Occupational Medicine 2009;**59:**89–95
doi:10.1093/occmed/kqn171

IN-DEPTH REVIEW

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

Terry Brown

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].

Health & Safety Laboratory, Harpur Hill, Buxton, Derbyshire, UK.

Correspondence to: Terry Brown, Health & Safety Laboratory, Harpur Hill, Buxton, Derbyshire, UK. Tel: +1 (0)1298 218949; fax: +1 (0)1298 218590; e-mail: terry.brown@hsl.gov.uk

© The Author 2009. Published by Oxford University Press on behalf of the Society of Occupational Medicine.
All rights reserved. For Permissions, please email: journals.permissions@oxfordjournals.org

Downloaded from http://occmed.oxfordjournals.org/ by guest on January 30, 2012

Table 1. Occupations and industries with potential exposure to quartz in Great Britain

Industry	Number of workers exposed
Construction	449 930
Manufacture of other non-metallic mineral products	24 406
Manufacture of pottery, china and earthenware	21 769
Manufacture of machinery except electrical	16 253
Other mining	16 240
Manufacture of fabricated metal products, except machinery and electrical	8002
Manufacture of glass and glass products	6932
Manufacture of transport equipment	6420
Manufacture of other chemical products	5662
Land transport	5123
Iron and steel basic industries	3853
Electricity, gas and steam	3382
Non-ferrous metal basic industries	2406

Source: Pannett *et al.* [1].

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

Downloaded from http://occmed.oxfordjournals.org/ by guest on January 30, 2012

and estimated the combined RR was 2.76 (2.41–3.16), suggesting that lung cancer should be regarded as one of the important complications of silicosis/pneumoconiosis. In an analysis of studies published between 1966 and 2001, Kurihara and Wada [36] estimated a pooled lung cancer RR of 1.32 for silica-exposed workers, suggesting CS is a rather weak carcinogen. However, they also estimated that the lung cancer risk was higher (2.37) for silicotic patients, but 0.96 in non-silicotic subjects exposed to silica. However, some of the studies they included were unable to determine silicosis in their subjects; thus, the risk from silica itself may be smaller than 1.32; they concluded that silica exposure was less likely to directly increase lung cancer risk.

A more recent analysis of 45 papers published after the IARC 1997 monograph observed a similar pooled RR of 1.34 [37]. In cohort studies of silicotics only, the summary RR was slightly lower at 1.69 with 1.19 for exposed non-silicotic subjects. The authors also analysed separately studies where silicosis status was undefined and found a pooled RR of 1.25. For case–control studies with subjects with undefined silicosis status, the combined RR was 1.41 compared to 3.27 where it was defined, and 0.97 in non-silicotics.

Studies that provide the most convincing evidence of carcinogenicity indicate that increased risks of lung cancer are restricted to those groups with the highest cumulative exposure, suggesting the existence of a threshold. However, exposure–response relationships in the cohorts have not been consistent because exposure measures differ between studies, and this makes it challenging to carry out a meta-analysis. As a consequence, Steenland *et al.* [35] pooled data from 10 cohorts of CS-exposed workers and, in a nested case–control analysis of all the lung cancer cases, found that log of cumulative exposure to CS, with a 15-year lag, was a strong predictor of lung cancer. They also observed a monotonic trend with cumulative exposure, although the risk in the highest exposure group was only 1.6. The authors stated that the fact that the log of cumulative exposure provided a good fit to the data implied that the RR of lung cancer due to CS exposure tends to tail off at the highest doses, for which various reasons were given. Duration of exposure did not fit the data well indicating that intensity of exposure was an important metric. The authors stated that smoking would not be an issue in this internal analysis because it was assumed that the number of smokers was uniform across all exposure categories. They also did not exclude silicotic patients in the analysis, which as suggested above if removed from the analysis might have resulted in a lower risk estimate. Compared to other lung carcinogens, CS was shown to be weaker when measured by mass in the air, in comparison to chromium, nickel, cadmium and arsenic. In another analysis of the pooled cohort (six cohorts), Mannetje *et al.* [39] investigated the relationship between CS exposure and silicosis mortality and observed a significant dose–response relationship. However, the study did not investigate the relationship between lung cancer, CS exposure and silicosis.

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/

Downloaded from http://occmed.oxfordjournals.org/ by guest on January 30, 2012

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/m^3, 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/m^3 (2.25 mg/m^3-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/m^3 [65,66], although much fewer excesses were observed in construction and quarry industries [67,68]. In the quarry industry,

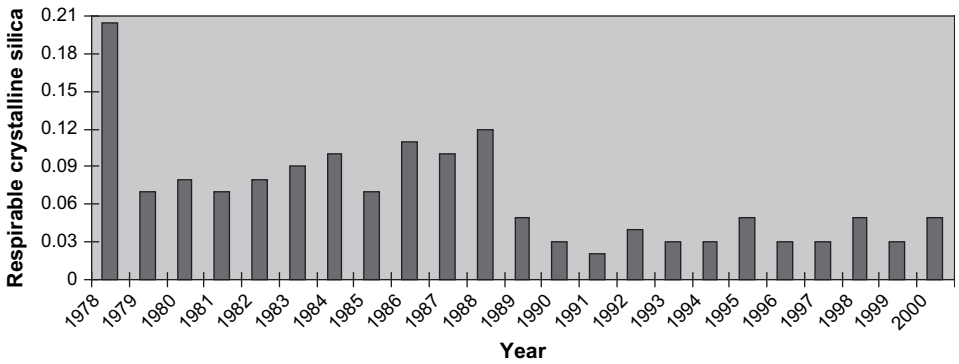

Figure 1. Changes in RCS levels in UK industrial silica sand quarries 1978–2000 Source: Brown and Rushton [71].

Downloaded from http://occmed.oxfordjournals.org/ by guest on January 30, 2012

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 preventing silicosis and encouraging smoking cessation in reducing lung cancer incidence in silica-exposed workers is emphasized.

Conflicts of interest

None declared.

References

1. Pannett B, Kauppinen T, Toikkanen J, Pedersen J, Young R, Kogevinas M. Occupational exposure to carcinogens in Great Britain in 1990–93: preliminary results. In: *Carex: International Information System on Occupational Exposure to Carcinogens*. Helsinki, Finland: Finnish Institute of Occupational Health, 1998.
2. Kauppinen T, Toikkanen J, Pedersen J *et al*. Occupational exposure to carcinogens in the European Union in 1990–93: preliminary results. *Carex: International Information System on Occupational Exposure to Carcinogens*. Helsinki, Finland: Finnish Institute of Occupational Health, 1998.
3. Pilkington A, Maclaren W, Searl A *et al*. *Scientific Opinion on the Health Effects of Airborne Crystalline Silica*. Edinburgh: Institute of Occupational Medicine, 1996; 1.
4. Sluis-Cremer GK, Hessel PA, Hnizdo E, Churchill AR. Relationship between silicosis and rheumatoid arthritis. *Thorax* 1986;**41:**596–601.
5. Klockars M, Koskela RS, Jarvinen E, Kolari PJ, Rossi A. Silica exposure and rheumatoid arthritis: a follow up study of granite workers 1940–81. *Br Med J* 1987;**294:**997–1000.
6. Rosenman KD, Moore-Fuller M, Reilly MJ. Connective tissue disease and silicosis. *Am J Ind Med* 1999;**35:**375–381.
7. Cowie RL. Silica-dust-exposed mine workers with scleroderma (systemic sclerosis). *Chest* 1987;**92:**260–262.
8. Bovenzi M, Barbone F, Betta A, Tommasini M, Versini W. Scleroderma and occupational exposure. *Scand J Work Environ Health* 1995;**21:**289–292.
9. Conrad K, Mehlhorn J, Luthke K, Dorner T, Frank KH. Systemic lupus erythematosus after heavy exposure to quartz dust in uranium mines: clinical and serological characteristics. *Lupus* 1996;**5:**62–69.
10. Brown LM, Gridley G, Olsen JH, Mellemkjaer L, Linet MS, Fraumeni JF Jr. Cancer risk and mortality patterns among silicotic men in Sweden and Denmark. *J Occup Environ Med* 1997;**39:**633–638.
11. Calvert GM, Steenland K, Palu S. End-stage renal disease among silica-exposed gold miners: a new method for assessing incidence among epidemiologic cohorts. *J Am Med Assoc* 1997;**277:**1219–1223.
12. Steenland K, Rosenman KD, Socie E, Valiante DJ. Silicosis and end-stage renal disease. *Scand J Work Environ Health* 2002;**28:**439–442.
13. Yu ITS, Tse LA, Wong TW, Leung CC, Tam CM, Chan ACK. Further evidence for a link between silica dust and esophageal cancer. *Int J Cancer* 2005;**114:**479–483.
14. Wernli KJ, Fitzgibbons ED, Ray RM *et al*. Occupational risk factors for esophageal and stomach cancers among female textile workers in Shanghai, China. *Am J Epidemiol* 2006;**163:**717–725.
15. Parent ME, Siemiatycki J, Fritschi L. Occupational exposures and gastric cancer. *Epidemiology* 1998;**9:**48.
16. Cocco P, Ward MH, Buiatti E. Occupational risk factors for gastric cancer: an overview. *Epidemiol Rev* 1996;**18:**218.
17. Partanen T, Pukkala E, Vainio H, Kurppa K, Koskinen H. Increased incidence of lung and skin cancer in Finnish silicotic patients. *J Occup Med* 1994;**36:**616.
18. Rafnsson V, Gunnarsdottir H. Lung cancer incidence among an Icelandic cohort exposed to diatomaceous earth and cristobalite. *Scand J Work Environ Health* 1997;**23:** 187–192.
19. Forastiere F, Lagorio S, Michelozzi P, Perucci CA, Axelson O. Mortality pattern of silicotic subjects in the Latium region, Italy. *Br J Ind Med* 1989;**46:**877–880.

Downloaded from http://occmed.oxfordjournals.org/ by guest on January 30, 2012

20. Steenland K, Beaumont JJ. A proportionate mortality study of granite cutters. *Am J Ind Med* 1986;**9:**189–201.
21. IARC. *Silica, Some Silicates, Coal Dust and Para-aramid Fibrils*. Lyon, France: International Agency for Research on Cancer, 1997; 1.
22. NIOSH. *Health Effects of Occupational Exposure to Respirable Crystalline Silica*. Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention, 2002; 1.
23. NT Program. ed. *Report on Carcinogens*. 11th edn. Research Triangle Park, NC: Department of Health and Human Services, Public Health Service, 2005.
24. Checkoway H, Franzblau A. Is silicosis required for silica-associated lung cancer? *Am J Ind Med* 2000;**37:** 252–259.
25. Hessel PA, Gamble JF, Gee JBL *et al*. Silica, silicosis, and lung cancer: a response to a recent working group report. *J Occup Environ Med* 2000;**42:**704–720.
26. McDonald C. Silica and lung cancer: hazard or risk. *Ann Occup Hyg* 2000;**44:**1–2.
27. Soutar CA, Robertson A, Miller BG, Searl A, Bignon J. Epidemiological evidence on the carcinogenicity of silica: factors in scientific judgement. *Ann Occup Hyg* 2000; **44:**3–14.
28. Wong O. The epidemiology of silica, silicosis and lung cancer: some recent findings and future challenges. *Ann Epidemiol* 2002;**12:**285–287.
29. Klein AK, Christopher JP. Evaluation of crystalline silica as a threshold carcinogen. *Scand J Work Environ Health* 1995;**21(Suppl. 2):**95.
30. McDonald JC, Castranova V, Vallyathan V, Wallace WE. Silica and lung cancer. In: *Silica and Silica-Induced Lung Diseases*. London: CRC Press, 1995; 383.
31. Attfield M, Costello J. Quantitative exposure-response for silica dust and lung cancer in Vermont granite workers. *Am J Ind Med* 2004;**45:**129–138.
32. Graham WGB, Costello J, Vacek PM. Vermont granite mortality study: an update with an emphasis on lung cancer. *J Occup Environ Med* 2004;**46:**459.
33. Smith AH, Lopipero P, Barroga VR. Meta-analysis of studies of lung cancer among silicotics. *Epidemiology* 1995;**6:** 617–624.
34. Tsuda T, Babazono A, Yamamoto E, Mino Y, Matsuoka H. A meta-analysis on the relationship between pneumoconiosis and lung cancer. *J Occup Health* 1997;**39:**285–294.
35. Steenland K, Mannetje A, Boffeta P *et al*. Pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multicentre study. *Cancer Causes Control* 2001;**12:**773–784.
36. Kurihara N, Wada O. Silicosis and smoking strongly increase lung cancer risk in silica-exposed workers. *Ind Health* 2004;**42:**303–314.
37. Pelucchi C, Pira E, Piolatto G, Coggiola M, Carta P, La Vecchia C. Occupational silica exposure and lung cancer risk: a review of epidemiological studies 1996–2005. *Ann Oncol* 2006;**17:**1039–1050.
38. Cocco P, Dosemeci M, Rice C. Lung cancer among silica-exposed workers: the quest for truth between chance and necessity. *Med Lav* 2007;**98:**3–17.
39. Mannetje A, Steenland K, Attfield M *et al*. Exposure-response analysis and risk assessment for silica and silicosis mortality in a pooled analysis of six cohorts. *Occup Environ Med* 2002;**59:**723–728.
40. Berry G, Newhouse ML, Antonis P. Combined effect of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. *Br J Ind Med* 1985;**42:** 12–18.
41. Steenland K, Thun M. Interaction between tobacco smoking and occupational exposures in the causation of lung cancer. *J Occup Med* 1986;**28:**110–118.
42. Gustavsson P. Low-dose exposure to asbestos and lung cancer: dose-response relations and interaction with smoking in a population-based case-referent study in Stockholm, Sweden. *Am J Epidemiol* 2002;**155:**1016–1022.
43. Wraith D, Mengersen K. A Bayesian approach to assess interaction between known risk factors: the risk of lung cancer from exposure to asbestos and smoking. *Stat Methods Med Res* 2008;**17:**171–189.
44. Cassidy A, Mannetje A, van Tongeren M *et al*. Occupational exposure to crystalline silica and risk of lung cancer. A multicenter case-control study in Europe. *Epidemiology* 2007;**18:**36–43.
45. Cherry NM, Burgess GL, Turner S, McDonald JC. Crystalline silica and risk of lung cancer in the potteries. *Occup Environ Med* 1998;**55:**779–785.
46. Hughes JM, Weill H, Checkoway H *et al*. Radiographic evidence of silicosis risk in the diatomaceous earth industry. *Am J Respir Crit Care Med* 1998;**158:**807–814.
47. Rosenman KD, Reilly MJ, Rice C, Hertzberg V, Tseng CY, Anderson HA. Silicosis among foundry workers. Implication for the need to revise the OSHA standard. *Am J Epidemiol* 1996;**144:**890–900.
48. Goldsmith DF, Guidotti TL. Combined silica exposure and cigarette smoking: a likely synergistic effect. In: Goldsmith DF, Winn DM, Shy CM, eds. *Silica, Silicosis, and Lung Cancer: Controversy in Occupational Medicine*. New York: Praeger, 1986; 451–459.
49. Greenland S, Rothman KJ. Concepts of interaction. In: Rothman KJ, Greenland S, eds. *Modern Epidemiology.* Philadelphia, PA: Lipincott-Raven, 1998; 329–342.
50. Saracci R. The interactions of tobacco smoking and other agents in cancer etiology. *Epidemiol Rev* 1987;**9:** 175–193.
51. HSE. Respirable crystalline silica—phase 2. In: *Hazard Assessment Document*. London: Health & Safety Executive, 2003.
52. Steenland K, Brown D. Silicosis among gold miners: exposure—response analyses and risk assessment. *Am J Public Health* 1995;**85:**1372–1377.
53. Hnizdo E, Sluis-Cremer G. Risk of silicosis in a cohort of white South African gold miners. *Am J Ind Med* 1993; **24:**447–457.
54. Schottenfeld D, Beebe-Dimmer JL. Advances in cancer epidemiology: understanding causal mechanisms and the evidence for implementing interventions. *Annu Rev Public Health* 2005;**26:**37–60.
55. Hinds MW, Cohen HI, Kolonel LN. Tuberculosis and lung cancer risk in nonsmoking women. *Am Rev Respir Dis* 1982;**125:**776–778.
56. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk

Downloaded from http://occmed.oxfordjournals.org/ by guest on January 30, 2012

in men and women: findings from the Renfrew and Paisley prospective population study. *Br Med J* 1996;**313:** 711–715.
57. Islam SS, Schottenfeld D. Declining FEV1 and chronic productive cough in cigarette smokers: a 25-year prospective study of lung cancer incidence in Tecumseh, Michigan. *Cancer Epidemiol Biomarkers Prev* 1994;**3:** 289–298.
58. Kuller LH, Ockene J, Meilahn E, Svendsen KH. Relation of forced expiratory volume in one second (FEV1) to lung cancer mortality in the Multiple Risk Factor Intervention Trial (MRFIT). *Am J Epidemiol* 1990;**132:** 265–274.
59. Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Ventilatory function and chronic mucus hypersecretion as predictors of death from lung cancer. *Am Rev Respir Dis* 1990;**141:**613–617.
60. Santillan AA, Camargo CA, Colditz GA. A meta-analysis of asthma and risk of lung cancer (United States). *Cancer Causes Control* 2003;**14:**327–334.
61. Tockman MS, Anthonisen NR, Wright EC, Donithan MG. Airways obstruction and the risk for lung cancer. *Ann Intern Med* 1987;**106:**512–518.
62. Zheng W, Blot WJ, Liao ML *et al*. Lung cancer and prior tuberculosis infection in Shanghai. *Br J Cancer* 1987;**56:** 501–504.
63. Saffiotti U. Lung cancer induction by crystalline silica. In: D'Amato R, Slaga T, Forland W, Henry C, eds. eds. *Relevance of Animal Studies to the Evaluation of Human Cancer Risk*. New York: Wiley-Lis, 1992; 57–69.
64. Muhle H, Takenaka S, Mohr U, Dasenbrock C, Mermelstein R. Lung-tumor induction upon long-term low-level inhalation of crystalline silica. *Am J Ind Med* 1989;**15:**343–346.
65. Easterbrook A, Brough P. *Silica Baseline Survey: Annexe 1: Brickmaking Industry*. Buxton: Health and Safety Laboratory, 2008.
66. Easterbrook A, Brough P. *Silica Baseline Survey: Annexe 3: Stonemasonry Industry*. Buxton: Health and Safety Laboratory, 2008.
67. Easterbrook A, Brough P. *Silica Baseline Survey: Annexe 2: Construction Sector*. Buxton: Health and Safety Laboratory, 2008.
68. Easterbrook A, Brough P. *Silica Baseline Survey: Annexe 4: Quarry Industry*. Buxton: Health and Safety Laboratory, 2008.
69. Creely KS, Van Tongeren M, While D *et al*. *Trends in Inhalation Exposure: Mid 1980s till Present*. Edinburgh: Institute of Occupational Medicine, 2006.
70. Yassin A, Yebesi F, Tingle R. Occupational exposure to crystalline silica dust in the United States 1988–2003. *Environ Health Perspect* 2005;**113:**255–260.
71. Brown TP, Rushton L. Mortality in the UK industrial silica sand industry: 1. assessment of exposure to respirable crystalline silica. *Occup Environ Med* 2005;**62:** 442–445.
72. Tjoe-Nij E, Hilhorst S, Spee T *et al*. Dust control measures in the construction industry. *Ann Occup Hyg* 2003;**47:** 211–218.
73. Rushton L, Hutchings S, Brown T. The burden of cancer at work: estimation as the first step to prevention. *Occup Environ Med* 2008;**65:**789–800.
74. Cocco P. Multifactorial aetiology of lung cancer among silica-exposed workers. *Ann Acad Med Singapore* 2001;**30:** 468–474.
75. Cherrie JW, Van Tongeren M, Semple S. Exposure to occupational carcinogens in Great Britain. *Ann Occup Hyg* 2007;**51:**653–664.

Downloaded from http://occmed.oxfordjournals.org/ by guest on January 30, 2012