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. These conclusions led the IARC to classify crystalline silica as 2A – that is, “probably carcinogenic to humans”.

The evidence on which these judgements are based was summarised in an editorial published in 1989. 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 1993 and Baltimore in April 1994 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. 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 1993 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).
Table 1  Studies based on populations defined by exposure to crystalline silica

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Population studied</th>
<th>Overall lung cancer mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checkoway et al</td>
<td>Cohort</td>
<td>Diatomite workers</td>
<td>SMR 1.43</td>
<td>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</td>
</tr>
<tr>
<td>McLaughlin et al</td>
<td>Nested case-control</td>
<td>Pottery workers and miners</td>
<td>NA</td>
<td>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 &quot;limited support&quot; for association of silica exposure and lung cancer; relationship with silicosis</td>
</tr>
<tr>
<td>Kuniak et al</td>
<td>Cohort</td>
<td>Metal miners</td>
<td>SMR 2.25</td>
<td>No exposure response for silica exposure; radon shows best relationship; also arsenic; author attributes excess primarily to radon with contribution to risk by arsenic</td>
</tr>
<tr>
<td>Merlo et al</td>
<td>Cohort</td>
<td>Refractory brick workers</td>
<td>SMR 1.77; with 19 + years of exposure, SMR 2.01</td>
<td>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</td>
</tr>
<tr>
<td>Neuberger et al</td>
<td>Cohort</td>
<td>Mixed industries</td>
<td>SMR: foundries 164; other metal industries 133; ceramics and glass 237; stone and construction 294</td>
<td>Increased risk response in the presence of silica</td>
</tr>
<tr>
<td>Meijers et al</td>
<td>Case-control</td>
<td>Ceramic industry</td>
<td>OR 1.11 (0.77–1.61)</td>
<td>Non-significant trend for OR to increase with duration of employment and silica exposure; there is little to relate silica exposure and cancer risk; no information regarding silicotics</td>
</tr>
<tr>
<td>Mehnert et al</td>
<td>Cohort</td>
<td>Slate quarry workers</td>
<td>SMR 109, interpreted as &quot;no overall increase&quot;; excess risk found in silicotics (SMR 183)</td>
<td>Tendency for risk to increase with time after first exposure</td>
</tr>
<tr>
<td>Thomas</td>
<td>Cohort</td>
<td>Union pottery and ceramic workers</td>
<td>SMR 1.43 for ceramic workers</td>
<td>Lung cancer mortality increased with talc exposure, not silica; possible relationship with non-fibrous talc; author indicates that silica as &quot;co-factor or promoter cannot be ruled out&quot;</td>
</tr>
<tr>
<td>Winter et al</td>
<td>Cohort</td>
<td>Pottery workers</td>
<td>SMR 1.4 (1.07–1.8)</td>
<td>Weak relation between increasing silica exposure and lung cancer risk; smoking taken into account</td>
</tr>
<tr>
<td>Costello et al</td>
<td>Cohort</td>
<td>Vermont granite workers</td>
<td>SMR 1.16</td>
<td>Elevated lung cancer risk only in stone shed workers employed prior to 1930</td>
</tr>
<tr>
<td>Mastrangelo et al</td>
<td>Case-control</td>
<td>High silica exposure region of the country</td>
<td>Increased risk only in the presence of silica</td>
<td>Weak silica and strong smoking effect; some dose dependency of risk</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Population studied</th>
<th>Overall lung cancer mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moulin et al.</td>
<td>Cohort</td>
<td>Stainless steel production</td>
<td>Only foundry workers within this population had an excess: SMR 2.29; 3.34 in 30 + yrs since hire</td>
<td>Excess lung cancer incidence confined to those who had worked in foundries &gt;20 yrs; &quot;Correlation&quot; found between silica exposure and lung cancer incidence during follow up (through 1985); probable confounders</td>
</tr>
<tr>
<td>Sheerson et al.</td>
<td>Incidence from cancer registry</td>
<td>Foundry workers</td>
<td>Morbidity ratio 1.3 (95% CI 1.12 to 1.51)</td>
<td>Excess lung cancer incidence confined to those who had worked in foundries &gt;20 yrs; &quot;Correlation&quot; found between silica exposure and lung cancer incidence during follow up (through 1985); probable confounders</td>
</tr>
<tr>
<td>Amandus et al.</td>
<td>Cohort</td>
<td>Metal miners</td>
<td>SMR 1.73 (95% CI 0.94 to 2.9) in silicotics; 1.18 (0.98 to 1.42) in non-silicotics</td>
<td>Apparent exposure response relationship but thought to be best related to radon exposure by the authors</td>
</tr>
<tr>
<td>Hnizdo et al.</td>
<td>Cohort</td>
<td>Gold miners</td>
<td>RR = 1.023 per 1000 particle years; overall SMR not given</td>
<td>No exposure response; likely confounding by PAH; chromium compounds</td>
</tr>
<tr>
<td>Ahlman et al.</td>
<td>Cohort</td>
<td>Copper and zinc miners, iron ore miners</td>
<td>SMR 2.33</td>
<td>Excess lung cancer incidence confined to those who worked in foundries &gt;20 yrs; &quot;Correlation&quot; found between silica exposure and lung cancer incidence during follow up (through 1985); probable confounders</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>Case-control</td>
<td>Cancer patients</td>
<td>SMR 3.7</td>
<td>No exposure response; likely to have been confounding exposures (radon, PAH)</td>
</tr>
<tr>
<td>Siemiatycki et al.</td>
<td>Case-control</td>
<td>Cancer patients</td>
<td>SMR 3.7</td>
<td>Exposure response limited to smokers; probable radon confounding</td>
</tr>
<tr>
<td>Hessel et al.</td>
<td>Case-control</td>
<td>Necropsy cases; varying exposures</td>
<td>No excess by silica exposure or silicosis</td>
<td>Smoking taken into account; weak design</td>
</tr>
<tr>
<td>Hodgson et al.</td>
<td>Cohort</td>
<td>Tin miners</td>
<td>Overall SMR approximately 160</td>
<td>No exposure response; likely radon confounding</td>
</tr>
<tr>
<td>Koskela et al.</td>
<td>Cohort</td>
<td>Granite workers</td>
<td>SMR 220 (those followed up 15 + yrs)</td>
<td>No exposure response; likely radon confounding; unexplained deficiencies of deaths in other cancers</td>
</tr>
<tr>
<td>Lyne et al.</td>
<td>Incidence</td>
<td>Occupational and cancer registries</td>
<td>RR in foundries (up to 1.73) and miners (up to 5.02)</td>
<td>No exposure response; weak design (record linkages); probable confounding exposures</td>
</tr>
</tbody>
</table>

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 1.27). Mortality of white men in the USA was used as the reference population, but comparison against local county rates gave similar results. Semi-quantitative 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 in a Dutch ceramic plant, was essentially negative in that 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 Thomas, 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 UK 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. 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 Neuberger on the experience of Austrian workers in a variety of dusty trades. This study and two others by McLaughlin et al. in China and by Kusiak 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 miners' 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. 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, but excess risk decreased for compensated relative risk (RR 1.9), but no increase without silicosis (RR 0.9). The remaining two reports, one on Vermont granite workers and the other on German slate quarry workers by Mehnert et al., 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. in Finnish granite workers, and the cohort study of Hnizdo and colleagues in South Africa. 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) 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.

A case-control study of silica and lung cancer in the North Carolina "dusty trades" industry was recently presented. 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-years 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 and the other at the annual meeting of the British Thoracic Society in December 1992 (Benn et al.). 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. 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 0.78 to 2.12) and the 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.
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),20,21 the cases of silicosis were ascertained from registers of persons compensated for
the disease or admitted to hospital with this diagnos-
sis. Apart from the question of whether mor-
tality 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 sil-
icosis. 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 indi-
cations from silicosis surveillance in Ontario
that smokers were more likely to have a diag-
nosis of silicosis than non-smokers.28 The study
by Amandus et al20,21 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 rea-
sonably satisfactory design and presentation,
and primarily concerned with the effects of
exposure to crystalline silica on the risk of lung
cancer. Of these, nine6791012-16 provided some
evidence of excess risk in exposed workers
(or a subgroup) and two17 failed to do so. How-
ever, of the nine “positive” studies only one1 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 seri-
ous 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,10 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 con-
fined 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 ade-
quately 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 un-
quantifiable selection bias.

In an earlier review1 the criteria of Bradford-
Hill were applied to the issue of causal in-
ferences based on evidence available to the

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

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Population studied</th>
<th>Silicosis</th>
<th>No silicosis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forastiere et al39</td>
<td>Case-control</td>
<td>Ceramic workers</td>
<td>RR 3-9</td>
<td>RR 1-4</td>
<td>Excess mainly found in those with silicosis but not those who were non-smokers; no obvious confounding of job exposures</td>
</tr>
<tr>
<td>Mehnert et al40</td>
<td>Cohort</td>
<td>Slate quarry workers</td>
<td>SMR 1-83</td>
<td>SMR 0-91</td>
<td>Tendency for risk to increase with time since first exposure</td>
</tr>
<tr>
<td>McCaughan et al41</td>
<td>Nested case-control</td>
<td>Pottery workers and miners</td>
<td>OR 0-5</td>
<td>OR 1-0</td>
<td>Significant risk increase with silica exposure in tin miners (PAH, radon, arsenic likely important confounders); non-significant exposure response in pottery workers</td>
</tr>
<tr>
<td>Mastrangelo et al42</td>
<td>Case-control</td>
<td>Mines and quarries</td>
<td>RR 1-8</td>
<td>RR 0-9</td>
<td>Weak silica and strong smoking effect; some dose dependency of risk</td>
</tr>
<tr>
<td>Amandus et al43</td>
<td>Cohort</td>
<td>US metal miners</td>
<td>SMR 1-73</td>
<td>SMR 1-18</td>
<td>Smoking taken into account; excess lung cancer risk in those with silicosis; radon confounding could not be excluded</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Lung cancer mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merlo et al44</td>
<td>SMR 6-81</td>
<td>Smoking adjustment made; the author states that the excess risk is due to silicosis</td>
</tr>
<tr>
<td>Infante-Rivard et al45</td>
<td>SMR 3-5</td>
<td>SMR increased after 10 and 15 years latency, never reaching significance; no relationship with severity of silicosis</td>
</tr>
<tr>
<td>Carta et al46</td>
<td>SMR 1-29 (0-8-2-0) SMR 4-11 in heavy smokers</td>
<td>Increasing trend with severity of silicosis and exposure duration; smoking alone did not explain findings</td>
</tr>
<tr>
<td>Chia et al47</td>
<td>9 cases of lung cancer among 159 registered silicotics; standardized incidence ratio (SIR) 2-01 (95% CI 0-92 to 3-81)</td>
<td>Excess risk in 280 patients with silicosis from ceramics industry</td>
</tr>
<tr>
<td>Tomling et al48</td>
<td>SMR = 188 (95% CI 85 to 356)</td>
<td>Increasing risk with duration of employment and latency; asbestos, PAH exposure excluded; increasing trend with severity of silicosis; all lung cancers in smokers</td>
</tr>
<tr>
<td>Ng et al49</td>
<td>SMR 2-03 (95% CI 1-35 to 2-93)</td>
<td>No exposure response shown; employment in the ceramics industry was risk factor</td>
</tr>
<tr>
<td>Chiyotani et al50</td>
<td>SMR 6-03 (95% CI 5-29 to 6-77) in 1941 hospitalised silicotics</td>
<td>Smoking did not explain the risk</td>
</tr>
<tr>
<td>Finklestein et al51</td>
<td>SMR 188-366</td>
<td>No exposure response; possible smoking confounding; increased risk in compensated subjects with silicosis</td>
</tr>
</tbody>
</table>

SMR = standardised mortality ratio; 95% CI = 95% confidence interval; PAH = polycyclic aromatic hydrocarbons.
Exposure to cancer that the diatomite have to diemological evidence has and diatomite workers. This on stronger in smoking that be that level of silica. if link to sufficient duces lung disease. In: Proceedings of the International Conference on Diatomite Health Effects, 18-20 April, 1994, Baltimore (in press).


ternational Agency for Research on Cancer (IARC), 1990: 29-42.


