Exposure to crystalline silica and risk of lung cancer: the epidemiological evidence

H Weill, J C McDonald

This review updates the published epidemiological literature since 1986, a year chosen because the International Agency for Research on Cancer (IARC) conducted a thorough review of papers published before that date. The IARC working group concluded at that time that the evidence for carcinogenicity of crystalline silica in experimental animals was *sufficient*, while in man it was *limited*.¹ These conclusions led the IARC to classify crystalline silica as 2A – that is, “probably carcinogenic to humans”.² The evidence on which these judgements are based was summarised in an editorial published in 1989.³ Only brief reference will be made to papers published before that date. For the present review, relevant factors taken into account include: (1) the distinction between silica exposure and silicosis; (2) study design and quality; (3) confounding exposures, including smoking; and (4) demonstration of dose dependency.

Very few studies are available of cohorts, defined by their employment, that have been exposed to crystalline silica but not to other potentially carcinogenic materials. As with most other epidemiological studies which focus on lung cancer as the primary outcome of interest, smoking could rarely be accounted for fully in the reviewed literature. Also, past silica exposure levels could only be approximated or ranked in an ordinal fashion, if exposure was estimated at all.

Literature review

We have reviewed the principal epidemiological papers published since 1986 which deal with the relationship between silica, silicosis, and lung cancer. Preliminary reports from several of these had already been published before 1987 and were taken into account by the IARC working group. In addition, oral presentations from meetings held in San Francisco in October 1993⁴ and Baltimore in April 1994⁵ are considered, with comments on several which were relevant. To facilitate discussion, the salient features of the large portion of the *published* reports are set out in the accompanying tables, classified into those which are primarily concerned with the effects of exposure to crystalline silica per se (tables 1 and 2), and those which

have examined primarily the risk of lung cancer in registered silicosis (tables 3 and 4).

EXPOSURE TO CRYSTALLINE SILICA

The papers examined in this class are set out in table 1. These, by reason of design and quality, provide results which can be interpreted fairly readily; others in table 2 are, for various reasons, less clearcut. There is no sharp distinction between these two sets, but those in table 1 warrant more detailed comment.

Two papers stand out from the rest in providing results which are both new and convincing. The first of these, published in 1991 by Merlo *et al*,⁶ is based on a cohort of 1022 men employed for six months or more in the manufacture of refractory bricks in Genoa, Italy. There were no obvious confounding exposures, but the role of smoking was not assessed and the type of crystalline silica to which the men were exposed was not defined. By the end of 1986, 243 men had died, 28 from lung cancer (standardised mortality (SMR) 1.51; 95% CI 1.00 to 2.18) and 40 from non-malignant respiratory diseases (SMR 2.41). There was some suggestion that risk in both these disease categories was highest in workers employed for 20 or more years before 1957 when dust controls were introduced, but no other indication of exposure dependency was reported. The SMR values were calculated against Italian national rates; no information was given on the incidence of lung cancer in the Genoa area of north-west Italy where the national rates may well not apply.

The paper by Checkoway *et al* published in 1993⁷ is based on a cohort of 2570 white male workers employed for one year or more in the mining and calcining of diatomaceous earth in California, the latter a process which converts the biogenic amorphous silica to cristobalite. Possible confounding exposure from the earlier use of asbestos in some parts of the plant was considered by the investigators. They described the steps taken to exclude workers from the cohort whose job titles were known to be associated with regular exposure to asbestos (see below for further discussion on this point).

**Tulane University
School of Medicine,
New Orleans,
Louisiana, USA**
H Weill

**National Heart and
Lung Institute,
London, UK**
J C McDonald

Correspondence to:
Dr H Weill,
Tulane Medical Center,
Section of Environmental
Medicine, Box SL15,
1430 Tulane Avenue,
New Orleans, Louisiana
70112, USA.

Table 1 Studies based on populations defined by exposure to crystalline silica

Reference	Study design	Population studied	Overall lung cancer mortality	Comments
Checkoway <i>et al</i> ⁷	Cohort	Diatomite workers	SMR 1.43	SMR increased from 1.19 to 2.74 by exposure gradient; possible asbestos confounding is being re-evaluated; main exposure was to cristobalite; relationship with silicosis unknown but being investigated
McLaughlin <i>et al</i> ¹³	Nested case-control	Pottery workers and miners	NA	Significant risk increase with silica exposure in tin miners (PAH, radon, arsenic likely important confounders); non-significant exposure response in pottery workers; author states: only "limited support" for association of silica exposure and lung cancer; relationship with silicosis
Kusiak <i>et al</i> ¹⁴	Cohort	Metal miners	SMR 2.25	No exposure response for silica exposure; radon shows best relationship; also arsenic; author attributes excess primarily to radon with contribution to risk by arsenic
Merlo <i>et al</i> ⁶	Cohort	Refractory brick workers	SMR 1.77; with 19+ years of exposure, SMR 2.01	Risk increased with years since hire; no effect of smoking shown; must be considered as relating silica exposure with lung cancer risk – no information on silicosis or other exposures
Neuberger <i>et al</i> ¹²	Cohort	Mixed industries	SMR: foundries 164; other metal industries 133; ceramics and glass 237; stone and construction 294	No exposure response; confounders likely for some groups
Meijers <i>et al</i> ⁸	Case-control	Ceramic industry	OR 1.11 (0.77–1.61)	Non-significant tendency for OR to increase with duration of employment and silica exposure; there is little to relate silica exposure and cancer risk; no information regarding silicosis
Mehnert <i>et al</i> ¹⁷	Cohort	Slate quarry workers	SMR 109, interpreted as "no overall increase"; excess risk found in silicotics (SMR 183)	Tendency for risk to increase with time since first exposure
Thomas ⁹	Cohort	Union pottery and ceramic workers	SMR 1.43 for ceramic workers	Lung cancer mortality increased with talc exposure, not silica; possible relationship with non-fibrous talc; author indicates that silica as "co-factor or promoter cannot be ruled out"
Winter <i>et al</i> ¹⁰	Cohort	Pottery workers	SMR 1.4 (1.07–1.8)	Weak relation between increasing silica exposure and lung cancer risk; smoking taken into account
Costello <i>et al</i> ¹⁶	Cohort	Vermont granite workers	SMR 1.16	Elevated lung cancer risk only in stone shed workers employed prior to 1930
Mastrangelo <i>et al</i> ¹⁵	Case-control	High silica exposure region of the country	Increased risk only in presence of silicosis	Weak silica and strong smoking effect; some dose dependency of risk

SMR=standardised mortality ratio; NA=not applicable; OR=odds ratio; PAH=polycyclic aromatic hydrocarbons.

Table 2 Studies of populations exposed to crystalline silica but difficult to interpret

Reference	Study design	Population studied	Overall lung cancer mortality	Comments
Moulin <i>et al</i> ³¹	Cohort	Stainless steel production	Only foundry workers within this population had an excess: SMR 2.29; 3.34 in 30+ yrs since hire	No exposure response; likely confounding by PAH; chromium compounds
Sherson <i>et al</i> ³²	Incidence from cancer registry	Foundry workers	Morbidity ratio 1.3 (95% CI 1.12 to 1.51)	Excess lung cancer incidence confined to those who had worked in foundries >20 yrs; "Correlation" found between silicosis at time of radiography (1967–9) and lung cancer incidence during follow up (through 1985); probable confounders
Amandus <i>et al</i> ²⁶	Cohort	Metal miners	SMR 1.73 (95% CI 0.94 to 2.9) in silicotics; 1.18 (0.98 to 1.42) in non-silicotics	Authors stated that radon could be confounding; increased risk primarily in silicotics; smoking taken into account
Hnizdo <i>et al</i> ¹⁹	Cohort	Gold miners	RR=1.023 per 1000 particle years; overall SMR not given	Apparent exposure response relationship but thought to be best related to radon exposure by the authors
Ahlman <i>et al</i> ³³	Cohort	Copper and zinc miners	SMR 2.33	No exposure response; likely to have been confounding exposures (radon, PAH)
Chen <i>et al</i> ³⁴	Cohort	Iron ore miners	SMR 3.7	Exposure response limited to smokers; probable radon confounding
Siemiatycki <i>et al</i> ³⁵	Case-control	Cancer patients	OR=1.7 in those with heaviest silica exposure	Smoking taken into account; weak design
Hessel <i>et al</i> ³⁶	Case-control	Necropsy cases; varying exposures	No excess by silica exposure or silicosis	No exposure response; likely radon confounding
Hodgson <i>et al</i> ³⁷	Cohort	Tin miners	Overall SMR approximately 160	SMR from 83 to 447 with increasing time underground; probable radon, arsenic confounding
Koskela <i>et al</i> ¹⁸	Cohort	Granite workers	SMR 220 (those followed up 15+ yrs)	No dose dependency demonstrated; unexplained deficiencies of deaths in other cancers
Lynge <i>et al</i> ³⁸	Incidence	Occupational and cancer registries	RR in foundries (up to 1.73) and mines (up to 5.02)	No exposure response; weak design (record linkages); probable confounding exposures

SMR=standardised mortality ratio; RR=relative risk; OR=odds ratio; 95% CI=95% confidence interval; PAH=polycyclic aromatic hydrocarbons.

By the end of 1987, of 628 deaths observed, 59 were from lung cancer (SMR 1.43) and 77 were from non-malignant respiratory disease (SMR 2.27). Mortality of white men in the USA was used as the reference population, but comparison against local county rates gave similar results. Semiquantitative measures of cumulative exposure, estimated from work histories and information of past environmental conditions in the plant, were shown to correlate with relative risks for both lung cancer and non-malignant respiratory disease. A weighting procedure, applied to adjust these exposure estimates for respirator use, could conceivably

have introduced some bias into the analyses. As judged by the limited information obtained on cigarette smoking, there was no indication of important confounding from this source. A study of past chest radiographs in this cohort, the results from which will be linked to updated mortality information, has been initiated but this investigation is still underway.

Of the remaining reports in table 1, four were based on pottery or ceramic workers. One of these, a case reference study by Meijers *et al*⁸ in a Dutch ceramic plant, was essentially negative in that both the slight increase in lung cancer risk (odds ratio (OR)=1.11) and

quantitative relation to silica exposure were well within 95% confidence limits.

In a cohort study of American pottery workers by Thomas⁹ 52 deaths from lung cancer were observed against 36.4 expected (SMR 1.43). This excess was largely explained by work in the sanitary ware division where exposure to non-fibrous talc was suggested as a possible confounder. In another study of pottery workers in the UK¹⁰ the excess was similar; 60 deaths were observed against 42.8 from national rates (SMR 1.40) or 45.6 from local rates (SMR 1.32). In the American study there was a deficiency of cancer deaths at other anatomical sites (observed 72, expected 85.7). The British study suffered from uncertainty over completeness of follow up, but was free from important confounding exposures and demonstrated some evidence that risk was related to cumulative exposure even after allowance for smoking habit. Findings from a cohort study of some 7000 British pottery workers were presented at the Baltimore meeting. The study showed significantly increased SMR values for lung cancer (1.33) and for non-malignant respiratory diseases (1.69) against national rates, but fell to 0.93 and 1.43, respectively, against local rates.¹¹ As 70% of the deaths in this cohort occurred locally, the authors concluded that the study showed little evidence of excess lung cancer risk. Further results from this investigation will be more informative as the available data include smoking habit, radiographic findings, and quantitative estimates of exposure to silica.

Of the other studies listed in table 1, five were based primarily on mining and quarrying, and the fifth by Neuberger¹² on the experience of Austrian workers in a variety of dusty trades. This study and two others by McLaughlin *et al*¹³ in China and by Kusiak¹⁴ in Canada found significantly increased risks of lung cancer, but all were subject to serious confounding by established carcinogens such as arsenic and radon and are therefore difficult to assess. In the study of Ontario uranium miners¹⁴ mortality from lung cancer was "clearly related to exposure to short lived radon progeny". The study from China was based on a cohort of 68 285 metal miners and pottery workers. Confounding was less of a problem in the pottery workers than in the miners, but although lung cancer in pottery workers was related to silica exposure, it was not related to silicosis and the dose-response gradient showed no significant trend.

A case referent study by Mastrangelo *et al*¹⁵ from the Veneto region of Italy, where the main exposures were in quarrying, tunneling and mining, showed evidence of increased lung cancer risk after stratification for smoking in men compensated for silicosis (relative risk (RR) 1.9), but no increase without silicosis (RR 0.9). The remaining two reports, one on Vermont granite workers¹⁶ and the other on German slate quarry workers by Mehnert *et al*,¹⁷ showed slightly raised SMR values which were well within the 95% confidence limits.

In almost all the papers shown in table 2, increased risks of lung cancer were reported but, for the most part, this could have resulted

from exposure to a variety of other carcinogens – for example, polycyclic aromatic hydrocarbons (PAH) in foundries, and radon and arsenic in mines. Exceptions were the study by Koskela *et al*¹⁸ in Finnish granite workers, and the cohort study of Hnizdo and colleagues in South Africa.¹⁹ In the Finnish study there were 31 deaths from lung cancer against 19.9 expected, and 18 deaths from gastrointestinal cancers against 11.5 expected, but 10 deaths from other cancers against 22.9 expected. Thus, there was no significant overall excess mortality from malignant disease nor, indeed, from other causes. The South African study appeared at first to show a systematic association between estimated dust exposure and lung cancer risk in gold miners. However, further analyses (presented at the San Francisco meeting)⁴ have shown that only lung cancer of the small cell type was related to respirable silica exposure. As cases of this type were not associated with silicosis *per se*, the authors have suggested that radiation, which was relatively high before the mid 1950s, may have been responsible for these findings.^{20 21}

A case-control study of silica and lung cancer in the North Carolina "dusty trades" industry was recently presented.²² It showed a "small but significant" risk of lung cancer in relation to cumulative silica exposure overall (at a cumulative rate of exposure of 10 mg/m³.yrs odds ratios increased from 1.17 to 1.32 when lag periods were increased from 10 to 30 years). This effect was particularly evident in mining and manufacturing of silica and its products, but not for other sources of workplace exposure to silica such as foundries, stone crushing, and a "miscellaneous" category. The excess was mainly in men diagnosed as having silicosis (OR 2.91, 95% CI 1.04 to 8.17), but there was also some evidence of an increase in all members of the cohort who had been exposed to silica (SMR 1.13, 95% CI 0.86 to 1.45).

We are aware of the results of two further cohort studies which have been presented orally, one at an international meeting in Cincinnati in September 1992 (Carta *et al*)²³ and the other at the annual meeting of the British Thoracic Society in December 1992 (Benn *et al*).²⁴ Neither reported evidence of excess risk, but final assessment must await their full publication. Investigators at the US National Institute of Occupational Safety and Health (NIOSH) have performed an update of their mortality study at the Homestake Mine, the results of which have recently been presented.²⁵ Mortality from lung cancer was not significantly increased when national rates were used (1.13; 95% CI 0.93 to 1.36); there was a marginal excess when county rates were employed (1.27; 95% CI 1.02 to 1.55), but no exposure response relationship was seen. This contrasted markedly with the substantial excess of silicosis and tuberculosis, and a strongly positive exposure response gradient for these causes of death.

SILICOSIS AND LUNG CANCER

There are now at least 20 studies which suggest that men diagnosed as having silicosis are at

Table 3 Studies of populations exposed to silica with lung cancer risk estimated for those with and without silicosis

Reference	Study design	Population studied	Lung cancer mortality		Comments
			Silicosis	No silicosis	
Forastiere <i>et al</i> ³⁹	Case-control	Ceramic workers	RR 3.9	RR 1.4	Excess mainly found in those with silicosis but not those who were non-smokers; no obvious confounding job exposures
Mehnert <i>et al</i> ¹⁷	Cohort	Slate quarry workers	SMR 1.83	SMR 0.91	Tendency for risk to increase with time since first exposure
McLaughlin <i>et al</i> ¹³	Nested case-control	Pottery workers and miners	OR 0.5 OR 1.9	OR 1.0 OR 1.0	Significant risk increase with silica exposure in tin miners (PAH, radon, arsenic likely important confounders); non-significant exposure response in pottery workers
Mastrangelo <i>et al</i> ¹⁵	Case-control	Mines and quarries	RR 1.8	RR 0.9	Weak silica and strong smoking effect; some dose dependency of risk
Amandus <i>et al</i> ⁴⁰	Cohort	US metal miners	SMR 1.73	SMR 1.18	Smoking taken into account; excess lung cancer risk in those with silicosis; radon confounding could not be excluded

RR=relative risk; SMR=standardised mortality ratio; OR=odds ratio.

Table 4 Selected studies of patients with silicosis identified by registry, compensation, or admission to hospital

Reference	Lung cancer mortality	Comments
Merlo <i>et al</i> ⁴¹	SMR 6.81	Smoking adjustment made; the author states that the excess risk is due to silicosis
Infante-Rivard <i>et al</i> ⁴² Carta <i>et al</i> ²³	SMR 3.5 SMR 1.29 (0.8–2.0) SMR 4.11 in heavy smokers	SMR increased after 10 and 15 years latency, never reaching significance; no relationship with severity of silicosis
Chia <i>et al</i> ⁴³	9 cases of lung cancer among 159 registered silicotics; standardized incidence ratio (SIR) 2.01 (95% CI 0.92 to 3.81)	Increasing trend with severity of silicosis and exposure duration; smoking alone did not explain findings
Tornling <i>et al</i> ⁴⁴	SMR=188 (95% CI 85 to 356)	Excess risk in 280 patients with silicosis from ceramics industry
Ng <i>et al</i> ⁴⁵	SMR 2.03 (95% CI 1.35 to 2.93)	Increasing risk with duration of employment and latency; asbestos, PAH exposure excluded; increasing trend with severity of silicosis; all lung cancers in smokers
Chiyotani <i>et al</i> ⁴⁶	SMR 6.03 (95% CI 5.29 to 6.77) in 1941 hospitalised silicotics	No exposure response shown; employment in the ceramics industry was risk factor
Finkelstein <i>et al</i> ⁴⁷ Zambon <i>et al</i> ⁴⁸	SMR 188–366 SMR 239	Smoking did not explain the risk No exposure response; possible smoking confounding; increased risk in compensated subjects with silicosis

SMR=standardised mortality ratio; 95% CI=95% confidence interval; PAH=polycyclic aromatic hydrocarbons.

substantial risk of dying from lung cancer. Some of the more recent of these are summarised in tables 3 and 4, and others are included in studies where the primary interest has been in silica exposure per se. In every study, except possibly that conducted by Amandus *et al* (table 3),^{26,27} the cases of silicosis were ascertained from registers of persons compensated for the disease or admitted to hospital with this diagnosis. Apart from the question of whether mortality in the general population is an appropriate basis for comparison with such cases, patients ascertained in this way are highly selected and by no means representative of all cases of silicosis. In particular, many compensated cases are likely to have respiratory symptoms and impaired function related, in part, to cigarette smoking. It is not simply a matter of the smoking level, but that men whose smoking has led to symptoms are more likely to seek or be granted compensation. There are also indications from silicosis surveillance in Ontario that smokers were more likely to have a diagnosis of silicosis than non-smokers.²⁸ The study by Amandus *et al*^{26,27} was relatively free from this type of bias in that their cases were identified among workers exposed to silica examined routinely by chest radiography and symptom questionnaire by the Industrial Commission for North Carolina.

Discussion

Eleven studies were identified as being of reasonably satisfactory design and presentation,

and primarily concerned with the effects of exposure to crystalline silica on the risk of lung cancer. Of these, nine^{6,7,9,10,12–16} provided some evidence of excess risk in exposed workers (or a subgroup) and two^{8,17} failed to do so. However, of the nine “positive” studies only one⁷ showed a significant excess, evidence of an exposure gradient for risk, and apparent absence of obvious confounders, except for asbestos, which is being more fully investigated. In the remaining eight there existed either serious confounding, a relationship between lung cancer and silicosis, not silica, the absence of dose dependency, or some combination of these. The epidemiological database is quite inadequate for reliable assessment of risk as, with the possible exception of the Homestake studies,²² which were negative, and that of Checkoway,⁷ no attempts have been made so far to study exposure response in quantitative terms. The extent to which any risk of lung cancer associated with silica exposure is confined to those with silicosis is also uncertain. The five studies shown in table 3 suggest that those without silicosis were at little or no excess risk, but in none of these was allowance adequately made for smoking. Although studies using silicosis registries have raised the question of a link between the risk of lung cancer and exposure to silica, they cannot contribute to any formal risk assessment because of the unquantifiable selection bias.

In an earlier review³ the criteria of Bradford-Hill were applied to the issue of causal inferences based on evidence available to the

IARC working group in 1986. It was concluded that the results were not consistent and varied greatly in strength. However, they were biologically plausible and reasonable in their specificity and time relationships. Except for the fact that the diatomite study has now shown a clear exposure response,⁷ the situation today has not changed much.

In conclusion, since 1986 the epidemiological evidence has become somewhat stronger in suggesting a link between exposure to silica and risk of lung cancer. This is primarily (but not exclusively) the result of the study on diatomite workers.⁷ This study showed an overall excess of lung cancer risk, dealt with smoking in a reasonable manner, and showed dose dependency with estimated exposure to crystalline silica. Although the question of possible confounding by asbestos exposure is under detailed re-evaluation, such exposure would have to have been heavy and widespread to affect the results greatly.

In the absence of lung fibrosis, the evidence that exposure to crystalline silica in itself induces lung cancer must still be considered scanty and inconsistent but biologically plausible. Resolution of this question will depend on further large cohort studies in which there are no important confounding exposures, and where estimates of past exposure to silica are sufficient to demonstrate an exposure response, if present. Clearly, such studies must include populations exposed primarily to quartz. The link between lung cancer and pulmonary fibrosis, as seen with asbestos,²⁹ fibrosing alveolitis,³⁰ and now it seems with silicosis, is an important phenomenon for which several possible explanations have been offered. Fibrogenesis may predispose to carcinogenesis (for example, the two processes may share common growth factors and subsequent cellular proliferation); the two diseases may simply reflect level of exposure to a causal agent; or it could be that cigarette smoking predisposes to fibrosis and is the main cause of the cancer. These three concepts are not mutually exclusive, and indeed may all play their part.

- 1 International Agency for Research on Cancer. Monographs on the evaluation of the carcinogenic risk of chemicals to humans. *Silica and some silicates*. Volume 42. Lyon: International Agency for Research on Cancer (IARC), 1987.
- 2 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Overall evaluations of carcinogenicity: an updating of IARC monographs*. Supplement 7, Volumes 1-42. Lyon: World Health Organization (WHO), 1987.
- 3 McDonald JC. Silica, silicosis, and lung cancer. *Br J Ind Med* 1989;46:289-91.
- 4 *Proceedings of the Second International Symposium on Silica, Silicosis, and Cancer*. 28-30 October 1993, San Francisco (in press).
- 5 *Proceedings of the International Conference on Crystalline Silica Health Effects*, 18-20 April 1994, Baltimore. *Appl Occup Environ Hyg* (in press).
- 6 Merlo F, Costantini M, Reggiardo G, Ceppi M, Puntoni R. Lung cancer risk among refractory brick workers exposed to crystalline silica: a retrospective cohort study. *Epidemiology* 1991;2:299-305.
- 7 Checkoway H, Heyer NJ, Demers PA, Breslow NE. Mortality among workers in the diatomaceous earth industry. *Br J Ind Med* 1993;50:586-97.
- 8 Meijers JM, Swaen GM, Volovics A, Slangen JJ, Van Vliet R. Lung cancer risk and lung cancer in ceramic workers: a case-control study. *Int J Epidemiol* 1990;19:19-25.
- 9 Thomas TL. Lung cancer mortality among pottery workers in the United States. In: Simonato L, Fletcher AC, Saracci R, Thomas TL, eds. *Occupational exposure to silica and cancer risk*. Lyon: International Agency for Research on Cancer, 1990:75-82.
- 10 Winter PD, Gardner MJ, Fletcher AC, Jones RD. A mortality follow-up study of pottery workers: preliminary findings on lung cancer. In: Simonato L, Fletcher AC, Saracci R, Thomas TL, eds. *Occupational exposure to silica and cancer risk*. Lyon: International Agency for Research on Cancer, 1990:83-94.
- 11 Cherry N, McNamee R, Burgess G, Turner S, McDonald JC. Cohort mortality study of British pottery workers exposed to crystalline silica: preliminary report. In: *Proceedings of the International Conference on Crystalline Silica Health Effects*, 18-20 April, 1994, Baltimore (in press).
- 12 Neuberger M, Kundi M. Occupational dust exposure and cancer mortality - results of a prospective cohort study. In: Simonato L, Fletcher AC, Saracci R, Thomas TL, eds. *Occupational exposure to silica and cancer risk*. Lyon: International Agency for Research on Cancer, 1990:65-74.
- 13 McLaughlin JK, Chen JQ, Dosemeci M, Chen RA, Rexing SH, Zhen W, et al. A nested case-control study of lung cancer among silica exposed workers in China. *Br J Ind Med* 1992;49:167-71.
- 14 Kusiak RA, Ritchie AC, Muller J, Springer J. Mortality from lung cancer in Ontario uranium miners. *Br J Ind Med* 1993;50:920-8.
- 15 Mastrangelo G, Zambon P, Simonato L, Rizzi P. A case-referent study investigating the relationship between exposure to silica dust and lung cancer. *Int Arch Occup Environ Health* 1988;60:299-302.
- 16 Costello J, Graham WG. Vermont granite workers' mortality study. *Am J Ind Med* 1988;13:483-97.
- 17 Mehnert WH, Staneczek W, Mohner M, Konetzke G, Muller W, Ahlendorf W, et al. A mortality study of a cohort of slate quarry workers in the German Democratic Republic. In: Simonato L, Fletcher AC, Saracci R, Thomas TL, eds. *Occupational exposure to silica and cancer risk*. Lyon: International Agency for Research on Cancer, 1990:55-64.
- 18 Koskela RS, Klockars M, Järvinen E, Rossi A, Kolari PJ. Cancer mortality of granite workers 1940-1985. In: Simonato L, Fletcher AC, Saracci R, Thomas TL, eds. *Occupational exposure to silica and cancer risk*. Lyon: International Agency for Research on Cancer, 1990:43-54.
- 19 Hnizdo E, Sluis-Cremer GK. Silica exposure, silicosis, and lung cancer: a mortality study of South African gold miners. *Br J Ind Med* 1991;48:53-60.
- 20 Hnizdo E, Murray J, Klempman S. Histological type of lung cancer in relation to silica dust and silicosis in South African gold miners. In: *Proceedings of Second International Symposium on Silica, Silicosis, and Cancer*, 28-30 October 1993, San Francisco (in press).
- 21 Hnizdo E. Risk of silicosis in relation to fraction of respirable quartz (letter). *Am J Ind Med* 1994;25:771-2.
- 22 Shy CM, Blair A, Amandus H, Wolf S, Heineman E. A case-control study of silica and lung cancer in the North Carolina dusty trades industry. In: *Proceedings of Second International Symposium on Silica, Silicosis, and Cancer*, 28-30 October 1993, San Francisco (in press).
- 23 Carta P, Cocco PL, Casula D. Mortality from lung cancer among Sardinian patients with silicosis. *Br J Ind Med* 1991;48:122-9.
- 24 Benn RT, Hutchings SJ, Thomas PG, Elliott RC, Osman J, Jones RD. Lung cancer in a population exposed to silica. *Thorax* 1993;48:436.
- 25 Steenland K, Brown D. Mortality study of gold miners exposed to silica and nonasbestiform amphibole minerals: an update. In: *Proceedings of Second International Symposium on Silica, Silicosis, and Cancer*, 28-30 October 1993, San Francisco (in press).
- 26 Amandus HE, Shy C, Wing S, Blair A, Heineman EF. Silicosis and lung cancer in North Carolina dusty trades workers. *Am J Ind Med* 1991;20:57-70.
- 27 Amandus HE, Castellan RM, Shy C, Heineman EF, Blair A. Reevaluation of silicosis and lung cancer in North Carolina dusty trades workers. *Am J Ind Med* 1992;22:147-53.
- 28 Finkelstein MM. Silicosis surveillance in Ontario: detection rates, modifying factors, and screening intervals. In: *Proceedings of Second International Symposium on Silica, Silicosis, and Cancer*, 28-30 October, 1993, San Francisco (in press).
- 29 Hughes JM, Weill H. Asbestosis as a precursor of asbestos related lung cancer: results of a prospective mortality study. *Br J Ind Med* 1991;48:229-33.
- 30 Turner-Warwick M, Lebowitz M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis and lung cancer. *Thorax* 1980;35:496-9.
- 31 Moulin JJ, Wild P, Mantout B, Fournier-Betz M, Mur JM, Smagghe G, et al. Mortality from lung cancer and cardiovascular diseases among stainless-steel producing workers. *Cancer Causes Control* 1993;4:75-81.
- 32 Sherson D, Svane O, Lynge E. Cancer incidence among foundry workers in Denmark. *Arch Environ Health* 1991;46:75-81.
- 33 Ahlman K, Koskela RS, Kuikka P, Koponen M, Annanmaki M. Mortality among sulfide ore miners. *Am J Ind Med* 1991;19:603-17.
- 34 Chen SY, Hayes RB, Liang SR, Li QG, Stewart PA, Blair A, et al. Mortality experience of haematite mine workers in China. *Br J Ind Med* 1990;47:175-81.
- 35 Siemiatycki J, Gerin M, Dewar R, Lakhani R, Begin D, Richardson L. Silica and cancer associations from a multicenter occupational exposure case-referent study. In: Simonato L, Fletcher AC, Saracci R, Thomas TL, eds. *Occupational exposure to silica and cancer risk*. Lyon: In-

- ternational Agency for Research on Cancer (IARC), 1990: 29–42.
- 36 Hessel PA, Sluis-Cremer GK, Hnizdo E. Silica exposure, silicosis, and lung cancer: a necropsy study. *Br J Ind Med* 1990;47:4–9.
 - 37 Hodgson JT, Jones RD. Mortality of a cohort of tin miners 1941–1986. *Br J Ind Med* 1990;47:665–76.
 - 38 Lynge E, Kurppa K, Kristofersen L, Malker H, Sauli H. Occupational groups potentially exposed to silica dust: a comparative analysis of cancer mortality and incidence based on the Nordic occupational mortality and cancer incidence registers. In: Simonato L, Fletcher AC, Saracci R, Thomas TL, eds. *Occupational exposure to silica and cancer risk*. Lyon: International Agency for Research on Cancer, 1990:7–20.
 - 39 Forastiere F, Lagorio S, Michelozzi P, Cavariani F, Arca M, Borgia P, et al. Silica, silicosis and lung cancer among ceramic workers: a case-referent study. *Am J Ind Med* 1986;10:363–70.
 - 40 Amandus HE, Costello J. Silicosis and lung cancer in United States metal miners. *Arch Environ Health* 1991;46:82–9.
 - 41 Merlo F, Doria M, Fontana L, Ceppi M, Chesi E, Santi L. Mortality from specific causes among silicotic subjects: a historical prospective study. In: Simonato L, Fletcher AC, Saracci R, Thomas TL, eds. *Occupational exposure to silica and cancer risk*. Lyon: International Agency for Research on Cancer, 1990:105–11.
 - 42 Infante-Rivard C, Armstrong B, Petitclerc M, Cloutier LG, Theriault G. Lung cancer mortality and silicosis in Quebec, 1938–1985. *Lancet* 1989;ii:1504–7.
 - 43 Chia SE, Chia KS, Phoon WH, Lee HP. Silicosis and lung cancer among Chinese granite workers. *Scand J Work Environ Health* 1991;17:170–4.
 - 44 Tornling G, Hogstedt C, Westerholm P. Lung cancer incidence among Swedish ceramic workers with silicosis. In: Simonato L, Fletcher AC, Saracci R, Thomas TL, eds. *Occupational exposure to silica and cancer risk*. Lyon: International Agency for Research on Cancer, 1990:113–9.
 - 45 Ng TP, Chan SL, Lee J. Mortality of a cohort of men in a silicosis register: further evidence of an association with lung cancer. *Am J Ind Med* 1990;17:163–71.
 - 46 Chiyotani K, Saito K, Okubo T, Takahashi K. Lung cancer risk among pneumoconiosis patients in Japan, with special reference to silicotics. In: Simonato L, Fletcher AC, Saracci R, Thomas TL, eds. *Occupational exposure to silica and cancer risk*. Lyon: International Agency for Research on Cancer, 1990:95–104.
 - 47 Finkelstein M, Liss GM, Krammer F, Kusiak RA. Mortality among workers receiving compensation awards for silicosis in Ontario 1940–1985. *Br J Ind Med* 1987;44:588–94.
 - 48 Zambon P, Simonato L, Mastrangelo G, Winkelmann R, Saia B, Crepet M, et al. Mortality of workers compensated for silicosis during the period 1959–1963 in the Veneto region of Italy. *Scand J Work Environ Health* 1987;13:118–23.