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Lung cancer among silica-exposed workers: the quest for Truth between chance and necessity

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Key words

Silica; silicosis; lung neoplasms; occupational health; carcinogenesis

Summary

Background: *In 1997, IARC upgraded crystalline silica to a Group 1 human carcinogen. However, the IARC report itself acknowledged variations in risk depending on inherent characteristics of the crystalline silica or external factors affecting its biological activity or distribution of its polymorphs.* **Methods:** *We reviewed silica physical and physico-chemical properties and how such properties may affect its interaction with the target cells. Studies of silica, silicosis and lung cancer published from 1997 onwards are then reviewed in the search of any new advances in knowledge about silica carcinogenicity. Finally, other possible confounding factors contributing to inconsistent findings on silica, silicosis, and lung cancer are reviewed.* **Results:** *Host factors, physico-chemical characteristics of the surface of silica particles, exposure circumstances, and the mineral ore composition experimentally affect the ability of silica particles of inducing release of reactive oxygen species (ROS) and TNF-α by alveolar macrophages, possibly accounting for the great variation in lung cancer risk among dust exposed workers across the individual studies. Most recent epidemiological studies do not consider such complex pattern of modifying factors, and they keep replicating inconsistent findings. The hypothesis of a silicosis-mediated pathway, although more consistent from an epidemiological perspectives, and reassuring in terms of the effectiveness of current standards in preventing lung cancer risk among silica exposed workers, does not seem to explain elevated risks at low silica exposure levels.* **Conclusion:** *Future studies of lung cancer risk among workers exposed to silica-containing dust should consider measurement of ROS and TNF-α release by workplace dust samples as intermediate end-points predicting lung cancer risk better than silica concentration, allowing to more effectively address preventive action.*

Riassunto

«Tumore polmonare nei lavoratori esposti a silice: la ricerca della verità tra caso e necessità». *Nel 1997, l'Agenzia Internazionale per la Ricerca sul Cancro rivalutò la cancerogenicità umana della silice cristallina classificandola nel Gruppo 1. Tuttavia, la stessa Monografia IARC sottolineò l'esistenza di variazioni del rischio in relazione a caratteristiche intrinseche della silice cristallina o a fattori esterni, capaci di influenzare la sua bioattività, o al rapporto tra le specie polimorfe della silice stessa nella polvere inalata. In questo lavoro sono state esaminate le proprietà fisico-chimiche della silice e le modalità attraverso le quali tali proprietà possono interferire con l'interazione*

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con le cellule bersaglio. Quindi, sono stati riesaminati gli studi epidemiologici su silice, silicosi e cancro del polmone pubblicati dal 1997 ad oggi, allo scopo di verificare il loro contributo all'avanzamento delle conoscenze riguardo alla cancerogenicità della silice. Infine, sono stati esaminati i possibili confondenti capaci di dare luogo a risultati contrastanti nello studio dell'associazione tra silice, silicosi e cancro polmonare. Fattori individuali, le caratteristiche fisico-chimiche della superficie delle particelle di silice, le circostanze dell'esposizione, e la composizione geologica del minerale estratto e della sua matrice sono in grado di influenzare sperimentalmente la capacità della silice di determinare il rilascio di radicali ossidanti (ROS) e di TNF-α da parte dei macrofagi alveolari, costituendo una possibile spiegazione della grande variabilità del rischio di cancro polmonare nei lavoratori esposti a polveri nei singoli studi. Gli studi epidemiologici più recenti non hanno considerato l'importanza di questo complesso insieme di fattori di modificazione, e continuano a ripetere risultati contrastanti. L'ipotesi di un percorso eziologico mediato dalla comparsa della silicosi, sebbene giustificato da una più chiara evidenza epidemiologica, e rassicurante dal punto di vista dell'efficacia degli attuali TLV nel prevenire il tumore polmonare tra i lavoratori esposti a silice, non sembra in grado di rendere conto del frequente riscontro di un rischio elevato a bassi livelli di esposizione a silice. Ulteriori studi sul rischio di cancro polmonare nei lavoratori esposti a polveri contenenti silice dovrebbero prendere in considerazione la misurazione del rilascio di ROS e TNF-α per effetto di polveri campionate negli ambienti di lavoro, quale condizione intermedia in grado di predire il rischio di cancro polmonare in maniera più precisa rispetto alla semplice concentrazione della silice, permettendo di implementare azioni preventive più efficaci.

Introduction

Early reports of an elevated prevalence of lung tumors in autopsies of silicosis patients (57), paved the way to an unceasing scientific debate in the Occupational Health arena on a direct or silicosis-mediated role of silica in lung carcinogenesis, which has been continuing for the last 50 years. In 1987, the International Agency for Research on Cancer (IARC) classified crystalline silica as a probable human carcinogen (Group 2a) (39), and 10 years later upgraded its evaluation to a Group 1 human carcinogen (40). Silica dust is a typical exposure in most mining environments and in numerous outdoor workplaces, and pulmonary silicosis is known since ancient times to be its most typical health consequence. However, the quest for Truth about the nature and etiology of the wasting miners disease crosses centuries. Likewise, although speeded up by the modern communication devices, the scientific debate about silica as a lung carcinogen has extended over the last 50 years without reaching unanimously shared conclusions.

The 1997 IARC commission on silica evaluation did not reach an unanimous agreement, as testified by the unusual statement about the fact that its carcinogenicity "*...was not detected in all industrial circumstances studied",* perhaps depending "*...on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs*" (40). Weaknesses leading to such a statement have been highlighted (22). Understanding exactly under which "industrial circumstances" silica manifests its human carcinogenicity, and what exactly are the internal and external factors modifying it, is not trivial, as it is required to implement effective preventive and regulatory measures against health effects resulting from occupational exposure to the most abundant mineral on Earth.

A role of chance and confounding is plausible. Other authors have addressed the issue from a statistical perspective, with pooled analyses of the cohort studies fitting a priori established criteria (70), or creating new ways of modeling lung cancer risk by dose of inhaled silica (71). In this paper, *a*. a biological mechanism based on the different physicochemical properties of workplace dusts is proposed as an alternative explanation for inconsistent findings; *b*. the reports published after the 1997 IARC Monograph are reviewed to explore any progress towards a better understanding of the apparently odd silica-lung cancer relationship; and *c*. attempts to assess other potential factors contributing to variation in risk are illustrated.

MECHANISMS OF SILICA TOXICITY AND CARCINOGENICITY

Silica is a *particulate toxicant*. As such, its reactivity is related to the chemical reactions between the particle surface and the biological matter (31). Several factors, including crystalline structure, form and size of the particle, hydrophilicity/ hydrophobicity of the surface, age of the particle - in terms of time since fractured - capacity of generating free radicals, and presence of contaminants modify the biological response to silica at comparable exposure levels (32). As each cellular response elicited is related to a specific physico-chemical feature of the silica surface (33), differences in lung cancer risk among silica-exposed cohorts are to be expected if features effective in increasing lung cancer risk differ across the respective workplaces.

Also, the definition of silica covers a wide range of forms and properties, which mainly result from covalency and flexibility of the Si-O bond. The nature of Si-O bond affects the crystalline/amorphous form of the mineral, as well as its solubility in water and other biological media (32). Inflammatory, fibrogenic and genotoxic activity of silica particles in rats by intratracheal instillation varied in 4 silica polymorphs, depending on their aluminium, and possibly iron, content (34). Besides, changes in silica toxicity, as measured by percent cell survival, and silica transforming activity in cell cultures, varied greatly whether MQZ, a quartz polymorph, was administered alone or combined with hematite or one of two titanium dioxide (TiO_2) polymorphs, anatase or rutile (61). In fact, a reduction in silica toxicity and neoplastic transforming activity was observed when hematite or anatase, which has not transforming activity by itself, were combined with MQZ silica. Instead, an increase in silica cytotoxicity was obtained with rutile, unable as anatase to induce any transforming activity by itself, with a reduction in cell survival and no effect, unless at the highest doses, in reducing MQZ-induced transforming activity when administered in combination. Most workplace dusts include various contaminants either from the original mineral or acquired during the process, such as metal ions, which link to silanol groups at the surface of silica particles, thus generating dusts with quite different surface properties, and, therefore, biological activity (33).

One silica surface property of major relevance in lung carcinogenicity might be its ability of generating reactive oxygen species (ROS). Fubini et al. compared the potential of releasing HO• radicals and the consequent ability of transforming Syrian Hamster Embryo (SHE) cells in various quartz dusts, differently modified by changing grinding procedures and presence of impurities, and in one type of amorphous diatomaceous earth (33). For all the samples, the number of transformed cells was strongly correlated with the amount of HO• released. An indirect clue for ROS role in increasing the transforming activity of silica particles stems from the finding of a dose-dependent decrease in intracellular glutathione (GSH) observed in isolated rat alveolar macrophages (AM) exposed to silica (83). In the presence of highly oxidised iron ions on the quartz surface, the -SH groups of cysteine and GSH rapidly shift to the disulphide form, via a radical mechanism. Administering n-acetylcysteine (NAC), a GSH precursor, markedly reduced silica-induced ROS formation, changes in membrane permeability and DNA strand breaks (28). If the ability of releasing active oxygen and nitrogen species, which seems to be responsible of silica transforming activity in cell culture, were also relevant in silica carcinogenicity, measuring such a property in dust samples from different workplaces would provide a summary metric of their carcinogenic potential, which might at least in part account for the inconsistent lung cancer risk thus far observed among silica exposed workers. Another indirect mechanism might stem from the release of AM cytokines, such as TNF-α and interleukin-8 (IL-8), also contributing to secondary genotoxicity in target cells (34). Chen et al. provided preliminary evidence that it might indeed be so (18, 19). As an indicator of ROS formation, they measured the Guinea pigs AM ability of releasing hydrogen peroxide (in nmol/3x10^5 AM), incubated with dust samples from four Chinese tin mines (19), as well as the concentration of TNF-α (in unit/ml) in the supernatant of a rat AM suspension in Ham's F12 medium. Dust samples differed in particle size dis-

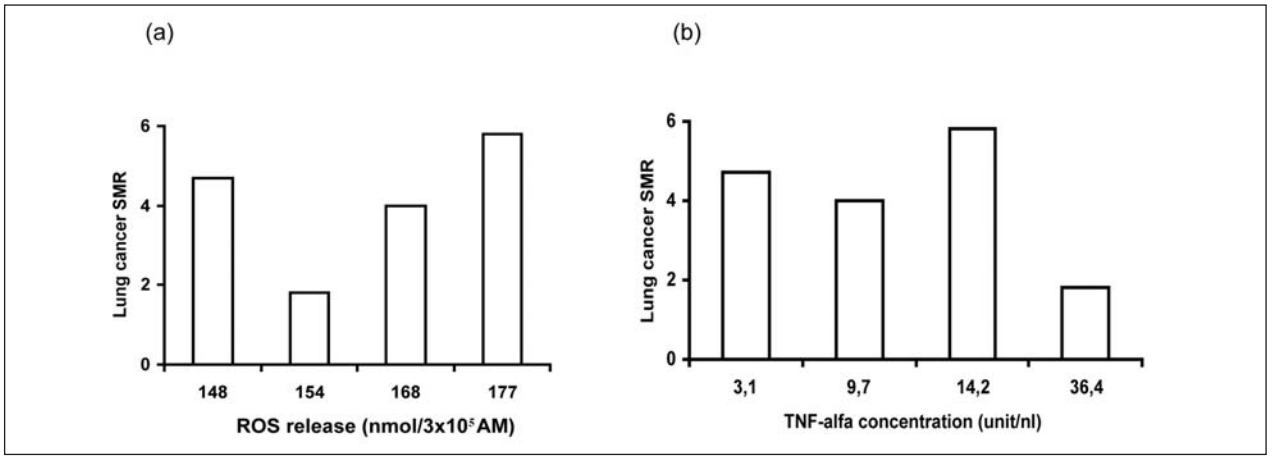

Figure 1 - Lung cancer SMR in 4 Chinese tin mines in relation to ROS release in guinea pigs AM (a) and TNF-α concentration in a suspension of rat AM (b) by dust samples from the respective mine [modified from references 14 and 15)

tribution, silica concentration and arsenic concentration (18). ROS and TNF-α release after incubation with the four dust samples were compared with those obtained with a blank, corundum (an inert material) as the negative control, and DQ12 (a standard quartz) as the positive control. The same authors also conducted a 20-year mortality follow up in the same four mines, and calculated the SMR for lung cancer and pneumoconiosis. Interestingly, while the pooled lung cancer SMR was elevated (16, 50), this result was not consistent in the individual mines (figure 1). Also, ROS release differed between the respective dust samples at concentrations ≥60 μg/10^6 AM, but not at lower concentrations. Differences in TNF-α concentration were also evident at any dust concentration tested in the range 15-120 μg/10^6 AM. Based on the data reported in their publications, we used Poisson regression analysis to assess lung cancer risk associated with high silica exposure in two Chinese tin mines, with reference to the relatively low silica exposure in the other two mines. Risk associated with high level silica exposure was only moderately elevated (RR=1.6; 95% C.I. 1.0, 2.5). After introducing TNF-α release as a covariate, a strong increase in lung cancer risk was associated with low level of TNF-α release by samples of specific workplaces (RR=2.6; 95% C.I. 1.8, 3.8), while risk associated with high level silica exposure was only slightly decreased (RR=1.5; 95% C.I. 1.0, 2.4). No such association was observed with ROS release. However, only four different dust samples were tested, and their physical characteristics do not seem enough distant from each other. Besides, other factors need to be considered to explain the variation in lung cancer risk associated with specific dusts. Nonetheless, extending such tests to a greater number of dust samples with substantial mineralogical differences might provide deeper insights into the mechanisms of lung carcinogenesis among silica exposed workers.

Further workplace factors, such as particle size and concurrent exposure to other lung carcinogens, and other typically individual factors, such as immune function and ability of scavenging reactive oxygen species, also need to be considered as potential modifiers of the biological response to silica at comparable exposure levels, altogether being responsible of the great variation in lung cancer risk. Further studies addressing such circumstances would be of foremost help in designing more effective preventive strategies.

REVIEW OF THE RECENTLY PUBLISHED REPORTS (1996-2006)

How did the scientific literature, published following the 1997 IARC Monograph, cope with the complex conditions affecting silica toxicity and car-

cinogenicity, and therefore the outcome in terms of lung cancer risk? Tables 1 a-b summarizes the results of such epidemiological studies on silicosis (a, N=11), silica exposure (b, N=25) and lung cancer, including updates of previous cohort studies. Reviews, metanalyses, and pooled analyses are not included in tables 1 a-b.

1. Silicosis as a cause of lung cancer

Although results were contradictory, a few autopsy surveys of silicosis patients, describing an elevated prevalence of lung cancer arising around the fibrotic lesions, initiated the debate on the silicosis-lung cancer link (57). In absence of a proper epidemiological design, the conclusions of both positive and negative reports were mainly speculative. Large occupational surveys and experimental findings shifted the balance towards negative, until the majority of the epidemiological studies conducted in the last 20 years confirmed the association (40). Settling the controversy has practical relevance. In fact, if silicosis were the necessary step leading to lung cancer (24, 30), enforcing the current silica standards would protect workers against lung cancer risk as well. Alternatively, a direct silica-lung cancer association is suggested (15, 21), which implies that regulatory standards should be revised accordingly.

In a Polish cohort, mortality from lung cancer was elevated only among pneumoconiotic workers in nonferrous foundries and in the metallurgical industry, but not among pneumoconiotic workers in refractory, china, and ceramics manufacturing plants or quarries, suggesting confounding by other workplace exposures (68). A 2-fold excess lung cancer mortality was reported among silicosis patients in Hong Kong (12), mostly from the construction industry, with relatively isolated, although not quantified, exposure to silica. The risk pattern

Table 1 a - *Results of studies exploring the association between silicosis with lung cancer risk published after the 1997 IARC Monograph on silica*

Year	First author	Study population	Association	Concurrent exsposure	Update	Confirmed
Case control studies						
1998	Hnizdo et al.	South African gold miners	+	none	no	-
1998	Finkelstein	Ontario patients with silicosis	+	none	no	-
2001	Cocco et al.	Chinese dusty trades (tungsten, tin and iron mines and potteries)	-	arsenic, cadmium chromium, nickel, PAH, radon daughters	yes	yes
2002	Tsuda et al.	Refractory brick production workers	+	none	no	-
Cohort studies						
1996	Starzynski et al.	Polish pneumoconiootics	-	none	no	-
1997	Oksa et al.	Finnish pneumoconiotics	-	various	no	-
1998	De Klerk and Musk	Western Australia gold miners	+	none	yes	yes
2000	Chan et al.	Chinese (Hong Kong) patients with silicosis	-	none	no	-
2001	Carta et al.	Italian silicotics from lead and zinc mines and granite quarriers	-	radon daughters	yes	yes
2001	Berry G	Australian compensation list	+	chronic obstructive lung disease	no	-
2004	Ulm et al	German compensated workers from granite quarries	+	none	no	-

Table 1 b - *Results of studies exploring the association between silica exposure with lung cancer risk published after the 1997 IARC Monograph on silica*

Year	First author	Study population	Association	Concurrent exsposure	Update	Confirmed
Case control studies						
1997	Hnizdo et al.	South African gold miners	+	none	no	-
1999	Ulm et al.	German stone, quarrying and ceramic industries	-	diesel exhaust, radon daughters, PAH, welding fumes, heavy metals, asbestos, and other fibers	no	-
2000	Rogriguez et al.	Spanish steel and iron foundries	+	PAH, various other carcinogens	no	-
2001	Cocco et al.	Chinese dusty trades (tungsten, tin and iron mines and potteries)	+	arsenic, cadmium, chromium nickel, PAH, radon daughters	yes	no
2002	Watkins et al.	Asphalt roofing manufacturing and asphalt production	-	PAH	no	-
2002	Tsuda et al.	Refractory brick production workers	+	none	no	-
2002	Chen et al.	Chinese tin miners	-	arsenic	yes	yes
2005	Mc Donald et al.	US Industrial sand workers	+	none	yes	yes
Proportional mortality studies						
1999	Fillmore et al.	Death certificates 24 states. JEM identified silica	+	various	no	-
Cohort studies						
1997	Checkoway et al.	Diatomaceous earth industry	+	asbestos?	no	-
1997	Rafnsson and Gunnarsdottir	Icelandic diatomaceous earth and cristobalite workers	+	none	yes	yes
1998	De Klerk and Musk	Western Australia gold miners	-	none	yes	yes
1998	Cherry et al.	Pottery, refractory, and sandstone industries in Stoke-on-Trent, UK	+	none	no	-
1999	Checkoway et al.	Diatomaceous earth industry workers	+	none	yes	yes
2000	Moulin et al.	French stainless steel and metallic alloys industry	+	numerous (no association with asbestos in this study)	no	-
2001	Carta et al.	Italian lead and zinc miners	-	radon daughters	yes	yes
2001	Marsh et al.	US man-made vitreous fiber production workers	-	arsenic, asbestos, asphalt, epoxy, formaldehyde, polycyclic aromatic hydrocarbons, phenolics, silica, styrene, and urea	no	-
2003	Coggiola et al.	Italian talc miners and millers unexposed to asbestos	-	talc	yes	yes
2004	Graham WG	Vermont granite shed and quarries	-	none	yes	yes
2004	Attfield and Costello	Vermont granite workers	+	none	no	-
2004	Moshammer and Neuberger	Austrian workers undergoing check ups	+	none	no	-
2004	Isidro Montes et al.	Spanish coal miners	-	Coal dust	no	-
2005	Chen et al.	Chinese tin miners	+	arsenic	yes	yes
2005	McDonald et al.	North American sand industry	+	none	yes	yes

was similar among surface and underground workers; it was independent on duration of exposure to silica and profusion of small opacities in both groups; and it was not modified by tuberculosis. The authors concluded that smoking rather than silicosis accounted for most of the observed excess (12). A significant excess mortality from silicosis in an asbestos-free talc mining and milling cohort was not accompanied by a parallel increase in lung cancer mortality (7). A follow up of silicosis patients, using multiple analytical procedures, concluded that cigarette smoking, airflow obstruction, and low level exposure to radon daughters accounted for the modest increase in lung cancer risk observed in the cohort, rather than the radiological severity of silicosis or the cumulative exposure to silica (8). Also, no association with silicosis was observed in a nested case-control study of Chinese tin miners (17). However, overall, Chinese silica-exposed workers had a 40% increase in lung cancer risk associated with radiological diagnosis of pneumoconiosis (23), which did not increase by severity of silicosis. Adjusting by cumulative dose of silica exposure, or by radiological evidence of progression in silicosis stage (as derived from subsequent radiographs compared to the first diagnosis) did not affect the association (23).

On the other hand, Finnish subjects affected by silicosis had a 2.7-fold increase in lung cancer incidence (56); workers from the German stone and quarry industry compensated for silicosis were at increased risk of developing lung cancer (77); the excess lung cancer mortality in a cohort of Western Australian gold miners was concentrated among silicotic workers (24); and, although with differences across workplaces, lung cancer was the only cancer site showing a significant excess mortality in a cohort of men compensated for silicosis in New South Wales, Australia (6). Also, a nested case-control of lung cancer cases within a cohort of silica-exposed workers in Ontario, Canada, showed a 3.3-fold increase in lung cancer risk associated with silicosis, as defined by pulmonary radiographs classified as category ≥1/0 based on the International Labour Office (ILO) classification of pneumoconiosis. Adjustment by cumulative radon exposure resulted in an increased Odds Ratio (OR), and empirical evidence suggested that there was not confounding by smoking (30). Lung cancer risk was also significantly associated with silicosis in South African gold miners (37), in Italian men and women compensated for silicosis (47), and in a Japanese population-based case-control study (74), with patients presenting small opacities running a risk higher than those with large opacities. Small cell carcinoma appeared to be more frequently diagnosed among silica-exposed than silica-unexposed study subjects.

2. Silica as a cause of lung cancer

Table 1b shows the studies exploring the silica-lung cancer association. While the majority of studies yielded positive results, even independent analyses conducted on the same cohort, such as the Vermont granite workers, lead to opposite interpretations (2, 36). A survival analysis with Cox proportional modeling of a cohort of Austrian workers undergoing regular check ups showed an increased hazard ratio for lung cancer among workers exposed to non-fibrous particulates, including silica (51). An update of the mortality experience in a Californian cohort of diatomaceous earth workers, exposed to crystalline silica as a contaminant of amorphous silica, found a significant increasing trend in lung cancer risk with exposure to respirable crystalline silica lagged 15 years, which did not vary depending on whether a radiographic diagnosis of silicosis was posed or not (13). The authors concluded that silicosis is not necessarily required for silica-related lung carcinogenesis, confirming results from their earlier report (14). Icelandic diatomaceous earth and cristobalite workers also showed an increasing trend in lung cancer incidence, although not supported by statistical significance (58). When analyzing data with a 15-year time lag, an increasing trend in lung cancer risk by cumulative silica exposure was also observed among a cohort of US industrial sand workers (69), and the excess was confirmed in another cohort study and in a nested case-control analysis of 105 of the lung cancer cases identified in that cohort (49). Also, in two European nested case-control studies of silica-exposed workers in various trades,

and in one Japanese population based case-control study, the smoking-adjusted lung cancer risk was significantly increased for average silica exposure (20), or for combined exposure to silica and polycyclic aromatic hydrocarbons (PAH) (52), but results in the European studies conflicted when trends by duration of exposure or cumulative exposure were explored, and silica exposure estimates in the Japanese case-control study were not detailed enough to explore trends (74). Estimating silica exposure based on occupation and industry title in several millions of death certificates in a US death certificates data base, resulted in an increased mortality odds ratio from silicosis – which was meant as a test for the reliability of the exposure assessment - and from lung cancer among the exposed (29). Exposure to crystalline silica was mentioned among the factors contributing to an increase in lung cancer risk among Spanish iron and steel foundry workers, along with PAH and various other workplace carcinogens, in a nested case-control study (59). No attempt was made in this study to explore the association with individual exposures.

The conclusions about an excess risk for lung cancer, and particularly small cell lung cancer, associated with cumulative dust exposure among South African gold miners featured possible interpretations, including 1. the fact that subjects with high dust exposure are more likely to develop silicosis, and, therefore, are at increased risk of lung cancer; or 2. high levels of exposure to silica dust on its own is important in the pathogenesis of lung cancer and silicosis is coincidental; or 3. high levels of silica dust exposure may be a surrogate for the exposure to radon daughters (37).

In contrast with these reports, in a cohort study of Western Australia gold miners, lung cancer incidence increased with log cumulative silica exposure, but the association disappeared once the onset of silicosis was taken into account. The authors, therefore, interpreted their result as supporting the etiologic role of silicosis and the absence of an independent silica effect (24). Radon daughters but not cumulative silica exposure were associated with lung cancer risk in an update of a cohort study of Italian metal miners (11), and lung cancer mortality was not elevated in another Italian cohort of an asbestos-free talc mine, where non malignant respiratory diseases was the only cause of death showing an excess, mainly due to silicosis (7). Exposure to arsenic was suggested as responsible for the association between cumulative dust exposure and lung cancer in a nested case-control study of Chinese tin miners (17). Cumulative exposure to silica was not associated with lung cancer mortality among a cohort of US man-made vitreous fibre production workers (48). Exposure to numerous other lung carcinogens occurred in this cohort, including arsenic, asbestos, PAH, and formaldehyde, but, after adjusting by smoking, none showed a consistent association with lung cancer. The same negative finding was observed in a case-control study of lung cancer within U.S. asphalt manufacturers to investigate whether there was an increased risk associated with measured and estimated exposure to asphalt fumes or respirable crystalline silica in these industries (80). A German case-control study of the stone, quarrying and ceramic industries, which excluded subjects with silicosis, found an OR of 0.85 (95% C.I. 0.58, 1.25) for a peak silica concentration ≥ 0.15 mg/m^3 with reference to lower concentrations, which did not increase with increasing exposure, and was confirmed using other exposure metrics (76). Concurrent exposures in this study included diesel exhaust, radon daughters, PAH, welding fumes, heavy metals, asbestos, and other fibers, but only the first two exposures were more frequent among cases. Recent studies of coal miners also keep providing negative results on the silica-lung cancer association (41).

Chance, confounding, differences in study design and genetic background may account for inconsistent findings across studies. However, profound differences in the silica-lung cancer association were observed within various Chinese dusty trades by facility type, although the study design and the genetic and social background were very much alike (16, 25, 50). In the combined analysis of the 29 mines and factories included in that study, lung cancer risk increased up to 1.6-fold for a cumulative silica exposure ranging 10.8-26.9 mg/m^3-years, with a decrease to 1.2 for a cumulative silica exposure of 27 mg/m^3-years or more. Limiting the analysis to subjects with radiographs

negative for silicosis, or adjusting the risk estimates by radiographic staging of silicosis did not change these figures (23). 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/m^3-years, was observed in a meta-analysis of data from 10 silica-exposed cohorts (70). Differently from the US industrial sand and diatomaceous earth cohorts, allowing for a 15-year time lag, or using other exposure metrics, did not change the results.

While the overall epidemiological evidence suggests that, under certain circumstances of exposure, silica behaves as a lung carcinogen (23, 40, 70), no major progress has been made thus far in identifying what exactly such circumstances are. Finding the answer is of paramount importance in preventing silica-related health effects other than silicosis, including lung cancer. However, most of the recent literature keeps repeating the traditional study designs, sometimes with additional features contributing to a more precise diagnosis or a more refined exposure assessment, oftentimes just updating the life status of old cohorts, in the attempt of increasing the statistical power or replicating the association under different exposure circumstances. In most instances, updates have confirmed earlier findings, leaving unchanged the uncertainties. Major developments in the scientific knowledge are not to be expected unless addressing the issue with new creative approaches.

The role of confounders in modifying or confounding the epidemiological association between silica, silicosis, and lung cancer

We herein try to answer three important questions:

1. Is silica itself responsible of increasing lung cancer risk, or does this result indirectly from silicosis? We previously discussed the practical implications underlying this question.

2. A role of non malignant respiratory disorders as independent risk factor for lung cancer has been repeatedly reported in the general population (1, 5). Lung tuberculosis, asthma, emphysema, and chronic bronchitis are specially prevalent among silica exposed workers, and an independent role of airways obstruction has been observed (11), and then confirmed (8) among silicosis patients. Do such conditions confound the silica-silicosis-lung cancer association?

3. Smoking has been considered in numerous case control studies, but how do other work place lung carcinogens interact with silica exposure?

a. Silicosis

The etiological model of a silicosis-mediated lung carcinogenicity of silica stresses the role of cytokines released by the alveolar macrophages during the inflammatory response. If so, the silicosis-lung cancer association would result from an unspecific mechanism shared with other fibrogenic lung diseases. Indeed, a 10-31% increase in lung cancer prevalence was reported among patients with idiopathic pulmonary fibrosis (53, 60, 75), while lung cancer incidence was more than 7-fold increased in patients with cryptogenic fibrosing alveolitis (38). Adjustment by smoking further increased risk. Besides, squamous cell carcinoma occurring in diffuse interstitial fibrosis (DIF)-associated pneumoconiosis preferentially arose from DIF areas 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 (42). Also, no evidence was found of an increasing lung cancer risk by radiological evidence of silicosis progression (23), while 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 (55). Therefore, under the hypothesis of silicosis as a necessary step for silica-related lung cancer development, we should consider silica-related lung fibrosis as one of the possible triggers, apparently less effective compared to other fibrogenic lung diseases.

The confounding effect of non malignant respiratory disorders has seldom been considered in studies of the silicosis-lung cancer associations. Previous diagnosis of chronic obstructive pulmonary disease (COPD) (1, 67) and obstructive

impairment of the ventilatory function (5, 8, 10, 73) have been shown to be independent risk factors for lung cancer, and clinical symptoms and functional signs of COPD frequently, but not constantly, accompany silicosis (65). Indeed, inhaled particles themselves, including crystalline silica, either alone or in association with smoking or workplace exposure to nitrogen or sulfur oxides, may cause airways obstruction (9), although clinical symptoms, such as chronic cough and phlegm, upon which the clinical diagnosis of chronic bronchitis is based, are mostly related to smoking (3, 65). 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 (73). Airways obstruction accounted for the small excess lung cancer risk observed in a mortality follow up of silicotic patients (8), and it was more frequently observed among Spanish silica-exposed compared to silica-unexposed lung cancer cases (4). On the other hand, deposition studies have shown that, among subjects with a clinical diagnosis of chronic bronchitis or asthma, whose airways obstruction would be expected to be more severe, particle deposition is increased in the proximal airways compared to the peripheral airways (35, 45). This would indicate that a smaller proportion of inhaled particles penetrates into the deep lung, which might actually decrease silicosis and lung cancer risk among these subjects relatively to coworkers unaffected by such diseases, with similar occupational and non-occupational exposures. In fact, 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, respectively), compared to subjects with a medical history for either two diseases (ORs=8.0, 23.1, 30.0, and 83.1, respectively) (21). Consistently with deposition studies, and with the pathological findings identifying the peripheral lung as the preferential site for lung cancer in DIF-associated pneumoconiosis (42), 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 for either disease (21). A similar modifying effect on the silicosis-lung cancer association has not been reported for pulmonary tuberculosis (21, 72, 81).

Concurrent exposure to various known workplace carcinogens might also be an important confounder. As silica workplace exposure levels are likely to be collinear with those of other lung carcinogens, levels which cause silicosis might be associated with higher exposure to such other lung carcinogens as well. Such a confounding effect was observed in Italian silicotic patients (8), and Chinese dusty trades, where risk was elevated only among silicotic subjects who were also exposed to each of five other lung carcinogens (23).

Further studies with detailed exposure data on silica as well as other workplace carcinogens, radiological and clinical data, are warranted before drawing conclusions on the nature of the silicosis-lung cancer association.

b. Silica

Possible modifying factors in the silica-lung cancer association are discussed below.

A. *Dust overload*. A modifying effect on the silica lung cancer association would result from particles deposition shift to the proximal airways instead of the peripheral lung following high level total dust exposure, similarly to what previously discussed for chronic bronchitis (54). 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/m^3 for unit density- 3 μm size-spherical particles (54). At such concentration, increased fibrotic foci were seen in rat, hamster and some mouse studies, although, as for silica, localized emphysema and tumors have been found in the rat model only. To explore separate effects of silica particles and dust overload, we can cross-tabulate lung cancer risk by categories of cumulative exposure to respirable silica and cumulative exposure to respirable dust. Such analysis can provide some indication on whether dilution of silica particles in the total in-

haled dust affects their interaction with biological targets. While results did not suggest an independent effect of total respirable dust on lung cancer risk, when a cumulative dose of respirable silica equal or below median (10.7 mg/m^3-years) was diluted in cumulative respirable dust doses above median (42.5 mg/m^3-years), no excess lung cancer risk was observed (table 2) (23). This was in contrast with the significant 40% excess associated with the same cumulative dose of silica, when combined with cumulative respirable dust doses below 42.5 mg/m^3-years. Therefore, we might raise the hypothesis that concomitant dust is an important risk modifier. Also, a shift in the particle deposition pattern to the upper airways in the lungs of the most heavily dust exposed workers would limit the effects of the associated silica exposure on the peripheral lung, similar to what presumably happens among subjects with chronic bronchitis.

B. *Exposure to other lung carcinogens*. In vitro studies have documented the binding of the silanol groups located in the quartz surface to the DNA phosphate backbone, as the mechanism for silica-induced neoplastic transformation (46, 62). We previously discussed silica-surface effect, 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 (66). *In vitro* surface properties of silica particles are also experimentally affected by their combination with other chemicals or minerals, such as poly-2-vinylpyridine-N-oxyde (PVPNO) and aluminium salts, and crystal surfaces of hematite and anatase (61), which might block critical steps of quartz cytotoxicity by interacting 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, and inhibiting or delaying silica-related fibrogenesis (27, 43, 78). Empirical and unfortunate attempts to prevent silicosis by spreading metallic aluminum or aluminum hydrate powder in the workplace to coat silica particles followed (46, 79), but the appearance of lung fibrosis among the workers, due to the massive inhalation of aluminium powder, caused immediate dismissal of such an unethical practice. More recent experimental work has shown a decrease in the biological effects of quartz associated with PVPNO, and aluminium lactate, which deposits ions over it. Shins et al. showed a reduction in IL-8 generation; reactive oxygen species (ROS) generation and DNA strand breaking in vitro (63, 64). BAL total cells count, PMN and macrophages cellular as well as DNA damage (44), and Macrophage Inflammatory Protein (MIP)-2 expression (26) were decreased in other studies. Other metals, minerals or chemicals, such as polycyclic aromatic hydrocarbons (PAH), in the dust might be capable of affecting such biological effects and, therefore, cell adhesion and/or uptake from phagocyting cells, either inhibiting or enhancing them, as experimentally shown in hamsters (39), by coating of silica surface. It is less likely that variations in the frequency of the gene polymorphisms, coding for the cytokines typically released by macrophages engulfing silica particles (82), would account for variations in lung cancer risk among silica exposed working populations. Also, in vitro experiments have shown that inhibition of quartz toxicity and transforming activity do not always come together, as previously discussed, suggesting that variations in silicosis and lung cancer risk following exposure to comparable silica levels should be expected.

As other known lung carcinogens are frequently part of dusty working environments, it is of interest to explore their modifying effect on silica-associat-

Table 2 - *Odds ratios (OR) and 95% confidence intervals (CI) for lung cancer by exposure to total respirable dust and silica above or below the respective median [modified from reference 9]*

Silica	Total respirable dust		
	Unexposed	0.1-42.4 mg/m^3-year	≥42.5 mg/m^3-year
Unexposed	1.0	-	-
0.1.10.7 mg/m^3-year	-	1.4 (1.0-1.9)	1.0 (0.5-1.9)
≥10.8 mg/m^3-year	-	1.5 (0.8-2.8)	1.4 (1.0-2.0)

ed lung cancer risk. Among Chinese workers exposed to silica but unexposed to PAH, nickel or radon-daughters, lung cancer risk was higher than among workers with the respective joint exposures (23). If confirmed, this result would suggest that concurrent exposure to other lung carcinogens might modify the silica-lung cancer risk, possibly through surface effects and/or apoptotic mechanisms. Further experimental and epidemiological research is warranted to clarify the effects of workplace exposure to multiple lung carcinogens and of the mineral composition of the inhaled dust on the silica-lung cancer association.

C. *Other lung diseases*. As observed for silicosis, subjects without a medical history for chronic bronchitis showed an increase in lung cancer risk with cumulative silica exposure, although 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 (21). Again, the modest association between lung cancer risk and cumulative silica persisted regardless medical history for pulmonary tuberculosis.

Conclusion

Silica exposure is still a major threat to the health of millions workers world wide. In most European and North American countries standard industrial hygiene implements, such as proper ventilation, wet drilling, and automatic drilling machinery, have allowed a strong reduction of respirable dust and silica exposure well below the current standards, particularly in mines and quarries. In other industries, such as sandblasting, silica use has been replaced or full protective equipment has been made available. There, strict surveillance of airborne silica concentration in all workplaces where such exposure might occur, taking proper registration of the exposed workers, and surveying and following up their health outcomes is mandatory. However, most mining work has been moved to developing countries, where prevention against occupational hazards simply does not exist. In these countries, just setting a surveillance system and implementing effective industrial hygiene strategies to prevent silicosis would be a great achievement. We must be aware, however, that it is quite possible that such strategies might not always be effective in preventing silica-related lung cancer in both industrialized and developing countries. A cost effective prevention of lung cancer among silica exposed workers would require identifying those workplaces where further action is necessary. Therefore, further studies of lung cancer risk among workers exposed to silica-containing dust are still needed, but a new creative epidemiological approach to the issue is indispensable. Keeping repeating the same path in the silica labyrinth does not help finding a way out. We suggest extending the Chinese experiment of measuring ROS and TNF-α release by workplace dust samples, which might predict lung cancer risk better than silica concentration, allowing to more effectively address preventive action.

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