

Lung Cancer Risk, Silica Exposure, and Silicosis in Chinese Mines and Pottery Factories: The Modifying Role of Other Workplace Lung Carcinogens

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Background *Aims of our study were to explore whether and to what extent exposure to other lung carcinogens, or staging and clinical features of silicosis modify or confound the association between silica and lung cancer.*

Methods *We used data from a nested case-control study, conducted in the late 1980s in 29 Chinese mines and potteries (10 tungsten mines, 6 copper and iron mines, 4 tin mines, 8 pottery factories, and 1 clay mine), that included 316 lung cancer cases and 1,356 controls, matched by decade of birth and facility type. The previous analysis of these data presented results by type of mine or factory.*

Results *In our study, pooling all 29 Chinese work sites, lung cancer risk showed a modest association with silica exposure. Risk did not vary after excluding subjects with silicosis or adjusting the risk estimates by radiological staging of silicosis. Strong correlation among exposures prevented a detailed evaluation of the role of individual exposures. However, lung cancer risk was for the most part absent when concomitant exposure to other workplace lung carcinogens, such as polycyclic aromatic hydrocarbons (PAHs), nickel or radon-daughters, was considered. The cross classification of lung cancer risk by categories of exposure to respirable silica and total respirable dust did not show an independent effect of total respirable dust. Silicosis showed a modest association with lung cancer, which did not vary by severity of radiological staging, or by radiological evidence of disease progression, or by level of silica exposure. However, among silicotic subjects, lung cancer risk was significantly elevated only when exposure to cadmium and PAH had occurred.*

Conclusions *Our results suggest that, among silica-exposed Chinese workers, numerous occupational and non-occupational risk factors interact in a complex fashion to modify lung cancer risk. Future epidemiological studies on silica and lung cancer should incorporate detailed information on exposure to other workplace lung carcinogens, total respirable dust, and on surface size and age of silica particles to understand whether and to what extent they affect the carcinogenic potential of silica. Am. J. Ind. Med. 40:674–682, 2001. © 2001 Wiley-Liss, Inc.*

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INTRODUCTION

In 1995, two reviews of virtually the same published reports on silica and lung cancer came to different conclusions. One review summarized that “there is sufficient evidence to classify crystalline silica as a human carcinogen” [Klein and Christopher, 1995]. The second review concluded that “there is a little evidence of any increase in lung cancer in the absence of silicosis or at relatively low levels of exposure or disease prevalence” [McDonald, 1995]. However, in 1997, the International Agency for Research on Cancer (IARC) upgraded its evaluation of crystalline silica to a known human carcinogen [IARC, 1997]. The epidemiological studies reviewed by IARC pointed out important variations in silica-associated lung cancer risk by geographic area, type of study, type of industry, and levels of exposure, with inconsistent dose-response trends, and low risks frequently associated with the highest exposure levels. On the other hand, the experimental evidence for silica carcinogenesis has been criticized as based upon results in a single species of rodent, particularly the F-344 rat strain, while results for the Wistar rat strain were contradictory, as were those for Syrian hamsters, mice, and guinea pigs [Holland, 1995]. Moreover, in all experiments where tumors were observed, fibrosis was also present. Rats reportedly developed lung tumors following chronic inhalation of very high doses of many insoluble dusts, by triggering a series of events related to dust overload, defined as a significant prolongation of alveolar macrophages (AM) mediated particle clearance due to high pulmonary particle load [Oberdorster, 1995]. However, based largely on the same experimental studies, the conclusions of the IARC working group stated: “there is sufficient evidence in experimental animals for the carcinogenicity of quartz and cristobalite” [IARC, 1997].

A mortality follow-up of silica-exposed workers in 29 Chinese mines and factories in the late 1980s did not show an increased SMR for lung cancer overall, with significantly fewer than expected deaths in tungsten mines and pottery factories, no excess in iron/copper mines, and a significant twofold excess in tin mines [Chen et al., 1992]. Silicosis and pulmonary heart disease were common causes of death among these workers. A nested case-control study of this cohort found that lung cancer risk increased by cumulative exposure to silica in tin mines and potteries, while the trend was inverse in tungsten mines and iron/copper mines [McLaughlin et al., 1992]. Risk associated with the highest exposure category was 0.5 in tungsten mines, 0.7 in iron/copper mines, 2.1 in potteries, and 3.1 in tin mines. The association between silicosis and lung cancer was also

inconsistent: risk was significantly elevated in iron/copper mines and tin mines, and it was below unity in tungsten mines and potteries [McLaughlin et al., 1992].

Heterogeneity of results across human and experimental studies on silica carcinogenesis may reflect chance occurrences, bias or confounding, or perhaps a true biological phenomenon related to variation across countries and workplaces in the carcinogenic potential of inhaled dust. To investigate whether exposure to multiple workplace lung carcinogens, or to different levels of total respirable dust, or radiological staging of silicosis and its radiological progression over time might account for inconsistent results across studies of silica and lung cancer, and the resulting inconsistent opinions, we pooled data from our earlier collaborative study of Chinese mines and potteries [Chen et al., 1992; McLaughlin et al., 1992; Dosemeci et al., 1993].

Exposure levels to total and respirable dust, respirable silica, arsenic, radon-daughters, and polycyclic aromatic hydrocarbon (PAH), along with the proportion of the exposed workforce, has been previously described by mine and facility type [Chen et al., 1992; McLaughlin et al., 1992; Dosemeci et al., 1993, 1995]. Total dust exposure was greatest in pottery factories, while exposure estimates of respirable dust and respirable silica were highest in tungsten mines and tin mines. Exposures were high in all workplaces, however. For example, in iron and copper mines, where average exposure to silica was the lowest, in 1981–1987 it was still twice as high as the current US Permissible Exposure Limit (PEL) for dust, expressed as 100% silica (approximately $100 \mu\text{g}/\text{m}^3$) [U.S.OSHA, 1994]. Silica exposure was highest in the 1950s and it subsequently declined in all workplaces except pottery factories. Among the other workplace risk factors for lung cancer considered in the study, average exposure to cadmium in 1950–1987 was 2–4.5-times higher and exposure to PAH was 22–60 times higher than the current US PEL. Average exposure to arsenic, nickel, and radon-daughters in 1950–1987 were within current US PELs.

A strong correlation existed among all study exposures in tin mines, and for PAH and silica in tungsten and iron and copper mines. In order to test the validity of the retrospective exposure assessment used in the study, the association between silica exposure and silicosis and its linear increase with cumulative exposure was demonstrated in a separate analysis [Dosemeci et al., 1994].

METHODS

Details of the study, including diagnostic procedures, exposure monitoring data, Chinese systems for tracing vital

status, and follow-up details, have been published elsewhere [Chen et al., 1992; McLaughlin et al., 1992; Dosemeci et al., 1993]. Briefly, a collaborative study between the US National Cancer Institute, the US National Institute for Occupational Safety and Health, and the Chinese Tongji Medical University was undertaken in the late 1980s, in 29 Chinese mines and factories: 10 tungsten mines, located in the Jaingxi, Henan, and Hunan provinces; 6 copper and iron mines in Hubei province; 4 tin mines in Guangxi province; and 8 pottery factories and 1 clay mine also in Jiangxi and Hunan provinces. Personnel records, rosters, and files from these factories and mines were used to compile a list of all employees with at least 1 year of employment in 1972–1974, with personal data including job history. The total cohort was approximately 68,000. Industrial hygiene data were available from the 1950s for total dust, particle size, and percent free silica, and were used to estimate an exposure level for each job by calendar-year periods. Measurements of current exposure to total dust, respirable dust, and thoracic dust were made, and the percent free silica (quartz) determined. Radon-daughters, arsenic, PAH, cadmium, nickel, talc, and asbestos exposure determinations were also conducted in each of the 29 mines and factories by both US and Chinese industrial hygienists. This information allowed estimation of exposure to each occupational hazard for a total of 1,392 facility/job title combinations over 14 calendar periods starting from 1950 [Dosemeci et al., 1993]. Average exposure levels to total dust and respirable silica decreased during the study period in all mines, with the sharpest drop in the 1960s [Dosemeci et al., 1995]. However, exposure levels did not decrease over time in pottery factories. Exposure to asbestos and talc in the study mines and factories was minimal and was not considered in this analysis.

Registries of employees with silicosis are required by law in Chinese workplaces with silica exposure, and chest X-rays are given yearly to dust-exposed workers, which allowed identification of silicotics among cohort members. Information on silicosis stage at the first diagnosis, any subsequent changes in radiological diagnosis and staging of the disease, and the dates of diagnosis were available for each study subject.

Vital status of cohort members from date of entry (January 1972 to December 1974) through December 31, 1989 was obtained. For the nested case-control analysis, 319 male cohort members who died from lung cancer were identified. Diagnosis of lung cancer was based primarily on death certificates, but also included information from work and hospital records. There was, however, insufficient pathological data available to distinguish with assurance among the various lung cancer histological types. The nested case-control analysis was restricted to male lung cancer cases, because the vast majority of cohort members (95%) were men, and only 11 lung cancer cases occurred

among women. Overall, 1,358 male cohort members were randomly selected as controls, approximately 4:1 matched to cases by decade of birth and mine or factory. In order to be eligible, controls must have survived to an age equal or greater than the age of the index case at diagnosis. Further information on demographics, medical history, and personal habits such as smoking was acquired by questionnaire from the study subject or his next of kin [McLaughlin et al., 1992].

For the present analysis, we included only study subjects with available questionnaire information, which led to exclusion of five subjects, three cases and two controls, leaving for study 316 cases and 1356 controls. Cumulative exposure to occupational risk factors for lung cancer among matched controls was truncated at the age of diagnosis of lung cancer in the index case.

Silicosis was classified in three ways: 1) a yes/no classification, which included dubious classifications (correspondent to the ILO 0/1 categorization) among non-silicotic subjects; 2) by radiological staging, using the Chinese classification of silicosis; 3) according to the progression (yes/no) in radiological staging compared to the first positive radiograph, as derived from subsequent X-ray exams.

Odds ratios (OR) and their 95% confidence intervals (95% CI) were generated by unconditional logistic regression with the GMBO program in the Epicure[®] software. All risk estimates were adjusted by age at first exposure (continuous), and cigarettes per day (never smokers, ≤ 15 cigarettes/day, 16–25 cigarettes/day, and ≥ 26 cigarettes/day). Adjustment by year of birth did not change the results.

RESULTS

The inconsistency of the association between silica exposure and lung cancer risk by mine/facility type in this study population was previously described [McLaughlin et al., 1992]. In the present analysis of the pooled study population, we observed a modest association, with a significant 60% excess lung cancer risk in the third quartile of cumulative exposure to silica and a decrease to a non-significant 20% excess in the fourth quartile (model 1, Table I). Limiting the analysis to subjects with radiographs negative for silicosis, adjusting the risk estimates by radiological stage of silicosis (models 2 and 3, Table I), or including subjects whose radiographs were classified as dubious among non-silicotics (not shown in the tables) did not change the risk estimates associated with silica exposure. Among silicotics, lung cancer did not show an upward trend by cumulative exposure to respirable silica (Table II). However, risk increased by severity of silicosis for the first three levels of cumulative silica exposure but not in the highest. Such an increase in risk by severity of silicosis stage was no longer evident after combining all

TABLE I. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Lung Cancer by Quartiles of Cumulative Exposure to Respirable Silica for all Facilities Combined

	Quartiles of cumulative exposure to respirable silica (mg/m ³ /year)								
	Unexposed	0.01–3.7		3.8–10.7		10.8–26.9		≥27	
Cases/ Controls	OR	Cases/ Controls	OR (95% CI)						
Model I									
68/384	1.0	54/250	1.1 (0.8–1.7)	67/239	1.5 (1.0–2.2)	70/235	1.6 (1.1–2.4)	57/248	1.2 (0.8–1.9)
Model II									
67/370	1.0	44/205	1.1 (0.7–1.7)	43/155	1.5 (0.9–2.3)	37/132	1.5 (0.9–2.5)	16/69	1.3 (0.7–2.5)
Model III									
68/384	1.0	54/250	1.1 (0.8–1.7)	67/239	1.5 (1.0–2.3)	70/235	1.6 (1.0–2.4)	57/248	1.1 (0.7–1.7)

Model I : risk estimates are adjusted by age at first exposure (continuous) and smoking (four categories of cigarettes/day).

Model II : same as model I, but analysis limited only to non-silicotics (X-rays classified as dubious are also excluded).

Model III : risk estimates adjusted also by radiological classification of pneumoconiosis. (Chinese classification).

categories of silica exposure. Adjusting the risk estimates by quartiles of cumulative silica exposure did not change lung cancer risk associated with the various stages and classifications of silicosis (Table III). Overall, the association between silicosis and lung cancer was modest, and it did not vary by radiological evidence of progression in silicosis stage as derived from subsequent radiographs compared to the first diagnosis.

In our earlier case-control analysis, strong collinearity among exposures within mine/facility type did not allow for the separation of the effects of silica exposure from those related to exposure to other lung carcinogens [McLaughlin et al., 1992]. Lung cancer risk did not increase significantly

by quartiles of cumulative exposure to cadmium, nickel, or radon-daughters, while a modest significant increase in risk was observed in the highest quartile of exposure to arsenic (OR = 1.7) and to PAH (OR = 1.4). In this study, the stratified analysis of lung cancer risk associated with respirable silica by exposure to each of the other five lung carcinogens evaluated showed that lung cancer risk was higher among subjects exposed to silica but not to nickel, radon-daughters or PAH (Table IV a–e). Risk associated with silica exposure did not vary among workers by exposure to arsenic and cadmium. Excluding silicotic subjects did not change the ORs. Even in our pooled analysis, no study subject had exposure to PAH or any of the

TABLE II. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Lung Cancer by Quartiles of Cumulative Exposure to Respirable Silica and Silicosis Stage

	Silicosis		
	Negative	Class 1	Class 2–3
Respirable silica			
Unexposed	67/370 ^A	0/2	0/0
	1.0 ^B	—	—
0.01–3.7 mg/m ³ /year	44/205	4/11	2/5
	1.1 (0.7–1.7) ^C	1.9 (0.6–6.5)	1.7 (0.3–9.5)
3.8–10.7 mg/m ³ /year	43/155	7/30	3/5
	1.4 (0.9–2.3)	1.0 (0.4–2.6)	3.4 (0.6–19.2)
10.8–26.9 mg/m ³ /year	37/132	15/32	10/20
	1.5 (0.9–2.4)	2.3 (1.1–4.7)	2.6 (1.1–6.0)
≥27 mg/m ³ /year	16/69	24/67	15/73
	1.3 (0.7–2.4)	1.7 (1.0–3.1)	1.1 (0.6–2.1)

A = number of cases and controls; B = OR adjusted by age at first exposure (continuous) and cigarette smoking (four categories); C = 95% confidence interval.

TABLE III. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Lung Cancer by Radiological Categorization of Silicosis (Chinese Classification) and by Radiological Evolution of Silicosis for all Facilities Combined

Radiological classification	Cases/Controls	Model I		Model II	
		OR	95% CI	OR	95% CI
Silicosis (all stages)	80/245	1.4	1.1–2.0	1.5	1.0–2.1
Dubious*	29/180	0.7	0.5–1.1	0.6	0.4–1.0
Class 1 silicosis	50/142	1.4	1.0–2.1	1.4	0.9–2.1
Class 2–3 silicosis	30/103	1.3	0.8–2.0	1.3	0.8–2.2
Non-progressive Silicosis	53/152	1.5	1.1–2.2	1.5	1.0–2.3
Progressive silicosis	27/93	1.3	0.8–2.1	1.4	0.8–2.4

*Chest X-rays classified as dubious are included among non-silicotics.

**Correspondent to the 0/1 ILO category.

Model I: Risk estimates are adjusted by age at first exposure (continuous) and smoking (four categories of cigarettes/day).

Model II: Risk estimates are adjusted also by cumulative silica exposure (quartiles of cumulative respirable silica).

other lung carcinogens considered in this study in the absence of silica exposure, which prevented a more detailed study of interaction effects.

The stratified analysis of lung cancer risk associated with silicosis by exposure to each of the five non-silica lung carcinogens showed that risk was elevated only among silicotic subjects who were exposed to these carcinogens (Table V). Lung cancer risk associated with exposure to arsenic and exposure to radon-daughters was significantly elevated only among non-silicotic subjects.

As no study subject had exposure to silica alone or exposure to respirable dust other than silica alone, a complete study of the independent effect of dust overload was not possible. However, lung cancer risk associated with quartiles of cumulative exposure to total respirable dust over all study industries combined was 1.3, 1.5, 1.3, 1.3, only slightly different from the risks observed for quartiles of cumulative exposure to respirable silica reported in Table I. Also, the stratified analysis of lung cancer risk by categories of cumulative exposure to respirable silica and total respirable dust did not show an independent effect of the latter (Table VI).

DISCUSSION

The aims of this study were to investigate whether clinical and radiological severity of silicosis, concurrent exposure to other workplace lung carcinogens and total respirable dust could account for inconsistent results on the silica-lung cancer link reported in the literature and observed in a previous analysis of the same data set of Chinese mines and pottery factories. Data were available also for exposure to arsenic, nickel, radon-daughters, and

TABLE IV. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Lung Cancer by Exposure to Silica and Exposure to Arsenic, Cadmium, Nickel, Radon-Daughters, and PAHs

	Unexposed	Exposed
a) Arsenic		
Silica	67/384 ^A	1/0
Unexposed	1.0 ^B	—
	138/523	110/449
Exposed	1.4 (1.0–1.9) ^C	1.3 (0.9–1.9)
b) Cadmium		
Silica	67/384 ^A	1/0
Unexposed	1.0 ^B	—
	73/282	175/690
Exposed	1.3 (0.9–2.0) ^C	1.3 (1.0–1.9)
c) Nickel		
Silica	67/384 ^A	1/0
Unexposed	1.0 ^B	—
	54/167	194/805
Exposed	1.7 (1.1–2.6) ^C	1.3 (0.9–1.7)
d) Radon-daughters		
Silica	68/384 ^A	0/0
Unexposed	1.0 ^B	—
	138/457	110/515
Exposed	1.6 (1.1–2.2) ^C	1.1 (0.8–1.6)
e) PAHs		
Silica	67/384 ^A	1/0
Unexposed	1.0 ^B	—
	18/41	230/931
Exposed	2.4 (1.3–4.4) ^C	1.3 (0.9–1.8)

A = number of cases and controls; B = OR adjusted by age at first exposure (continuous) and cigarette smoking (four categories); C = 95% confidence interval.

TABLE V. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Lung Cancer by Silicosis and Exposure to Arsenic, Cadmium, Nickel, Radon-Daughters, and PAHs

	Unexposed	Exposed
a) Arsenic		
Silicosis	172/818 ^A	33/89
No	1.0 ^B	1.7 (1.1–2.6)
	64/293	47/156
Yes	1.1 (0.8–1.5) ^C	1.3 (0.9–2.0)
b) Cadmium		
Silicosis	123/613 ^A	17/53
No	1.0 ^B	1.5 (0.8–2.7)
	113/498	63/192
Yes	1.1 (0.8–1.5) ^C	1.5 (1.0–2.2)
c) Nickel		
Silicosis	108/507 ^A	13/44
No	1.0 ^B	1.3 (0.7–2.5)
	128/604	67/201
Yes	0.9 (0.7–1.2) ^C	1.4 (0.9–2.0)
d) Radon-daughters		
Silicosis	166/762 ^A	40/79
No	1.0 ^B	2.2 (1.4–3.3)
	70/349	40/166
Yes	0.9 (0.7–1.3) ^C	1.0 (0.7–1.6)
e) PAHs		
Silicosis	82/416 ^A	3/9
No	1.0 ^B	1.6 (0.4–6.8)
	154/695	77/236
Yes	1.0 (0.8–1.4) ^C	1.5 (1.0–2.1)

A = number of cases and controls; B = OR adjusted by age at first exposure (continuous) and cigarette smoking (four categories); C = 95% confidence interval.

PAH, which are well established lung carcinogens, as well as for cadmium, for which the evidence is less conclusive. The most recent literature, however, supports the hypothesis of a positive association between occupational exposure to cadmium and lung cancer [IARC, 1993; Hayes, 1997; Sorahan and Lancashire, 1997].

The present pooled analysis was meant to address the issue of collinearity in exposure to the various risk factors within the same facility type, and particularly among tin miners [McLaughlin et al., 1992]. Apart from radon and arsenic, which were not found in Chinese potteries, average level of all the other occupational hazards in this study varied by facility type. In other words, none of them was typical of the exposure profile in a specific type on industry. For instance, exposure to PAH occurred in all facilities, but the average cumulative exposure was high in tungsten mines, where respirable silica was also high, and low in potteries, where respirable silica was relatively low. Average

TABLE VI. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Lung Cancer by Categories of Total Respirable Dust and Respirable Silica Exposure

	Total respirable dust		
	Unexposed	0.1–42.4 mg/m ³ /year	≥42.5 mg/m ³ /year
Respirable Silica	67/384 ^A	1/0	0/0
Unexposed	1.0 ^B	—	—
	0/0	109/426	12/63
0.1–10.7 mg/m ³ /year	—	1.4 (1.0–1.9) ^C	1.0 (0.5–1.9)
	0/0	18/56	109/427
≥10.8 mg/m ³ /year	—	1.5 (0.8–2.8)	1.4 (1.0–2.0)

A = Number of cases and controls; B = OR adjusted by age at first exposure (continuous) and cigarette smoking (four categories); C = 95% confidence interval.

cumulative exposure to PAH was also high in iron and copper mines, where respirable silica was low, and it was medium in tin mines, where the average cumulative exposure to respirable silica was high. Pooling data contributed to increase the variance of cumulative exposures to the individual occupational hazards, allowing a partial discrimination among their effects.

We found a modest association between silica and lung cancer, which was more evident among subjects exposed to silica but unexposed to PAH. Risk was also higher among workers exposed to silica but unexposed to nickel and radon-daughters, although all these subjects were also exposed to PAH. Lung cancer risk associated with quartiles of cumulative exposure to respirable silica persisted after limiting the analysis to non-silicotics or adjusting for silicosis. However, among heavily exposed workers, lung cancer risk did not increase linearly with quartiles of cumulative exposure to respirable silica, showing instead a decline in the highest quartile of cumulative exposure. Silicosis also showed a modest association with lung cancer, which did not vary by clinical stage or radiological evidence of progression in subsequent exams compared with the first diagnosis, and persisted after adjusting for cumulative exposure to silica. However, lung cancer risk was increased only among silicotics exposed to another lung carcinogen. Risk associated with exposure to arsenic was more elevated and risk associated with exposure to radon-daughters only showed up among non-silicotic subjects.

In our study, controls were matched to cases also by facility type, which might raise the suspicion of overmatching inducing an underestimation of the true association. If overmatching had occurred, its effects would have also appeared in the previous analysis, which was conducted separately by facility type. This was not the case, as both positive and negative associations were observed. However, the nested case-control strategy is a common standard

procedure in occupational epidemiology to examine in greater detail the relationship between disease risk and exposure level, or specific work areas, within an industrial cohort.

On average, cases started exposure 1 year earlier than controls (age at starting exposure: cases: 30.3 years, *sd* 16.3; controls: 31.5 years, *sd* 16.6), and age at first diagnosis of silicosis in lung cancer cases was also very close to that among controls (cases: 51.6 *sd* 12.7; controls 52.1 *sd* 12.4). Age at death among lung cancer cases was 57.2 *sd* 9.3. Therefore, we did not consider competing risk for death due to silicosis or its complications before diagnosis of the lung cancer as a plausible explanation for our findings.

Binding of the DNA phosphate backbone to the silanol groups in the quartz surface, close to the sites of oxygen radicals production, has been suggested as the mechanism for silica-induced neoplastic transformation [Saffiotti et al., 1996]. A reduction in silica toxicity and neoplastic transforming activity in cultured cells was observed when hematite or anatase, a polymorph of titanium dioxide (TiO₂), were combined with silica [Saffiotti and Ahmed, 1995]. This would indicate that crystal surfaces of hematite and anatase, non-toxic by themselves, may block critical steps of quartz cytotoxicity. In contrast, rutile, another TiO₂ polymorph, enhanced quartz cytotoxicity but did not modify its transforming activity, providing an example of dissociation between toxic and transforming effects. Total surface area, the increased level of hydroxyl radicals generated by freshly cut silica, and the consequent increase in cytotoxicity compared to aged quartz, also point to a silica-surface effect as an important variable to be considered [Shoemaker et al., 1995]. In fact, grinding, heating, and etching, as well as the presence of contaminants, water and other ions strongly influence surface properties of silica particulate [Fubini et al., 1995]. Whether silica-induced fibrogenicity and neoplastic transformation are both related to oxygen radicals released by silanol groups on the surface of silica particles is still unclear. However, the ability of metallic iron, hematite, or iron chloride to inhibit or delay fibrogenesis due to silica has been shown long ago in numerous experimental species [Vogliazzo and Ghezzi, 1963]. It is possible that these and other substances interact with the silanol groups on the surface of the silica particle, thus reducing its ionization and the generation of silicon-based or oxygen-based free radicals. Indeed, binding of poly(2-vinylpyridine-*N*-oxyde (2-PVPNO) to the silanol groups in the quartz surface markedly reduced quartz toxicity in vitro [Kilburn, 1992]. Based on the early experimental findings, attempts to prevent silicosis by spreading metallic aluminum or aluminum hydrate powder in the workplace were made in a few countries [Kilburn, 1992; Mao et al., 1995; Walters and DuBois, 1995]. The aim of this practice was to coat the silica particles, thus reducing the solubility of their surface layer. The appearance of lung fibrosis following

exposure to aluminum powder caused cessation of the practice.

On the other hand, intratracheal administration of benzo(a)pyrene together with silica resulted in a significantly increased number of respiratory tumors in hamsters, while a report on tumor occurrence in rats did not study a reference group receiving quartz alone [IARC, 1997]. These results, and the fact that no isolated exposure to lung carcinogens other than silica occurred in our study, suggest caution in interpreting our stratified analysis of the combined effects of silica and other workplace lung carcinogens. Nonetheless, they point out that detailed information on all workplace exposures is required to understand whether and in what direction they may affect silica toxicity and carcinogenicity.

Another reason for the present analysis was to consider the effect of total respirable dust, in which silica particles are diluted. When the volume of inhaled dust corresponds to 6% of that of alveolar macrophages, dust overload on the pulmonary clearance has been estimated to occur [Oberdorster, 1995]. The calculated concentration of spherical particles with unit density and 3 μm size, required to reach this volume, is 0.8 mg/m³. In laboratory studies using numerous rodent models, exposures well above overload concentrations have resulted in prolonged particle clearance time, inflammation, and cell proliferation [Oberdorster, 1995]. Increased fibrotic foci were seen in rat, hamster, and some mouse studies. However, localized emphysema and tumors have been found in the rat model only. Fibrosis has been documented in the present study population [U.S.OSHA, 1994], with response showing a linear upward trend as exposure to respirable dust increased, up to levels well beyond human pulmonary clearance overload, albeit estimated from animal data.

A complete separation between dust overload effects and any specific silica effects in relation to lung cancer risk is not feasible in an epidemiological study of human workplace exposure. Based on data from the present study, a greater exposure to total respirable dust did not change the risk associated with a cumulative exposure to respirable silica above 10.8 mg/m³/year, while the modest but significant increase in risk associated with cumulative exposure to silica below 10.7 mg/m³/year did not show up among subjects also exposed to total respirable dust above 42.5 mg/m³/year. A dilution effect of the associated carcinogenic exposures, and a shift in the particle deposition pattern toward the upper airways in the lungs of the most heavily exposed workers [Love and Muir, 1976], might have antagonized the effects of dust overloading, if this were among the mechanisms playing a role in increasing lung cancer risk among various silica exposed working populations.

The most recent literature, exploring the silica/silicosis/lung cancer relationship, seems to repeat the previous

contradictory findings [Cherry et al., 1998; De Klerk and Musk, 1998; Finkelstein, 1998; Checkoway et al., 1999; Ulm et al., 1999; Chan et al., 2000; Moulin et al., 2000; Steenland and Sanderson, 2001]. Also, a pooled analysis of 10 industrial cohorts exposed to silica resulted in a modest association with lung cancer risk [Steenland et al., 2001], similar in size to the one we observed in the present study. Further research is needed in order to understand the complex pattern of interactions leading to lung cancer among silica-exposed workers; 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; and to explain the apparent paradox of a lower lung cancer risk in some workplaces with high-level silica exposure. Novel epidemiological approaches are required, which incorporate more detailed exposure information.

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