactions

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Background Establishing a clear relationship between workplace exposures and cancer is often difficult. The latent period for cancer development can make it difficult to establish a definite cause–effect relationship. The picture is further complicated by variable job histories, concomitant exposure to other carcinogens and other factors such as genetic susceptibility and poor nutrition. The lack of accurate and detailed record keeping may potentially mask informative differences among group of workers. Removing or reducing exposures to probable and known carcinogens, however, can prevent workplace cancer.

Aim This paper gives an overview of the literature reporting investigations of the relationship between exposure to silica and development of lung cancer with a focus on the controversy concerning the roles of silicosis and smoking in the development of cancer.

Method A literature search was conducted to identify epidemiologic papers on silica, silicosis and lung cancer using electronic databases (MEDLINE, PubMed, Web of Science) from 1996 onwards and paper bibliographies.

Results If silicosis were the necessary step leading to lung cancer, enforcing the current silica standards would protect workers against lung cancer risk as well. Alternatively, a direct silica–lung cancer association that has been suggested implies that regulatory standards should be revised accordingly.

Conclusion Further research is needed in order to understand the complex pattern of interactions leading to lung cancer among silica-exposed workers (and cancers and workplace exposures in general) and to understand whether and to what extent other workplace lung carcinogens, total respirable dust and total surface size and age of silica particles affect the carcinogenic potential of silica. In addition, the apparent paradox of a lower lung cancer risk in some workplaces with high-level silica exposure needs further investigation.

Key words Lung cancer; occupation; silica; silicosis.

Introduction

Silica is the name given to a group of minerals composed of silicon and oxygen, the two most abundant elements in the earth’s crust. It occurs most commonly in a crystalline form, and more rarely an amorphous state. The three main crystalline forms are quartz, tridymite and cristobalite, the first being so abundant that it is often used in place of the general term crystalline silica (CS). Cristobalite and tridymite are found in rocks and soil and are produced in some industrial operations when quartz or amorphous silica is heated (such as foundry processes, calcining of diatomaceous earth, brick and ceramics manufacturing and silicon carbide production). Quartz is a common component of soil and rocks and consequently workers are potentially exposed to quartz dust in many occupations and industries (Table 1). In 1990–93, Carex estimated ~600 000 workers were exposed to CS in Great Britain [1] with >3 million in Europe [2].

Occupational exposure to respirable crystalline silica (RCS) is a serious but preventable health hazard. Prolonged exposure to RCS has long been known to cause one of the oldest known industrial diseases, silicosis, and it has been observed that there is a greater risk in workers exposed to very fine particles of CS, as found in quartz and cristobalite flours [3]. More recent epidemiological studies of occupational exposure to RCS have reported an increased incidence of (or mortality from) extrapulmonary diseases such as rheumatoid arthritis [4–6], scleroderma [7,8], other autoimmune diseases [9,10] and non-malignant renal disease [11,12].
This paper gives an overview of the literature reporting investigations of the relationship between exposure to silica and development of lung cancer with a focus on the controversy concerning the roles of silicosis and smoking in the development of cancer.

Methods

A literature search was conducted to identify epidemiologic papers on silica, silicosis and lung cancer using electronic databases (MEDLINE, PubMed, Web of Science) from 1996 onwards and paper bibliographies. Key search terms were combined to obtain the most relevant papers (lung cancer, silicosis, occupational and silica).

Carcinogenic effects of silica exposure

Several studies have found an association between RCS exposure and a number of cancers, including oesophageal [13,14], stomach [15,16], skin [17,18] and bone [19,20]. However, the findings have been inconsistent and in most studies, there has been joint exposure to other risk factors. More important is the link between RCS exposure and the risk of lung cancer.

In 1997, the International Agency for Research on Cancer (IARC) reclassified CS from a Group 2A to a Group 1 carcinogen, after assessment of epidemiological studies where there was a low possibility of confounding from other exposures. IARC concluded that there was sufficient evidence in humans to classify CS inhaled in the form of quartz or cristobalite from occupational sources as carcinogenic to humans [21]. In addition, the National Institute for Occupational Safety and Health [22] and the National Toxicology Program [23] have also concluded CS is a human carcinogen. However, the IARC working group noted that the carcinogenicity was not found in all industrial circumstances studied and was perhaps dependent on the inherent characteristics of the CS or on external factors affecting its biological activity or distribution of it polymorphs; a long debate followed the monograph’s publication [24–28], and continues today.

This complex issue was highlighted when two 1995 reviews of virtually the same published reports on CS and lung cancer came to different conclusions: one summarized ‘there is sufficient evidence to classify CS as a human carcinogen’ [29], whereas the second concluded that ‘there is little evidence of any increase in lung cancer in the absence of silicosis or at relatively low levels of exposure or disease prevalence’ [30]. More recently two studies of Vermont granite workers came to opposite conclusions, further illustrating the controversies of the issue [31,32]. Attfield and Costello [31] suggested in consideration of the lack of other occupational confounding exposures that there was an exposure–response association between CS and lung cancer. However, Graham et al. [32] attributed the overall excess risk of lung cancer to confounding by smoking rather than exposure to CS dust.

Lung cancer and the role of silicosis

In the studies considered by IARC, they reported that lung cancer risk tended to increase with cumulative exposure to RCS, duration of exposure, peak intensity of exposure, the presence of silicosis and length of follow-up time from diagnosis of silicosis. However, the findings were not consistent, i.e. those that observed a relationship with cumulative exposure did not always observe one with duration of exposure and vice versa.

Since the IARC publication in 1997, there have been in excess of 50 papers published of studies exploring the association between CS exposure (and silicosis) and lung cancer, plus a number of reviews [34–37]. Studies of the risk of lung cancer in subjects on silicosis case registers have consistently shown an excess risk. However, a number of studies have pointed out that it is not clear to what extent these increased risks represent a direct effect of CS exposure, a secondary effect of the silicosis, preferential inclusion of subjects suffering from the effects of smoking or bias in diagnostic accuracy [24,27,38].

Several meta-analyses have examined the risk of lung cancer in populations exposed to CS. Prior to the IARC (1997) monograph, Smith et al. [33] calculated the pooled relative risk (RR) to be 2.2 (95% confidence interval = 2.1–2.4), with slight variations between study types. Tsuda et al. [34] examined the relationship between pneumoconiosis and lung cancer in 32 studies.
Silica exposure and smoking interactions

Smoking is by far the largest risk for lung cancer and must be considered in any occupational study of lung cancer. Recent reviews of studies of the interaction between smoking and occupational exposure to asbestos suggest that it may be greater than additive but somewhat less than multiplicative [40–43]. In the study of the association of CS and lung cancer, the interaction of smoking and other factors is less clear, and some have suggested the investigation is at the same stage asbestos was 20 years ago [28]. However, results from a multi-centre case-control study do not suggest an interaction between tobacco smoking and exposure to silica on the risk of lung cancer beyond a multiplicative model [44]. The increased risk of exposure to CS was, however, less apparent after adjustment for smoking, indicating the possibility of some confounding from smoking. Smokers who were exposed to silica dust have been found to develop clinical silicosis more frequently than non-smokers exposed to the same dose [24,45–47], implying that silicotics who were smokers would have on average lower cumulative exposure to CS dust than silicotics who were non-smokers. The lower average exposure among smokers could then explain the lower risk when compared with non-smokers.

The situation is further complicated because, like asbestos, there appear to be interactions between physical and biological entities associated with lung cancer risk. Exposure circumstances capable of modifying the CS–lung cancer association include host factors, the composition of dust mixing, particularly concerning the co-occurrence of other known or probable lung carcinogens, total respirable dust, concentration of CS in respirable dust, type of CS and particle surface characteristics. These have been shown experimentally to induce the release of reactive oxygen species and tumour necrosis factor-α by alveolar macrophages, which possibly accounts for the great variation in lung cancer risk among dust-exposed workers across individual studies [38].

Cigarette smoking and silicosis, acting as an indicator of heavy CS dust exposure, are potential causes of lung cancer among workers exposed to CS dust, but their joint effects are unclear. Goldsmith and Guidotti [48] pointed out that the combined exposure to smoking and CS was associated with more lung cancer cases than expected from the sum of the estimates of their separate effects, which Greenland and Rothman [49] interpreted as a biological interaction or synergy. The problem is that the cohort studies do not have enough lung cancer cases among non-smoking subgroups to allow a proper analysis of the joint effects. In addition, if the age-specific mortality...
incidence rates for the general population, regardless of smoking habits, were used for calculating the expected numbers, the standardized mortality ratio of lung cancer might be artificially underestimated for non-smokers and overestimated for smokers [33,40,50].

In 2003, the Health & Safety Executive published a hazard assessment document on the carcinogenicity of RCS summarizing available evidence concerning the relationship between lung cancer and silicosis. This tends to show that excess lung cancer mortality in RCS-exposed workers is restricted to those with silicosis, and the more severe the category of silicosis, the higher the risk of lung cancer [51]. They concluded that the evidence also suggests that exposure to RCS insufficient to cause silicosis would be unlikely to lead to an increased risk of lung cancer. Thus, they concluded that reducing exposure to RCS in the workplace to levels that would reduce the risk of silicosis would reduce the risk of lung cancer, i.e. current occupational standards. However, some have suggested that these standards are not sufficiently protective to prevent the occurrence of chronic silicosis, and a number of studies have reported significant risks of silicosis over a working lifetime at CS concentrations that are below 0.05 mg/m³, the exposure limit at the time of the studies [46,47,52,53]. In a pooled analysis of six cohorts, the cumulative risk of death at an exposure of 0.05 mg/m³ (2.25 mg/m³-years) was estimated to be six per 1000 workers, i.e. above the risk of 1 deemed acceptable by the US Occupational Safety and Health Administration.

Although IARC have classified CS as a human carcinogen, this is still controversial, in particular the role of silica exposure versus that of fibrosis in persons with silicosis [24]. A causal link between chronic inflammation and cancer has been suspected for many years [54]. Chronic obstructive pulmonary disease is an independent predictor of lung cancer risk, and numerous studies report an increased risk of lung cancer among adults with asthma, tuberculosis or interstitial fibrosis in patients with systemic sclerosis [55–62]. Experimentally, studies have shown that in rats, inhaled CS causes fibrosis and lung cancer [63] and data indicate that the lung cancer risk occurs at relatively low doses [64]. However, in mice, CS causes fibrosis but not lung cancer, and in hamsters, it causes neither [63]. Kurihara and Wada [36] showed that silicosis is a risk factor for lung cancer and also showed a small risk in subjects exposed to silica including silicotic patients. It was suggested that CS induces lung cancer indirectly in humans. They also estimated that lung cancer risk in smokers with silicosis was double that in non-smokers with silicosis and suggested the data did not appear to indicate that the effects of silicosis and smoking on lung cancer risk are multiplicative. They concluded that preventing silicosis and encouraging smoking cessation might be the most effective measures to reduce lung cancer incidence in silica-exposed workers. However, the problem with silicosis is that under-diagnosis and under-reporting are frequent.

**Exposure trends**

According to Health & Safety Executive statistics, the number of deaths from silicosis in Great Britain (pneumoconiosis due to dust containing silica) has declined since 1993 (28 in 1993, 24 in 1999 and 10 in 2005) (http://www.hse.gov.uk/statistics/tables/dc01.htm), suggesting that exposure levels have dropped. Cherrie et al. [75] examined data on the National Exposure Database (NEDB) and estimated the ratio of the mean CS exposure level to the Occupational Exposure Level (OEL) was just 1.0, although the maximum exposure level to the OEL ratio approached 1000. However, there is no guarantee that the data in the NEDB are representative of industry because of the variety of purposes for which they were collected. In addition, the number of CS measurements stored in NEDB has significantly declined over the past 20 years, from 2000 in 1986–87 to 100 in 2005. CS exposure is believed to be certainly lower than it was 20 years ago (Cherrie, 2008). However, recent surveys in stonemasonry and brick making indicated a third of samples taken were greater than the current workplace exposure limit of 0.1 mg/m³ [65,66], although much fewer excesses were observed in construction and quarry industries [67,68]. In the quarry industry,
no significant changes in exposure over time have been seen [69] as in a number of US industries [70], although a recent study of UK industrial sand workers has shown levels to have dropped (Figure 1) [71]. Studies in the Dutch construction industry suggested that over half of the full-shift respirable quartz measurements were above the Dutch Occupational Exposure Limit with exposure being highly variable from day-to-day and between jobs and tasks [72].

If silicosis were the necessary step leading to lung cancer, enforcing that the current silica standards would protect workers against lung cancer risk as well. Alternatively, a direct silica–lung cancer association that has been suggested implies that regulatory standards should be revised accordingly.

**Conclusions**

Over the past 2 years, a project has been ongoing to update the proportions of cancers due to occupational exposures in Great Britain [73]. They indicated the importance of CS, showing that it is responsible for just under 800 male and >50 female lung cancer deaths, and under 900 and 60 registrations (http://www.hse.gov.uk/research/rrpdf/rr595ann6.pdf). Further research is needed in order to understand the complex pattern of interactions leading to lung cancer among silica-exposed workers (and cancers and workplace exposures in general) and to understand whether and to what extent other workplace lung carcinogens, total respirable dust and total surface size and age of silica particles affect the carcinogenic potential of silica. In addition, the apparent paradox of a lower lung cancer risk in some workplaces with high-level silica exposure needs further investigation. Further studies are required to examine whether the affects of silicosis with smoking are additive, multiplicative or other. Novel epidemiological approaches are required, which incorporate more detailed exposure information [74]. The possibility of substantially reducing the occupational cancer burden in the future because of the reduction in exposure levels has been highlighted, so that by 2025, these exposures will contribute very much <1% of all future cancers [75]. The importance of prevention of silicosis and encouraging smoking cessation in reducing lung cancer incidence in silica-exposed workers is emphasized.

**Conflicts of interest**

None declared.

**References**


