

Multifactorial Aetiology of Lung Cancer Among Silica-exposed Workers

P COCCO,*^{MD}

Abstract

In 1997, the International Agency for Research on Cancer (IARC) upgraded its evaluation of crystalline silica to a Group 1 human carcinogen. Criticism against such decision is based on the lack of consistency in experimental results across animal species, violation of an important principle for causality, such as the replication of findings under different circumstances of exposure, and the lack of a clear dose-response curve. The most recent epidemiological literature on the silica-silicosis-lung cancer link replicates the inconsistent findings that have been characterising 50 years of scientific debate in the occupational arena. Exposure circumstances capable of modifying the silica-lung cancer association include chronic bronchitis, composition of the dust mixing, particularly concerning co-occurrence of other known or probable lung carcinogens, total respirable dust, concentration of silica in respirable dust, type of crystalline silica and particle surface characteristics. The hypothesis of a silicosis-mediated pathway points toward an unspecific mechanism shared with other fibrotic conditions, for which silica might be just one of the triggers. In envisaging a multivariate multistep model of lung cancer among silica-exposed workers, silica might be considered as a “passive components of the sufficient cause”, i.e., one of the associated risk factors, concurrent or subsequent to the “active component(s) of the sufficient cause” (including, for instance, smoking, asbestos, radon-daughters, arsenic, hexavalent chromium, nickel, polycyclic aromatic hydrocarbons (PAH), and diesel exhausts among the external risk factors; and DNA repair enzymes polymorphism and spontaneous inactivation of tumour suppressor genes among the internal risk factors), which adds up in modulating the tumoral development in not easily predictable directions. If silica acts as a human lung carcinogen depending on certain occupational exposure circumstances, perhaps those circumstances and not silica itself should be classified for their human carcinogenicity potential.

Ann Acad Med Singapore 2001; 30:468-74

Key words: Carcinogenesis, Lung neoplasms, Occupational health, Silica, Silicosis

Introduction

The earliest reports of a wasting disease among miners date back in the 1500s, with the description by Paracelsus and Agricola of the so-called “mala metallorum” among Schneeberg miners. The presence of uranium in the ores from Schneeberg mines was discovered only in 1921, and the carcinogenic role of α -particles from radon-daughters in the non-uranium mining environment was acknowledged by the International Agency for Research on Cancer (IARC) in 1988.¹ Dust exposure is a main feature of the underground working environment, and radioactivity alone was not a valid explanation for excess lung cancer risks among underground miners as well as other dust-exposed workers. The hypothesis of a direct or silicosis-mediated lung carcinogenesis of silica among non-uranium miners and other dust-exposed workers has been the object of numerous studies and an unceasing scientific debate in the occupational health arena for the last 50 years.² “Con” arguments included

the low prevalence of neoplastic changes in the largest autoptic series of silicotic patients and in occupational surveys among non-uranium miners, and the negative experimental findings. “Pro” arguments included mainly autoptic case descriptions and some autoptic series of silicotics with elevated prevalence of lung tumours.² Following a new wave of epidemiological studies of silica and lung cancer in the 1980s, IARC classified crystalline silica in the Group 2a in 1987,³ and upgraded its evaluation to a Group 1 human carcinogen 10 years later.⁴ As silica is possibly the most studied and best-known occupational hazard, and silica polymorphs are major components of the earth crust, the IARC decision was somewhat surprising particularly for those European occupational researchers who participated in the past debate and dedicated most of their scientific activity to the study and the prevention of silicosis in the second half of 1900. No evidence of that past debate can be found in the IARC report. Qualitative aspects

* Assistant Professor of Research

Department of Public Health

Occupational Health Section, University of Cagliari, Italy

Address for Reprints: Dr Pierluigi Cocco, Department of Public Health, Occupational Health Section, University of Cagliari, via San Giorgio 12, 09124 Cagliari, Italy.

E-mail: coccop@pacs.unica.it

of experimental studies to be included in the evaluation of the experimental evidence for carcinogenicity are reported in the preamble at the beginning of every IARC Monograph. They include “the consistency of the results... across species and target organs”. However, while the majority of the IARC commission considered as “sufficient” the experimental evidence for silica carcinogenesis, only studies in rats were definitely positive, and evidence from experimental animals was questioned by one of the authors of those studies.⁵ Besides, silica exposure among coal miners was classified as exposure to coal dust (Group 3),⁴ implicitly recognising a change in the silica carcinogenicity according to the type of dust, and violating an important principle for causality expressed in the same preamble (“Associations that are replicated [...] under different circumstances of exposure are more likely to represent a causal relationship”). Finally, the difference in quartz toxicity depending on the minerals with which it is combined, and variation in risk by types of industry, besides those related to the type of silica polymorph, was acknowledged in the monograph.⁴ Other weaknesses in the IARC decision, described in the monograph, include the lack of consistent evidence for a silica-lung cancer relationship in ore mining studies which evaluated confounders, and the lack of direct quantification of silica exposure in cohort studies of quarry and granite works, ceramics and refractory brick industries, and foundries.⁴ Therefore, after 50 years of debate, a number of questions still await to be answered:

1. Is silica itself responsible for the increase in lung cancer risk or is it a silicosis-mediated effect, consistent with what was observed in other fibrotic and scar processes of the lung tissue?
2. Is there any independent role of other chronic pulmonary diseases, specially prevalent among silica-exposed workers such as pulmonary tuberculosis or chronic obstructive lung disease, in the occurrence of lung cancer as reported for the general population?
3. What type of interaction between tobacco smoking, silica exposure and exposure to other known lung carcinogens occurs in the work environment?
4. Could the observed association be the result of an unspecific mechanism such as dust overloading and the consequent failure by the lung clearing ability to cope with excessive dust exposure?

This paper will review some of the proposed hypotheses about the nature of the silica-silicosis-lung cancer link, using data from recently published reports,⁶⁻¹⁴ and other reports currently in press or pending review in peer-reviewed journals.^{15,16} Based on these results, a model of multifactorial lung cancer aetiology among miners will be proposed.

1. Silicosis-lung Cancer

A considerable part of the studies supporting the silica-lung cancer link actually found an increase in risk among workers compensated for or with a diagnosis of silicosis.⁴ A recent report replicated the finding among silica-exposed workers in Ontario, Canada. A 3.3-fold increase in lung cancer risk was associated with the radiological International Labour Office (ILO) category $\geq 1/0$, in comparison with subjects with a ILO category $\leq 0/1$.⁶ Adjustment for cumulative radon exposure resulted in an increased odds ratio (OR), and empirical evidence suggested that it was not confounded by smoking. Among Western Australia gold miners, the risk of mortality from lung cancer increased after compensation for silicosis but there was no evidence that exposure to silica caused lung cancer in the absence of silicosis.⁷ Smoking accounted for most of the 2-fold excess lung cancer mortality among 1490 silicotic patients in Hong Kong.⁸ In this cohort, 88% of the silicotic subjects had been employed in the construction industry, with relatively isolated, though not quantified, exposure to silica. The risk pattern was similar among surface workers compared to underground workers, it was independent on duration of employment in both groups, and it was not modified by tuberculosis status. Risk did not show a consistent relationship with either profusion of small opacities and duration of exposure to silica. The authors concluded that there was no conclusive evidence to support the hypothesis that lung cancer may be associated with silicosis.⁸ Indeed, the most recent literature seems to repeat the previous contradictory findings. Three still opened questions were tentatively addressed in a study of Chinese workers heavily exposed to silica:⁹

A. Lung cancer and silicosis type and stage. Chinese silica-exposed workers had a 40% increase in lung cancer risk associated with radiological diagnosis of pneumoconiosis (Chinese pneumoconiosis roentgen-diagnostic criteria $\geq$ class 1, correspondent to ILO categories $\geq 1/0$).⁹ Risk did not increase by severity of silicosis when all categories of silica exposure were jointly considered, or adjusting by quartiles of cumulative silica exposure, or by radiological evidence of progression in silicosis stage as derived from subsequent radiographs compared to the first diagnosis (non-progressive: OR, 1.5; 95% CI, 1.1-2.2; progressive: OR, 1.3; 95% CI, 0.8-2.1). However, when conducting the analysis within strata of cumulative silica exposure, a positive trend of lung cancer risk by severity of silicosis was observed in the second and third strata, but not in the highest or in the lowest (Table I).⁹ The aetiological model suggested for a silicosis-mediated lung carcinogenicity of silica, stresses the role of cytokines released by the macrophages during the inflammatory response.⁴ As other lung diseases, characterised by radiological features

TABLE 1: 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	1.0	0/2	0/0
	-	-	
0.01-3.7 mg/m ³ -years	1.1 (0.7-1.7)	1.9 (0.6-6.5)	1.7 (0.3-9.5)
3.8-10.7 mg/m ³ -years	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 -years	1.5 (0.9-2.4)	2.3 (1.1-4.7)	2.6 (1.1-6.0)
≥27 mg/m ³ -years	1.3 (0.7-2.4)	1.7 (1.0-3.1)	1.1 (0.6-2.1)
All subjects	1.0	1.4 (1.0-2.1)	1.3 (0.8-2.0)

Subjects with radiographs classified as suspected for silicosis are not included (modified from reference 15)

* Note: Silicosis diagnosis and staging was based on the 1963 Chinese pneumoconiosis roentgen-diagnostic criteria, which classified silicosis as suspected (correspond to the 0/1 ILO category) or as stage 1, 2 (approximately correspond to the p, q, r ILO categories), or stage 3 (approximately correspond to the A, B, C ILO categories).

typical of fibrosis, convey an even greater lung cancer risk,¹⁷⁻²¹ the silicosis-lung cancer association would result from an unspecific mechanism, for which silica is just one of the possible triggers. For instance, quite differently from what was described above for lung cancer risk by radiological evidence of progression of silicosis, a 34-fold increase in lung cancer incidence occurred among 24 Finnish male patients with progressive asbestosis, versus a 4.3-fold increase among 54 male patients without progression.¹⁷ Other reports indicate a prevalence of lung cancer ranging from 10% up to 31% among patients with idiopathic pulmonary fibrosis,¹⁸⁻²⁰ while lung cancer incidence was more than 7-fold increased in 890 patients with cryptogenic fibrosing alveolitis compared with 5884 control subjects drawn from the United Kingdom General Practice Research Database.²¹ Adjustment for smoking further increased the risk associated with cryptogenic fibrosing alveolitis in the UK study [adjusted relative risk (RR), 8.2; 95% CI, 4.7-11.5]. Besides, in a pathological report of 563 cases of non-asbestos pneumoconiosis, squamous cell carcinoma in diffuse interstitial fibrosis (DIF)-associated pneumoconiosis preferentially arose from areas of DIF and in the peripheral lung and in the lower lobes, rather than the central lung and upper lobes, as more frequently observed in pneumoconiosis without DIF and in non-pneumoconiotic patients.²² Therefore, as the lung cancer risk associated with silicosis averages about 2-fold across studies,⁴ if a specific silicosis-mediated effect is postulated for silica carcinogenesis, we should infer that such carcinogenicity is weaker than that associated with other fibrogenic lung diseases.

B. Confounding by exposure to other lung carcinogens. The confounding effect of concurrent exposures in the

silicosis-lung cancer association has seldom been evaluated. As silica levels may be collinear with exposure to other lung carcinogens in the mining environment, it is plausible that exposure levels which cause silicosis could be associated with higher exposure to other lung carcinogens as well. A first attempt was conducted by stratifying the analysis of lung cancer risk associated with silicosis by exposure to each of the other 5 known lung carcinogens in Chinese mines and potteries. In the study, risk was elevated only among silicotic subjects who were exposed to other lung carcinogens.⁹ These results need to be replicated in other studies with detailed monitoring of data before drawing conclusions about the nature of the silicosis/lung cancer relationship.

C. Effect modification by other lung diseases. Previous diagnosis of chronic obstructive pulmonary disease (COPD)^{23,24} and obstructive impairment of the ventilatory function²⁵ have been shown to be independent risk factors for lung cancer. Clinical symptoms and functional signs of COPD frequently, but not constantly, accompany silicosis.²⁶ Indeed, inhaled particles, including crystalline silica, either alone or in association with smoking or workplace exposure to nitrogen or sulphur oxides, may cause airways obstruction.²⁷ When airways obstruction occurs, mucociliary clearance is slowed, which may prolong the contact between the bronchoalveolar mucosa and inhaled particles. A longer retention time of inhaled carcinogens close to the target cells is likely to result in an increase of their effective dose.²⁸ In a follow-up of 724 silicotics, airway obstruction accounted for the small excess lung cancer risk observed in the study population.²⁹ Also, risk was highest among metal miners with low-level exposure to radon-daughters and obstructive impairment of ventilatory function, compared to metal miners exposed to radon-daughters but not suffering from airways obstruction or *vice versa*, while it was lowest among metal miners without either conditions.³⁰ However, deposition studies have shown that, among subjects with chronic bronchitis or asthma, particle deposition is increased in the proximal airways compared to the peripheral airways.^{31,32} This would indicate that a smaller proportion of inhaled particles penetrate into the deep lung, which might actually decrease risk of silicosis and lung cancer among these subjects compared to co-workers with normal respiratory function and similar occupational and non-occupational exposures. Indeed, risk of silicosis associated with cumulative silica exposure was higher among workers who did not have chronic bronchitis or asthma (ORs: 24.5, 50.3, 111, and 532), compared to subjects with a medical history for either of these two diseases (ORs: 8.0, 23.1, 30.0, and 83.1).⁹ Consistently with deposition studies, and with the pathological findings identifying the peripheral lung as the preferential site for lung cancer in DIF-associated pneumoconiosis,²² lung cancer risk was found not to be

elevated among silicotics with a medical history for chronic bronchitis or asthma, while it was significantly increased among silicotics who did not have a medical history of either diseases.⁹ A similar modifying effect on the silica-silicosis-lung cancer association has not been reported for pulmonary tuberculosis.^{9,33,34}

In conclusion, as Checkoway and Franzblau recently pointed out, after 50 years of debate and research, a number of problems still need to be considered to understand the nature of the silicosis/lung cancer association.³⁵

2. Silica-lung Cancer

A new analysis of the diatomaceous earth industry cohort found a significant increasing trend of lung cancer risk with cumulative silica exposure, up to 2.4-fold for exposures equal to or above 5 mg/m³-years (which would fit in the medium low-category of exposure of the Chinese study), unexplained by undetected radiological silicosis.¹⁰ The authors concluded that silicosis is not a necessary co-condition for silica-related lung carcinogenesis. In a nested case-control analysis of men employed in the pottery, refractory and sandstone industries of Stoke-on-Trent, UK, the smoking-adjusted lung cancer risk was significantly increased for average silica exposure, but there was no trend for duration of exposure or for cumulative exposure.¹¹ On the other hand, an increasing trend in lung cancer risk by cumulative silica exposure was observed among a cohort of US industrial sand workers, when analysing data with a 15-year time lag.¹² Another nested case-control of French workers producing stainless steel and metallic alloys, found no excess lung cancer risk for exposure to iron, chromium and/or nickel, cobalt, acid mists, and asbestos. After adjusting for smoking, risk was not significantly elevated for PAHs (OR, 1.6) and silica (OR, 1.8), with some indication of an increase with duration of exposure and cumulative exposure, though only a non-significant *P* value for trend was provided in the paper.¹³ In contrast with these reports, a German case-control study of the stone, quarry and ceramic industries, after excluding subjects with silicosis, found an OR of 0.85 (95% CI, 0.58-1.25) for a peak silica concentration of ≥ 0.15 mg/m³ with reference to a concentration of ≤ 0.15 mg/m³. Using other exposure metrics did not show a positive association with lung cancer risk, and risk did not increase with increasing exposure.¹⁴ Concurrent exposures in this study included diesel exhaust and radon-daughters, PAH, welding fumes, heavy metals, asbestos and other fibres, but only the first two exposures were more frequent among cases.

When independent of study design and genetic background, inconsistent findings across studies are frequently explained to random sampling bias. However, profound differences in the silica-silicosis-lung cancer

association were observed within various Chinese dusty trades by facility type, although the study design and the genetic and social background were the same.³⁶⁻³⁸ In the combined analysis of 29 mines and factories included in that study, lung cancer risk increased up to 1.6 for a cumulative silica exposure ranging 10.8 to 26.9 mg/m³-years, with a decrease to 1.2 for a cumulative silica exposure of 27 mg/m³-years or more (Table II). Limiting the analysis to subjects with radiographs negative for silicosis, or adjusting the risk estimates by radiological stage of silicosis, did not change these figures.¹⁵ Relative risks of similar size, with a linear increase up to a 60% excess in the highest category of cumulative exposure, corresponding to ≥ 12.8 mg/m³-years (median 28.0 mg/m³-years) was observed in a recent meta-analysis of data from 10 silica-exposed cohorts.¹⁶

Also, different from the US industrial sand cohort, analysing data with a 15-year time lag, or using other exposure metrics such as average, did not change the results.¹⁶ Possible modifying factors in the silica-lung cancer association are discussed below.

A. Effect modification by dust overload. The modifying effect of high levels of total dust exposure and of chronic bronchitis would result from particles deposition shift to the proximal airways instead of the peripheral lung.^{31,32} Dust overload has been estimated to occur when the volume of inhaled dust corresponds to 6% of that of alveolar macrophages, i.e. at concentrations around 0.8 mg/m³ for unit density—3 μ m size-spherical particles.³⁹ At such concentration, increased fibrotic foci were seen in rat, hamster and some mouse studies, although, as for silica, localised emphysema and tumours have been found in the rat model only. From these experimental studies, one should infer that, if the inflammatory reactions were the true risk factor for silica-exposed workers, dust itself

TABLE II: ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR LUNG CANCER BY QUARTILES OF CUMULATIVE EXPOSURE TO RESPIRABLE SILICA (MODIFIED FROM REFERENCE 15)

Quartiles of cumulative exposure to respirable silica (mg/m ³ -years)	Model I	Model II
Unexposed	1.0 -	1.0 -
0.01 - 3.7	1.1 (0.8-1.7)	1.1 (0.7-1.7)
3.8 - 10.7	1.5 (1.0-2.2)	1.5 (0.9-2.3)
10.8 - 26.9	1.6 (1.1-2.4)	1.5 (0.9-2.5)
≥ 27	1.2 (0.8-1.9)	1.3 (0.7-2.5)

Model I: risk estimates are adjusted for age at first exposure (continuous) and smoking

Model II: same as I, but analysis limited only to non-silicotics (radiographs which correspond to suspected pneumoconiosis category are also excluded)

(whatever its composition) might indirectly induce lung cancer among these workers. Addressing this issue with epidemiological tools is quite a difficult task, as isolated exposure to respirable silica or to silica-free total dust is quite a rare occurrence in the real-world workplaces. However, as the proportion of silica in respirable dust varies within a wide range across workplaces, some indications may derive from cross-tabulating lung cancer risk by categories of cumulative exposure to respirable silica and cumulative exposure to respirable dust. Such an analysis did not suggest an independent effect of the latter on lung cancer risk.¹⁵ As among subjects with chronic bronchitis, a shift in the particle deposition pattern to the upper airways in the lungs of the most heavily-exposed workers⁴⁰ would act as a defence mechanism, limiting the effects of associated carcinogenic exposures.

B. Effect modification by exposure to other lung carcinogens. *In vitro* studies have suggested the binding of the silanol groups in the quartz surface to the DNA phosphate backbone, as the mechanism for silica-induced neoplastic transformation.⁴¹ A silica-surface effect is suggested by the increase in cytotoxicity related to total surface area, and the increased level of hydroxyl radicals generated by freshly cut silica as compared to aged quartz.⁴² *In vitro* surface properties of silica particles are affected by the components of the dust mixing. For instance, a reduction in silica toxicity and neoplastic transforming activity was observed when haematite or anatase, a titanium dioxide (TiO₂) polymorph, were combined with silica, while an increase in silica cytotoxicity was obtained with rutile, another TiO₂ polymorph.⁴³ This would indicate that crystal surfaces of hematite and anatase may block critical steps of quartz cytotoxicity by interacting with the silanol groups on the surface of the silica particle, thus reducing its ionisation and the generation of silicon-based or oxygen-based free radicals, as already suggested in the 1960s.⁴⁴ The joint effect of exposure to silica and other known lung carcinogens was tentatively explored among Chinese workers: lung cancer risk was higher among workers exposed to silica but unexposed to PAH, nickel or radon-daughters,¹⁵ which would suggest that concurrent exposure to other lung carcinogens might modify the silica-lung cancer risk, possibly through surface effects and/or apoptotic mechanisms. However, experimental work in hamsters is at odds with such a hypothesis, as intratracheal administration of benzo(a)pyrene together with silica resulted in a significant increase in respiratory tumours.⁴ Further experimental and epidemiological research is warranted to understand the effects of workplace exposure to multiple lung carcinogens and of the mineral composition of the inhaled dust before drawing any conclusion.

C. Effect modification by other lung diseases. As observed for silicosis, subjects without medical history for chronic

bronchitis showed an increase in lung cancer risk with cumulative silica exposure, although again risk decreased in the highest quartile; while subjects with a medical history of chronic bronchitis showed no increase in lung cancer risk in any cumulative exposure category.⁹ Again, the modest association between lung cancer risk and cumulative silica persisted regardless of medical history for pulmonary tuberculosis.⁹

Overall, these results would suggest that, under certain circumstances of exposure, silica might behave as a lung carcinogen. However, such a statement leaves unanswered the above mentioned arguments against the IARC decision, does not consider the lack of a clear dose-response curve in most studies, and does not fit with the IARC criteria for classifying human carcinogens.

3. A Multifactorial Model of Lung Cancer Aetiology Among Miners

As it is with the case of most neoplasms, lung cancer requires a multistep concurrence of multivariate events reciprocally interconnected to form a complex net. Some knots in the net might be more important and missing them would result in a drastic reduction, if not disappearance of that neoplasm, as with asbestos and mesothelioma, or wood dust and adenocarcinoma of paranasal sinuses, for instance. These are commonly indicated as “causes” of the respective associated tumour, although they should be more properly defined as “active components of the sufficient cause”,⁴⁵ or as “necessary, but not sufficient, components of a sufficient, but not necessary, complex”.⁴⁶ In other words:

1. a given neoplasm might develop in the presence of different causal nets; and
2. in order for the causal net to be effective, the “active component” should occur in association with other conditions.

In the case of lung cancer, smoking is possibly the factor best fitting the definition of “active component”. It is interesting to note that smoking itself is a complex of multiple chemical and physical risk factors. Other known or probable occupational lung carcinogens, such as asbestos, arsenic, radon-daughters, hexavalent chromium, or diesel exhausts, which, quite differently from silica, show a consistent association in most studies and in different exposure circumstances, might also play a role as “active components”. Among internal risk factors, DNA repair enzymes polymorphism, and spontaneous inactivation of tumour suppressor genes might be considered as “active components” in a causal net. The role of silica seems more similar to those associated risk factors, concurrent or subsequent, environmental or occupational or individual – including phase I and phase II activating and deactivating genetic enzyme polymorphism, and other acquired risk

factors —, which add up as “passive components of the sufficient cause” in modulating the tumoral development.⁴⁵ The probabilistic concept of “cause”, i.e., the greater probability of disease status among exposed compared to unexposed, is not enough to describe as “causal” the relationship between “passive components of the sufficient cause” and disease. In other words, a positive epidemiological association, particularly if weak, although statistically significant and consistent across studies, is not enough. If we applied only such a parameter, we should define as “causal” the silica-silicosis-tuberculosis link, while such an association, although strong and consistent, could not exist in the absence of microbacterial infection (the “active component”). By applying an equivalent causal role to all factors showing an epidemiological association, active and passive components of the causal complex would be flattened at the same level. As a consequence, having missed the main target to be addressed with preventive measures, these might easily be ineffective.

In conclusion, the IARC classification system, while efficiently describing the human carcinogenicity of asbestos, wood dust, vinyl chloride or aromatic amines, seems less effective in describing more complex relationships such as the aetiology of lung cancer among silica-exposed workers. If silica acts as a human lung carcinogen depending on certain occupational exposure circumstances, perhaps those circumstances, and not silica itself should be classified, for their human carcinogenicity potential.

REFERENCES

1. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Vol. 43. Man-made mineral fibres and radon. Lyon, France: IARC, 1988.
2. Puccini C. The problem of cancer-silicosis [in Italian]. *Med Lav* 1960; 51:18-36.
3. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Vol. 42. Silica and some silicates. Lyon, France: IARC, 1987.
4. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Vol. 68. Silica, some silicates, coal dust and para-aramid fibrils. Lyon, France: IARC, 1997.
5. Holland L M. Animal studies of crystalline silica: results and uncertainties. *Appl Occup Environ Hyg* 1995; 10:1099-103.
6. Finkelstein M M. Radiographic silicosis and lung cancer risk among workers in Ontario. *Am J Ind Med* 1998; 34:244-51.
7. De Klerk N H, Musk A W. Silica, compensated silicosis, and lung cancer in Western Australian gold miners. *Occup Environ Med* 1998; 55: 243-8.
8. Chan C K, Leung C C, Tam C M, Yu T S, Wong T W. Lung cancer mortality among a cohort of men in a silicotic register. *J Occup Environ Med* 2000; 42:69-75.
9. Cocco P, Rice C, Chen J-Q, McCawley M A, McLaughlin J K, Dosemeci M. Non-malignant respiratory diseases and lung cancer among Chinese workers exposed to silica. *J Occup Environ Med* 2000; 42:639-44.
10. Checkoway H, Hughes J M, Weill H, Seixas N S, Demers P A. Crystalline silica exposure, radiological silicosis, and lung cancer mortality in diatomaceous earth industry workers. *Thorax* 1999; 54: 56-9.
11. Cherry N M, Burgess G L, Turner S, McDonald J C. Crystalline silica and risk of lung cancer in the potteries. *Occup Environ Med* 1998; 55: 779-85.
12. Steenland K, Sanderson W. Lung cancer among industrial sand workers exposed to crystalline silica. *Am J Epidemiol* 2001; 153:695-703.
13. Moulin J J, Clavel T, Roy D, Dananché B, Marquis N, Févotte J, et al. Risk of lung cancer in workers producing stainless steel and metallic alloys. *Int Arch Occup Environ Health* 2000; 73:171-80.
14. Ulm K, Waschulzik B, Ehnes H, Guldner K, Thomasson B, Schwebig A, et al. Silica dust and lung cancer in the German stone, quarrying and ceramics industries: results of a case-control study. *Thorax* 1999; 54:347-51.
15. Cocco P, Rice C, Chen J-Q, McCawley M A, McLaughlin J K, Dosemeci M. Lung cancer risk and silica exposure in Chinese mines and pottery factories: the modifying role of other workplace lung carcinogens. Abstracts of the 14th International Conference on Epidemiology in Occupational Health (EPICOH); Oct 1999, Herzliya, Israel. Israel: EPICOH, 1999:8.
16. Steenland K, t'Mannetje A, Boffetta P, Stayner L, Attfield M, Chen J-Q, et al. Pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multi-centric study. *Cancer Causes Control* 2001 (in press).
17. Oksa P, Klockars M, Karjalainen A, Huuskonen M S, Vattulainen K, Pukkala E, et al. Progression of asbestosis predicts lung cancer. *Chest* 1998; 113:1517-21.
18. Turner-Warwick M, Lebowitz M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis and lung cancer. *Thorax* 1980; 35:496-9.
19. Nagai A, Chiyotani A, Nakadate T, Konno K. Lung cancer in patients with idiopathic pulmonary fibrosis. *Tohoku J Exp Med* 1992; 167: 231-7.
20. Rouetbi N, Battikh M, el Kamel A. Diffuse interstitial pulmonary fibrosis and bronchial cancer. *Rev Pneumol Clin* 1999; 55:370-2.
21. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. *Am J Respir Crit Care Med* 2000; 161:5-8.
22. Katabami M, Dosaka-Akita H, Honma K, Saitoh Y, Kimura K, Uchida Y, et al. Pneumoconiosis-related lung cancers: preferential occurrence from diffuse interstitial fibrosis-type pneumoconiosis. *Am J Respir Crit Care Med* 2000; 162:295-300.
23. Skillrud D M, Offord K P, Miller R D. Higher risk of lung cancer in chronic obstructive pulmonary disease. *Ann Intern Med* 1986; 105: 503-7.
24. Alavanjia M C R, Brownson R C, Boice J D, Hock E. Preexisting lung disease and lung cancer among non smoking women. *Am J Epidemiol* 1992; 136:623-32.
25. Beaty T H, Cohen B H, Newill C A, Menkes H A, Diamond E L, Chen C J. Impaired pulmonary function as a risk factor for mortality. *Am J Epidemiol* 1982; 116:102-13.
26. Hunter D. The diseases of occupations. London, UK: The English Universities Press, 1964.
27. Carta P, Cocco P L, Aru G, Barbieri M T, Cocco E, Meloni M. Smoking and dust effect upon lung function of healthy workers. *Eur J Respir Dis* 1981; 62(suppl. 113):26-7.
28. Tockman M S, Anthonisen N R, Wright E C, Donithan M G. IPPB trial group, Johns Hopkins lung project: Airway obstruction and the risk for lung cancer. *Ann Intern Med* 1987; 106:512-8.

29. Carta P, Cocco P L, Casula D. Mortality from lung cancer among Sardinian patients with silicosis. *Br J Ind Med* 1991; 48:122-9.
30. Carta P, Cocco P L, Picchiri G F. Lung cancer mortality and airways obstruction among metal miners exposed to silica and low levels of radon daughters. *Am J Ind Med* 1994; 25:489-506.
31. Gaziano D, Seaton A, Ogilvie C. Regional lung function in patients with obstructive lung diseases. *BMJ* 1970; 2:330-3.
32. Love R G, Muir D C F. Aerosol deposition and airways obstruction. *Am Rev Respir Dis* 1976; 114:891-7.
33. Steinitz R. Pulmonary tuberculosis and carcinoma of the lung. A survey from two population based disease registries. *Am Rev Respir Dis* 1965; 92:758-66.
34. Wu A H, Fonham E T H, Reynolds P, Greenberg R S, Buffler P, Liff J, et al. Previous lung disease and risk of lung cancer among lifetime nonsmoking women in the United States. *Am J Epidemiol* 1995; 141:1023-32.
35. Checkoway H, Franzblau A. Is silicosis required for silica-associated lung cancer? *Am J Ind Med* 2000; 37:252-9.
36. McLaughlin J K, Chen J, Dosemeci M, Rong-An C, Rensing S H, Zhien 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.
37. Chen J, McLaughlin J K, Zhang J-Y, Stone B J, Luo J, Chen R-A, et al. Mortality among dust-exposed Chinese mine and pottery workers. *J Occup Med* 1992; 34:311-6.
38. Dosemeci M, Chen J-Q, Hearl F, Chen R-G, McCawley M, Wu Z, et al. Estimating historical exposure to silica among mine and pottery workers in the People's Republic of China. *Am J Ind Med* 1993; 24:55-66.
39. Oberdorster G. Lung particle overload: implications for occupational exposures to particles. *Regul Toxicol Pharmacol* 1995; 27:123-35.
40. Mao Y, Daniel L N, Knapton A D, Shi X, Saffiotti U. Protective effects of silanol group binding agents on quartz toxicity to rat lung alveolar cells. *Appl Occup Environ Hyg* 1995; 10:1132-7.
41. Saffiotti U, Williams A O, Daniel L N, Kaighn M E, Mao Y, Shi X. Carcinogenesis by crystalline silica: animal, cellular, and molecular studies. In: Castranova V, Vallyathan V, Wallace W E, editors. *Silica and Silica-Induced Lung Diseases*. Boca Raton, FL: CRC Press Inc, 1996:345-81.
42. Shoemaker D A, Pretty J R, Ramsey D M, McLaurin J L, Khan A, Teass A W, et al. Particle activity and in vivo pulmonary response to freshly milled and aged alpha-quartz. *Scand J Work Environ Health* 1995; 21(suppl 2):15-8.
43. Saffiotti U, Ahmed N. Neoplastic transformation by quartz in the BALB/3T3/A31-1-1 cell line and the effects of associated minerals. *Teratog Carcinog Mutagen* 1995; 15:339-56.
44. Vogliazzo U, Ghezzi I. Aspects of experimental silicosis in albino mice pre-treated with iron [in Italian]. *Med Lav* 1963; 54:289-301.
45. Rothman K J. Causation and causal inference. In: Fraumeni J F Jr, Schottenfeld D, editors. *Cancer Epidemiology and Prevention*. Philadelphia, PA: WB Saunders, 1982:15-21.
46. Salmon W. Scientific explanation and the causal structure of the world. Princeton, NJ: Princeton University Press, 1984.