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Meta-analyses of published epidemiological studies, 1979-2006, point to open causal questions in silica-silicosis-lung cancer research

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Key words

Silica; silicosis; lung cancer; meta-analysis

Summary

Background and Objectives: *Following up on a previous meta-analysis of lung cancer risk in individuals without silicosis, we provide more detailed results of silica associated lung cancer risk in both silicotics and non-silicotics. The objective was to examine in depth whether current data allows to answer the pressing question "does silica cause lung cancer in the absence of silicosis"?* **Methods:** *We updated earlier meta-analyses of silicosis and lung cancer and compared the results with our 2009 meta-analysis of risks in individuals without silicosis. We performed fixed (FE) and random (RE) effects meta-analyses, calculated heterogeneity statistics, stratified the study material, performed sensitivity analyses with modified study results and meta-regressions to detect effect modification.* **Results:** *In silicotics, lung cancer risks were found to be doubled in 38 studies (FE: RR=2.1; 95%CI=2.0-2.3). In non-silicotics, eight studies without smoking adjustment suggested marginally elevated risks (FE: RR=1.2; 95%CI=1.1-1.3; RE: RR=1.2; 95%CI=1.0-1.4) but three studies which were controlled for smoking showed null results (FE and RE: RR=1.0; 95%CI=0.8-1.3). Heterogeneity was substantial but could be linked to study characteristics, like sector of industry, and other second-level data in meta-regression. As no excess was observed for other smoking-related effects in studies of lung cancer among non-silicotics, smoking was not considered to be an important confounder or modifier.* **Conclusion:** *Our meta-analyses further substantiate evidence of a strong association between silicosis and lung cancer. However, questions remain regarding lung cancer caused by silica in non-silicotics. Ideally, future investigations should consider the entire exposure-response range between silica exposure, silicosis development and lung cancer occurrence, and analyze data in terms of processes taking intermediate confounding into account.*

Riassunto

«La metanalisi degli studi epidemiologici pubblicati nel 1979-2006 pone in rilievo domande di natura causale ancora aperte sul rapporto silice-silicosi-cancro del polmone». *Gli studi epidemiologici sul rischio di neoplasie polmonari nei lavoratori esposti a silice sono stati analizzati separatamente nei silicotici e non silicotici, allo scopo di indagare se, alla luce delle attuali conoscenze scientifiche, sia possibile rispondere al dibattito scientifico se la silice possa essere considerata un fattore causale di neoplasie polmonari in assenza di silicosi. Si tratta di una domanda*

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che ha rilevanti implicazioni dal punto di vista preventivo: infatti, qualora la silicosi fosse un elemento indispensabile perché i lavoratori esposti a silice manifestino un aumento del rischio di neoplasie polmonari, il rispetto degli attuali TLV, sufficienti a prevenire la silicosi, sarebbero applicabili anche alla prevenzione delle neoplasie polmonari; ma se così non fosse, il rischio di neoplasie polmonari potrebbe essere elevato a concentrazioni di silice di molto inferiori a quelle note quali determinanti di forme di silicosi rilevabili attraverso la diagnostica per immagini. Abbiamo aggiornato precedenti metanalisi degli studi su silicosi e cancro polmonare e confrontato i risultati con quelli di una recente metanalisi sul rischio di neoplasie polmonari in lavoratori esposti a silice che non svilupparono silicosi. Nei silicotici, il rischio di neoplasie polmonari è risultato doppio (RR=2,1; 95%CI=2,0-2,3). Nei non silicotici, il rischio risulta complessivamente moderatamente elevato (RR=1,2; 95%CI=1,1-1,3). Quest'ultimo risultato si osserva negli studi che non operarono alcun controllo per l'effetto del fumo di tabacco, ma non nei tre studi che operarono tale controllo (RR=1,0; 95%CI=0,8-1,3). Tuttavia, il fumo di tabacco non appare avere avuto un rilevante ruolo come confondente, in quanto altre patologie tabacco-correlate non sono apparse aumentate in relazione alle attese. L'analisi ha dimostrato una importante eterogeneità tra gli studi, in relazione alle caratteristiche degli studi ed al tipo di industria. La nostra metanalisi conferma la forte associazione esistente tra silicosi ed aumento del rischio di neoplasie polmonari. La questione se un aumento del rischio di neoplasie polmonari possa conseguire all'esposizione a silice indipendentemente dallo sviluppo di silicosi rimane aperta, in conseguenza dell'eterogeneità tra i risultati condotti in diversi ambienti lavorativi, apparentemente non spiegabile dai comuni confondenti. Ulteriori ricerche sull'argomento dovranno esplorare la relazione dose-risposta tra concentrazione ambientale di silice nelle polveri respirabili, sviluppo di silicosi e rischio di neoplasie polmonari all'interno di un ambito il più ampio possibile, ed analizzare i dati in termini di processo, tenendo debito conto dei possibili fattori di confondimento.

Introduction

Silica was classified as a group 1 carcinogen in 1997 (38) but there was controversial debate before, during and after the IARC classification as to under what circumstances silica is carcinogenic to humans. A 1995 meta-analysis (66) hypothesized a causal association between silicosis and lung cancer, either due to silicosis itself, or due to a direct effect of the underlying exposure to silica. Six other quantitative reviews (42, 43, 55, 72, 74, 78) followed between 1996 and 2006 as further attempts to analyze the epidemiological evidence over decades to better understand the causal pathway(s) between silica exposures and the development of lung cancer. And yet, the IARC 1997 decision continues to be disputed in principle, and details of causality are unsettled, which raise doubts about the effectiveness of preventive guidelines in the globalized world. A 2007 editorial gave a personal "yes" to the question: "Have we reached a point at which there is enough evidence to conclude that, at least under some circumstances, exposure to silica is causally associated with an increased risk of lung cancer?" (69). In our view, such judgement may seem justified for many but continues to be not enough in terms of prevention (29): in fact, in order to make sound public health decisions concerning silica at the low end of the exposure scale, we need to answer the causal question posed earlier by Checkoway and Franzblau (13): "Is silicosis required for silica-associated lung cancer?". Importantly, if silicosis is required to increase the risks of lung cancer, then the public health goal should be to prevent silicosis. But if it is not required, then lung cancer risks may be increased at much lower doses of silica not known to cause silicosis, implying that current exposure standards may not be appropriate to prevent lung cancer (29).

The above cited meta-analysis (66) published before the 1997 IARC decision (38) focussed on studies of lung cancer among silicotics. A search for further epidemiological studies of lung cancer in silicotics and of studies providing quantitative information about silica exposures and lung cancer risks in non-silicotics (27) was pursued through 12/2006. The present paper has two objectives: (a) To complement the previous meta-analysis (27) of the epidemiological studies in non-silicotics published up to 2007, presenting detailed results also

for silicotics, using meta-regression and including a larger number of studies compared to prior quantitative reviews (42, 43, 55, 66, 72, 74, 78), and by providing more extensive information on the methodological approaches that were used. (b) To suggest future research directions towards a possible answer to whether silica exposure increases lung cancer risk in the absence of silicosis by presenting the coherent logical thread and argumentation and detailing the step-wise analyses conducted. The aim of this paper is thus to provide more detailed information on some pressing issues concerned and to be thought-provoking to readers, so to contribute to the Italian as well as international debate on the guidelines for workplace surveillance of silica exposed workers.

Materials and methods

In this paper, we selected for inclusion studies which were published in English and provided estimates of relative risk (RR) of lung cancer, and the corresponding confidence interval (CI) or sufficient data to calculate the latter, for silicotics and/or non-silicotics.

"*Heterogeneity is common in meta-analyses of epidemiologic data and probably should be viewed as the expectation, rather than the exception*" (8). Therefore, to explore significant discrepancies between studies, and to ultimately decide which – if any – study results could be aggregated in meaningful summary estimates, we analyzed selected data via the following sequence:

Analysis step 1: Fixed, χ^2-adjusted (χ^2-a) and random effects summaries

We calculated fixed-effects summaries (FES) and corresponding CI for various combinations of studies by using the method of weighting by precision (36). The homogeneity of the data contributing to the summary RR estimates was examined by calculating appropriate χ^2 statistics. If heterogeneity was present we corrected the CI around the fixed-effects summaries (FES) to account for between-study variance, using a simple method based on the homogeneity χ^2 statistic, initially recorded by Armitage in 1985 (3) and applied by Shore et al. in 1993 (65). In addition, we computed random-effects summaries (RES) and their CI (23).

Analysis step 2: Exploring the source(s) of heterogeneity

To explore the source(s) of heterogeneity between results from individual studies we performed a series of subgroup analyses based on (a) study design, (b) smoking adjustment (yes or no), (c) record source (compensation, registry, medical examination) (d) geographical location of study and (e) periods of investigation. Moreover, guided by an influential analysis, we re-examined the studies with regard to possible biases with a view to which study might be excluded from or corrected for additional analyses (61). We followed the recommendation that the goal of an influential analysis, understood as a procedure to identify and evaluate outliers, is to warn the data analysts to examine more closely such extreme observations (41). Publication bias was assessed by a funnel plot of the log of RR for the individual studies by its standard error and by the tests suggested by Begg and Mazumdar (7), Egger et al. (26) and Duval and Tweedie (25).

Analysis step 3: Meta-regressions

To complement fixed-effects and random-effects, we also adopted a regression approach. Indeed, given heterogeneity, all kind of simple summaries – fixed, χ^2-adjusted and random – do not account for the implied effect modification, so that regression modelling of log RR is indicated (56). Residual χ^2 statistics were calculated to test for overdispersion in fixed-effect weighted least squares meta-regression models (34), after correcting the variance-covariance matrix appropriately (61). Moreover, random effects meta-regression models were fitted by restricted maximum likelihood to account for residual heterogeneity on the second data level (75). Separate models were fitted using each of the second-level variables together with an offset term as explanatory data. Additionally, after excluding collinear information, a full

model taking all variables into account simultaneously was estimated. Based on the results of these models, final meta-regression models were identified that captured the indicated effect modification and showed a sufficient statistical stability. Analyses were performed with Review Manager Version 4.2 (58) and with Stata® Version 9.2 (68) extended by its external meta command suite.

Results

In addition to the 23 investigations (1, 2, 4, 11, 15, 17, 18, 30, 33, 39, 44, 46, 47, 51, 52, 54, 57, 63, 64, 70, 77, 83, 84) found eligible for meta-analysis in 1995 (66), we identified 17 studies published thereafter with further information about lung cancer risks in silicotics (9, 12, 14, 16, 20, 22, 24, 32, 35, 37, 45, 48, 53, 67, 79, 80, 82). We did not include three of them in our meta-analyses: the 1999 case-control study by Ulm et al. (81) was not included because the controls had been occupationally exposed to silica dust, and, in the analysis of data, relative risk estimates were adjusted by year of first exposure and duration of exposure, implying overadjustment for variables correlated with the exposure measures in question (6). In 2006, Chen et al. (16) followed-up a subpopulation of their 1992 cohort study included in our analyses of lung cancer risks in silicotics, namely about 6.500 tin miners with significant arsenic exposures. Since arsenic exposures must be expected to have contributed significantly to lung cancer in these workers, we did not include this 2006 study in our meta-analyses. The recent study by Marinaccio et al. (45) reported mortality results from a large cohort of 14.000 men compensated for silicosis in the Tuscany region in Italy. In comparison with the 13 other compensation studies considered further in this paper, we noted relevant differences, including a very low estimate of mortality for lung cancer (SMR=1.10; 95%CI=1.03-1.18), and a significant decrease in overall mortality, and in mortality from a number of malignant and non malignant diseases (28).

In tables 1 and 2 we present information regarding study type, location, record source for the study individuals, industry, smoking adjustment, number of lung cancers, effect measures and their CIs together with the study weights for silicotics and for non-silicotics, respectively. We also indicate where corrections were made by us and where we calculated missing CIs from data provided in the publication. In contrast with the prior meta-analysis by Smith et al. 1995 (66), the studies by Zambon et al. 1986 (84) and Carta et al. 1991 (11) were replaced by the respective updates (10, 85). All 38 studies or subsets of these were used in a series of analyses. Results grouped by cohort or case-control study design, and smoking adjustment were compared with similar analyses previously published on 11 studies of non-silicotics (table 3).

As shown in table 3, summary relative risks of all 38 studies together, as well as combinations of investigations using the same study design, are compatible with a doubling of lung cancer risk in silicotics. In those instances with statistical evidence of heterogeneity between studies, the fixed-effects summaries (FES) did not differ substantially from the random-effects summaries (RES) both with regard to the point estimates and the CIs. The χ^2-adjusted 95% CIs and the more conservative CIs derived for the random-effects summaries were almost identical. The summary risk estimates for the 9 smoking-adjusted studies were similar to those derived from 29 studies which did not. However, despite a strong evidence for heterogeneity between studies which did not adjust for smoking, the respective FES and RES and their CIs were compatible.

Among non-silicotic subjects, there was a marginally increased RR estimate for all studies combined (FES: RR=1.2; 95%CI=1.1-1.3, χ^2-a 95%CI=1.1-1.4; RES: RR=1.2; 95%CI=1.0-1.3). Importantly, when the three studies which did adjust for smoking were combined, this set of rather homogeneous investigations showed null results. Eight studies without such adjustment (4, 14, 31, 47, 48, 52, 57, 64) suggested marginally elevated lung cancer risks, but this set of studies had to be considered heterogeneous and the 95% CI around the RES included the null value. As we previously showed in non-silicotics (27), publication bias was not a significant source of heterogeneity in results of lung cancer risk among silicotics: asymmetry

Table 1 - Summary of 38 studies of silicosis and lung cancer (1979-2006)

Author (Ref)	Year	Country	Record Source	Industry	Smoking-adjusted	Lung cancer deaths	Effect measure	95% CI	Absolute weight
Cohort studies							SMR		
Armstrong (4)	1979	Australia	Medical examination	Mining	–	21	1.1	0.6 - 2.0	10.6
Neuberger(51)	1986	Austria	Compensation	Miscellaneous	–	42	1.4	1.0 - 1.9	37.3
Westerholm (83)	1986	Sweden	Pneumoconiosis registry	Miscellaneous	–	17	4.4	2.0 - 8.3	7.6
Finkelstein (30)	1987	Canada	Compensation	Mining, surface	–	78	2.4	1.8 - 3.2	46.4
Zambon (85)	1987	Italy	Compensation	Miscellaneous	+	58	1.9	1.4 - 2.4	52.9
Puntoni (57)	1988	Italy	Compensation	Refractory brick	–	6	1.7	0.6 - 3.6	4.8
Infante-Rivard (39)	1989	Canada	Compensation	Miscellaneous	–	83	3.5	2.8 - 4.3*	83.5
Mehnert (47)	1990	Germany	Compensation	Quarry	–	9	1.8	0.8 - 3.5	7.1
Ng (52)	1990	China	Compensation	Miscellaneous	–	28	2.0	1.4 - 2.9	29.0
Tornling (77)	1990	Sweden	Pneumoconiosis registry	Miscellaneous	–	9	1.9	0.9 - 3.6	8.0
Amandus & Costello (1)	1991	USA	Medical examination	Mining	+	?	2.0	1.2 - 3.2	16.0
Amandus (2)	1991	USA	Medical examination	Miscellaneous	+	?	3.9	2.4 - 6.4	16.0
Chen (15)	1992	China	Silicosis registry	Miscellaneous	–	?	1.2	0.9 - 1.6	46.4
Dong (24)	1995	China	Medical examination	Refractory brick	+	35	2.1	1.4 - 2.9*	29.0
Goldsmith (35)	1995	USA	Compensation	Miscellaneous	–	39	1.9	1.4 - 2.6	40.1
Meijers (48)	1996	Netherlands	Medical examination	Ceramic	–	10	2.2	1.1 - 4.0*	9.2
Starzynski (67)	1996	Poland	Registry	Miscellaneous	–	107	1.3	0.8 - 2.0**	18.3
Wang (82)	1996	China	Medical examination	Metallurgical	–	104	2.4	2.0 - 2.9	111.3
DeKlerk (22)	1998	Australia	Medical examination	Goldmining	–	138	1.6	1.1 - 2.3	28.2
Checkoway (14)	1999	US	Surveillance program	Diatom. Earth	–	4	1.6	0.4 - 4.0	2.9
Chan (12)	2000	China	Silicosis registry	Miscellaneous	–	33	1.9	1.4 - 2.7	35.6
Carta (10)	2001	Italy	Medical examination	Metal mining	–	34	1.4	1.0 - 1.9	37.3
Berry (9)	2004	Australia	Compensation	Miscellaneous	–	94	2.2	1.7 - 2.6	85.1
Ulm (80)	2004	Germany	Compensation	Quarry	–	16	2.4	1.4 - 3.9	14.6

(continued)

Table 1 - Summary of 38 studies of silicosis and lung cancer (1979-2006)

Author (Ref)	Year	Country	Record Source	Industry	Smoking-adjusted	Lung cancer deaths	Effect measure	95% CI	Absolute weight
Case-control studies							OR		
Steenland (70)	1986	USA	Silicosis on death certificate	Granite	–	26	3.2	1.6 - 6.3†	8.2
Mastrangelo (46)	1988	Italy	Compensation	Miscellaneous	+	50	1.8	1.1 - 2.8	17.6
Cocco (18)	1990	Italy	Medical examination	Miscellaneous	+	15	2.4	1.0 - 6.2	4.6
Lagorio (44)	1990	Italy	Compensation	Miscellaneous	+	15	3.9	1.8 - 8.3	6.6
Hnizdo (37)	1997	Africa	Medical examination	Goldmining	–	78	2.5	1.2 - 5.2	7.1
Finkelstein (32)	1998	Canada	Surveillance program	Miscellaneous	–	41	3.3	1.3 - 8.2	4.5
Cocco (20)	2001	China	Medical examination	Miscellaneous	+	80	1.5	1.0 - 2.1	27.9
Tsuda (79)	2002	Japan	Death certificate	Refractory brick	+	?	2.7	1.4 - 5.4	8.4
Standardized incidence ratios							SIR		
Chia (17)	1991	Singapore	Silicosis registry	Miscellaneous	–	9	2.0	0.9 - 3.8	7.4
Sherson (64)	1991	Denmark	Medical examination	Foundry	–	11	1.7	0.9 - 3.1	10.0
Partanen (54)	1994	Finland	Silicosis registry	Miscellaneous	–	101	2.9	2.4 - 3.5	107.9
Oksa (53)	1997	Finland	Silicosis registry	Miscellaneous	–	15	2.7	1.5 - 4.5	12.7
Mortality odds ratio							MOR		
Schüler (63)	1986	Switzerland	National Accident Ins. Fund.	Miscellaneous	–	180	2.2	1.8 - 2.7†	93.5
Forastiere (33)	1989	Italy	Compensation	Ceramic	–	64	1.5	1.1 - 1.9	51.4

* Confidence intervals calculated based on Byar's approximation

** Pooled estimate calculated for Starzynski study

† Test-based confidence intervals based on Miettinen

Table 2 - Summary of 11 studies of non-silicotics and lung cancer (1979-2006)

Author (Ref)	Year	Country	Record Source	Industry	Smoking-adjusted	Lung cancer	Effect measure	95% CI	Absolute weight
Cohort studies							SMR		
Armstrong (4)	1979	Australia	Medical examination	Mining	–	38 O/22.2 E	1.7	1.2 - 2.3*	36.3
Puntoni(57)	1988	Italy	Compensation	Refractory brick	–	5 O/2.4 E	2.1	0.7 - 4.8	4.1
Mehnert (47)	1990	Germany	Compensation	Quarry	–	18 O/19.8 E	0.9	0.5 - 1.4	14.5
Amandus & Costello (1)	1991	USA	Medical examination	Mining	–	118 O/99.9 E	1.2	1.0 - 1.4	135.7
Dong (24)	1995	China	Medical examination	Refractory brick	+	30 O/27 E	1.1	0.7 - 1.6*	22.5
Finkelstein (31)	1995	Canada	Silicosis registry	Miscellaneous	–	19 O/21.76 E	0.9	0.5 - 1.4*	14.5
Meijers (48)	1996	Netherlands	Medical examination	Ceramic	–	20 O/29.5 E	0.7	0.4 - 1.0*	18.3
Checkoway (14)	1999	USA	Surveillance program	Diatom. Earth	–	48 O/40.6 E	1.2	0.9 - 1.6	46.4
Case-control studies							OR		
Mastrangelo (46)	1988	Italy	Compensation	Miscellaneous	+	86 Cases/95 C	0.9	0.6 - 1.2	32.0
Lagorio (44)	1990	Italy	Compensation	Ceramic	+	18 Cases/79 C	1.4	0.7 - 2.8	8.0
Standardized incidence ratios							SIR		
Sherson (64)	1991	Denmark	Medical examination	Foundry	–	150 O/119.5 E	1.3	1.1 - 1.5	159.7

* Confidence intervals calculated based on Byar's approximation.
O=Observed
E=Expected
C=Controls

Table 3 - Statistics for meta-analysis of silicosis and lung cancer (38 studies) and silica exposure and lung cancer among non-silicotics (11 studies, modified from Erren et al. 2009 (27)) combined, grouped by cohort or case-control study design, and smoking adjustment

	Number of studies	FES[1]	95% CI for RR†	χ^2-adjusted CI	Homogeneity χ^2-squared	Homogeneity degrees of freedom	Homogeneity p-value	RES[2]
All studies combined								
Silicotics	38	2.1	2.0 - 2.3	1.9 - 2.3	102.7	37	[4.3 E-08]*	2.1 (1.9 - 2.3)
Non-silicotics	11	1.2	1.1 - 1.3	1.1 - 1.4	17.5	10	[0.07]*	1.2 (1.0 - 1.3)
Cohort studies								
Silicotics	24	2.1	1.9 - 2.2	1.8 - 2.3	74.7	23	[2.2 E-07]*	2.0 (1.7 - 2.3)
Non-silicotics	8	1.2	1.1 - 1.3	1.0 - 1.4	13.5	7	[0.06]*	1.2 (1.0 - 1.4)
Case-control studies								
Silicotics	8	2.1	1.7 - 2.6	-	9.3	7	0.23	2.3 (1.8 - 2.9)
Non-silicotics	2	1.0	0.7 - 1.3	-	1.3	1	0.26	1.0 (0.7 - 1.5)
SIR								
Silicotics	4	2.7	2.3 - 3.2	-	3.4	3	0,34	2,6 (3.1 - 3.3)
Non-silicotics	1	1.0						
Smoking-adjusted								
Silicotics	9	2.1	1.8 - 2.4	1.7 - 2.5	13.4	8	[0.10]*	2.2 (1.8 - 2.7)
Non-silicotics	3	1.0	0.8 - 1.3	-	1.4	2	0.49	1.0 (0.8 – 1.3)
Not smoking-adjusted								
Silicotics	29	2.1	2.0 - 2.3	1.9 - 2.4	89.2	28	[2.6 E-08]*	2.0 (1.8 - 2.3)
Non-silicotics	8	1.2	1.1 - 1.4	1.1 - 1.4	14.2	7	[0.05]*	1.2 (1.0 - 1.4)

† exp (β±1.96*se*)

* Square brackets indicate substantial heterogeneity (i..e, P<0.10) in the data contributing to the summary RR; in these instances the confidence intervals for the fixed-effects summaries were χ^2 -adjusted (see text for details)

[1] Fixed effect summary: point estimate

[2] Random effect summary: point estimate and 0.95-confidence interval

Please note that 2 MOR studies among silicotics are not included in this table because there were no MOR studies among non-silicotics for comparison

was not obvious in the funnel plot for studies (figure 1). For the studies in silicotics, Begg's and Mazumdar's test had a p value of 0.35 for the correlation between the point estimate and its standard error and the bias co-efficient in Egger's test was -0.42 (p=0.49). For the 11 studies in non-silicotics previously analyzed (27), Begg's and Mazumdar's procedure yielded a p value of 0.41 and Egger's bias coefficient was estimated as -0.77 (p=0.34). "*Trim and fill*" analyses (25), based on the linear estimator, also revealed no clear indications of publication bias: in silicotics; just one small formal study (RR=0.94, fixed weight=7.6) was added to balance the funnel plot, in non-silicotics the procedure identified nothing to fill.

Heterogeneity

To further explore possible sources of heterogeneity, we examined the selected publications for information about study characteristics which could explain differences among the results. We

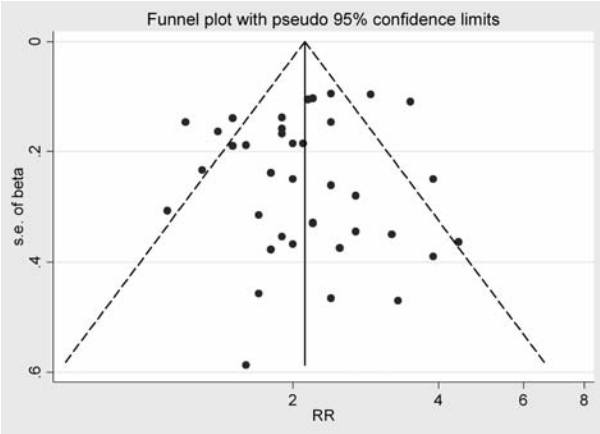

Figure 1 - Funnel plot to assess publication bias in 38 studies of silicosis and lung cancer

identified five studies as significant sources of the observed heterogeneity in the meta-analysis among silicotics (4, 15, 39, 51, 54). According to Partanen et al. (54), misclassification of silicosis and potential exposures to asbestos might have accounted for 30 per cent of the lung cancer risk observed in their study. Accordingly, we adjusted to 2.2 (95%CI=1.8-2.7) their published SIR of 2.9 (95% CI=2.4-3.5). Similarly, Infante-Rivard et al. (39) suggested that exposure to radon in mines and to polycyclic hydrocarbons in foundries – which were not assessed – could have confounded the high SMR of 3.5 (95%CI=2.8-4.3). Within the same study a SMR of 2.0 (95%CI=0.8-4.4) was observed in the granite industry which the authors suggested was presumably free from confounding. Based on the latter, our conservative correction via the comparison between mines and foundries with granite yielded an adjusted SMR of 2.3 (95%CI=1.9-2.9).

Three studies (4, 15, 51) with methodological biases could not be adjusted by us and were excluded from further analyses. Armstrong et al. (4) appeared to have commenced their retrospective follow-up of miners in Western Australia without taking silicosis as a time-dependent variable into account. This may have led to an inflation of person-years and, thus, to an underestimate of RR for lung cancer among silicotics. Neuberger et al. (51) and Chen et al. (15) seemed to have suffered from similar underestimations of lung cancer risks. The description of subjects and methods in the Austrian study leaves the possibility open that all years of observation in males aged 40 in 1950 were included to assess lung cancer risks in silicotics, rather than the sub-group with a diagnosis of silicosis. Chen et al. (15) explicitly worked with person-years at risk throughout the whole follow-up and did not consider when silicosis was actually diagnosed. In the Amandus et al. study (2), we replaced the smoking-adjusted RR in our first analyses by an SMR of 2.3 (95%CI=1.5-3.4), which was estimated in workers who had no exposure to other known carcinogens. The smoking-adjusted RR may have been overestimated because of a healthy-worker bias in the reference population, consisting of a selected group of non-silicotic workers.

Based on the remaining 35 studies, three of which with corrected RR estimates, repeated meta-analyses of lung cancer risks in silicotics yielded very similar summary estimates in the course of Analysis step 2 (FES: RR=2.1; 95%CI=1.9-2.2; RES: RR=2.1; 95%CI=1.9-2.2). Intriguingly, our exclusion of three studies and corrections of another three studies' results led to a pronounced reduction in heterogeneity. All 35 studies combined and the remaining 21 cohort studies showed almost identical RR estimates and CIs, but the overall χ^2-test was far from being significant (χ^2 = 39.3 on 34 degrees of freedom: p= 0.246). The summary risk estimates for 8 smoking-adjusted studies remained similar to those derived from 27 unadjusted studies. However, there was now no strong evidence for heterogeneity between the studies contributing to either one of the latter RRs, implying that these combinations did provide estimates of a generally applicable excess risk for individuals with silicosis from all these studies.

Confounding by smoking as a possible source of heterogeneity in studies of lung cancer among non-silicotics was previously discussed (27), as a 20% excess in lung cancer risk was calculated limited to eight studies that did not adjust for smoking, while no excess was calculated in three smoking-adjusted studies. However, smoking itself was not considered to be an important confounder in four of those eight unadjusted studies, as other smoking-related causes of death were not increased.

Meta-Regression

To further explore the reasons for heterogeneity between studies, we conducted separate meta-regressions for studies of lung cancer risks in silicotics and in non-silicotics. We studied potential effect modifications among silicotics using the modified data base as described above. Potential covariates in meta-regression models were previously listed (27).

In silicotics, without adding explanatory variables to the constant offset, the second-level variance was estimated as τ^2=0.0066 while reproducing the findings of the DerSimonian-Laird estimate (simple meta-analysis). The final model took two additional variables into account: an indicator for having adjusted for the calendar year of first exposure (meta-coefficient=0.75, p=0.041), and an indicator for ceramics industry (meta-coefficient= -0.27, p=0.043). The second-level variance reduced to τ^2=0.00056 and the residual χ^2 decreased to 30.6 (df=32, p=0.54). An exploratory investigation, generalizing the test for publication bias, detected a significant quadratic dependence on the fixed study weights even when adjusting for both explanatory variables of the final model. The residual χ^2 decreased further to 23.1 (df=30, p=0.81).

In non-silicotics, a trivial model comprising only an offset term estimated the second-level variance as τ^2=0.0187. In the final model, extended by the binary variables "SIR study" and "mining industry indicator", no overdispersion remained (τ^2=0), and the residual χ^2 decreased to 11.3 (df=8, p=0.18), no longer indicating a pronounced heterogeneity. The meta-coefficients (p-values) in this model were found to be 0.241 (0.031) for the SIR study indicator and 0.234 (0.033) for the mining industry indicator, indicating a significant and relevant effect modification by both variables. Exploratory analyses taking the study weights into account additionally did not reveal any further relevant structures.

Discussion

Our meta-analyses of epidemiological studies published over 27 years show that important questions regarding the causal relationships between silica, silicosis and the development of lung cancer remain unanswered. In individuals with silicosis, a twofold increase in lung cancer risk was observed a decade ago (66) and it is observed today. And yet, the exact nature of this association is unclear. At a first glance, the doubling of lung cancer risks in individuals with silicosis could be interpreted as pointing to the conclusion that there is a chain of causation between silica, silicosis and lung cancer: silicotic subjects have a higher risk of developing lung cancer and the risk of developing silicosis increases with increasing exposure to silica. Thus, silica dust is a human lung carcinogen. However, such reasoning continues to be a non-sequitur. Let random variable A be significantly and positively correlated with random variable B, and assume that B is significantly and positively correlated with random variable C also; this does not necessarily imply that A and C are positively correlated. Indeed, within such scenario, it is still possible that for A and C to be significantly and inversely correlated (40). Therefore, we agree with the suggestion by Checkoway and Franzblau (13) that silicosis and lung cancer should be treated as distinct entities whose cause-effect relations would not necessarily be linked.

An answer to the key question whether individuals who are exposed to silica, but have not developed silicosis, are at higher risk for lung cancer, remains elusive and the "non-silicosis-lung cancer conundrum" thus far unanswered. There were only three studies with information on lung cancer risks in non-silicotics which did adjust for the important risk factor "smoking". When combined, this set of investigations showed null results, evincing the absence of increased lung cancer risks in non-silicotics. Combining the eight studies without adjustment for smoking and combining all eleven studies suggested marginally elevated lung cancer risks. And yet, while our meta-analyses of 11 studies published between 1979 and 1999 showed a summary relative risk for all studies of 1.2, a test of homogeneity suggested that these studies have to be considered heterogeneous (27). This implied that differences between the eleven investigations could not be attributed simply to sampling vari-

ability or smoking, so that their combination did not provide estimates of a generally applicable excess risk of lung cancer in individuals in whom a diagnosis of silicosis was excluded. The χ^2-corrected 95% CI around the FES ranged from 1.1 to 1.3 and the 95% CI derived for the RES was 1.0 to 1.3. Considered individually, three cohort studies (1, 14, 64) and one case-control study included about 50 or more lung cancers. The summary relative risk for this subset evinced a statistically significant, albeit moderate, increase in lung cancer risk among non-silicotic individuals (FES: RR=1.2; 95%CI=1.1-1.3; RES: RR=1.2; 95%CI=1.1-1.4;). Considered collectively, while all 11 studies with lung cancer risk data in non-silicotics might be interpreted as possibly implying the existence of an effect, the CIs around the summary estimates included unity and the heterogeneity in the results warrants additional caution.

A systematic analysis of a possible dose-response relationship between silica exposures and lung cancer risks would have been desirable. Two studies with quantitative data (14, 20) and a pooled analysis of ten occupational cohorts, ignoring silicosis development (73), suggested a dose-response relationship, while no dose-response trend was evinced by the qualitative information in the Mehnert study (47). Overall, a dose-response relationship between silica exposure and lung cancer risks in non-silicotics can not be determined in view of very limited information.

Intriguingly, correcting and omitting a handful of studies which were characterized by or prone to relevant biases resulted in significant less heterogeneity of individual results contributing to the weighted averages. This is remarkable because the assessment and definition of silicosis and non-silicosis differed considerably within and between the studies included in our meta-analyses. However, while the χ^2-statistics showed no relevant heterogeneity after modifying the data set for silicotics, the meta-regression approach identified significant effect modification. Caution is warranted when interpreting these results, because both variables were positive for only one study each, which clearly restricts generalizability of the findings. The detected non-linear influence of the study weights points at residual structures even within the modified data about silicotics, that we were unable to explain by any of the recorded second-level variables. Because the data set of non-silicotics consists of only 11 studies, all regression findings are clearly limited. However, after taking a study type indicator and an indicator for mining industry into account, heterogeneity as reported in the simple meta-analysis disappeared.

In summary, even methodologically rigorous meta-analyses of today's rich epidemiological study base, including non-silicotics, do not allow to answer critical questions regarding the nature of the causal pathway(s) which may lead to lung cancer in silica-exposed individuals. On the basis of our sophisticated meta-analyses, we feel that statistical methodology has outstripped the capacity of the standard data collected in most studies to-date to provide the much-needed clarification of the very role of the established silicosis-lung cancer association. On logical grounds, silicosis could be part of the pathogenetic chain which leads to silica-associated cancer. Alternatively, or additionally, it could be a complex biomarker. Comprehensively, it may be a marker of relevant exposures to crystalline silica and a marker of susceptibility: to lung carcinogens, including silica, and/or to lung alterations and disease, including cancer. In this vein, numerous questions regarding documented links between interstitial diseases and lung cancer have already been posed (5, 21, 62).

Future epidemiological studies should focus on the conditions under which silica behaves as a lung carcinogen and on practical aspects of control. Studies which target the design and maintenance of safe exposure standards for crystalline silica are needed. Investigations of this kind must characterize dose-response relationships between silica and lung cancer in different industrial and geological settings and in different parts of the world. This will be particularly important for – but not limited to – developing countries where silicosis continues to be a major threat for workers. That it can be relevant for wealthy western countries, too, is evinced by suggestions that standards for exposure to crystalline silica designed to prevent silicosis may be set inappropriately high in the U.S. (71) and possibly

in Australia (22). Because adverse health effects following workplace exposure to crystalline silica are well established, efforts to lower workplace dust exposure to the lowest reasonably achievable level are warranted world wide even though there are open questions regarding the circumstances of its human carcinogenicity. Ultimately, exposure standards may have to differ as the physico-chemical characteristics of silica-containing dust can also differ within and across industries and this could be crucial for the interaction with biological tissues. It has already been proposed that variable results in meta-analyses – possibly including the ones reported here – may not only reflect interstudy variability as a random effect, but could stem from differences in the biological activity of silica particles inhaled in diverse exposure circumstances (19). Ideally, investigations should study populations with the entire exposure-response range between silica dust exposure, silicosis development and lung cancer occurrence; analyse all data in terms of processes; and should focus not mainly on elevated rates or risks, but on reduced failure times (49). Clear definitions of quantitative dust exposure and degree of silicosis must be provided. Moreover, it will be important to understand that silicosis acts as an intermediate confounder and produces healthy worker survivor selection biases, because past dust exposure is causing silicosis, but silicosis may reduce future dust exposure and may be linked to lung cancer risk. To take this appropriately into account, more complex analytical procedures are necessary than usual survival modelling with Poisson or Cox models (59). G-estimation is a candidate procedure that can be used to disentangle such complex relationships (60, 76), although considerable amounts of data are necessary to ensure sufficiently precise estimates. In addition, the statistical estimation of potential exposure standards should be incorporated into the modelling procedure, e.g., using a likelihood profile method (50).

It is also desirable that future studies control for smoking and other lung carcinogens. Ultimately, only such studies may yield an answer to the question whether silica increases lung cancer risks in non-silicotics, too. Realistically, any such study may have to investigate large populations, because the overall relative magnitude of silica-associated risks in workers who do not develop silicosis could be small and/or vary significantly by workplace.

CONFLICT OF INTEREST STATEMENT
The authors TCE and PM gave scientific advice to Eurosil (http://www.ima-eu.org/eurosil.html). PM received grants for scientific monitoring of a literature review project on silica dust exposure and health effects.

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