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A NESTED CASE-CONTROL STUDY OF LUNG CANCER AMONG SILICA EXPOSED WORKERS IN CHINA

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Introduction and Objective

- The role of silica in the causation of lung cancer is an ongoing debate.
- In 1997, a working group of International Agency for Research on Cancer (IARC) classified silica as a human carcinogen. However the working group stated also, that carcinogenicity in humans was not detected in all industrial circumstances.
- The epidemiological studies reviewed by this working group pointed out important variations in silica associated lung cancer risk by
  - geographic area
  - type of studies
  - type of industry
  - levels of exposure
  - with inconsistent dose-response trends.

To explore whether the observed association between silica exposure and lung cancer can be confounded by exposure to other occupational carcinogens, we conducted a nested case-control-study among a cohort of male workers in 29 Chinese mines and potteries.

Methods

Study population:

- Baseline cohort: 65,285 mines and pottery workers (Follow-up: 1972 – 1994)
- Cases: all 511 lung cancer cases
- Controls: 1879 controls ("density sampling" matched by age, mines/factories)

Exposure assessment:

- Development of a JEM for total dust bases on 2 million historical measurement data
- Development of exchange rates between total dust and respirable silica for various mines and facilities in an industrial hygiene survey.
- Calculation of silica exposure: total dust * exchange rate
- Assessment of exposure to radon, arsenic, carcinogenic PAH and smoking

Statistical analysis:

- Conditional logistic regression analysis
- Adjusted for exposure to arsenic, PAH, radon, and smoking.
- All analysis were lagged for 15 years.

Table1: Description of study population

	Tungsten	Potteries	Tin	Iron/copper
Cases (n)	172	120	144	75
Controls (n)	568	459	575	277
Ever smoker (%)	81.6	82.9	84.0	83.5
Respirable silica (mg/m³-year)				
Median (range)	4.8 (0 – 72.4)	2.1 (0 – 40.6)	2.6 (0 – 35.4)	0.2 (0 – 6.8)
Arsenic (µg/m³-year)				
Median (range)	6 (0 – 80.2)	2 (0 – 18)	92 (0 – 3542)	0.1 (0 – 3.1)
Carcinogenic PAH (µg/m³-year)				
Median (range)	24 (0 – 144)	199 (0 – 608)	0	27 (0 – 2000)
Radon (WLM)				
Median (range)	7.3 (0 – 94.7)	0	1.4 (0 – 10.2)	0.2 (0 – 311.4)

Table 2: Effect estimates (OR) without consideration of occupational confounders

Respirable silica (mg/m³-year)	Tungsten (OR*, 95% CI)	Potteries (OR*, 95% CI)	Tin (OR*, 95% CI)	Iron/copper (OR*, 95% CI)
Non-exposed	Reference	Reference	Reference	Reference
1. quintile (0.1–1.1)	2.0 (0.97 – 4.19)	0.8 (0.29 – 2.19)	1.6 (0.75 – 3.52)	1.0 (0.51 – 1.77)
2. quintile (1.1– 2.6)	1.4 (0.64 – 2.81)	1.3 (0.63 – 2.64)	1.9 (0.96 – 3.78)	1.3 (0.56 – 3.07)
3. quintile (2.6 – 5.4)	0.6 (0.32 – 1.30)	1.7 (0.82 – 3.58)	1.8 (0.94 – 3.29)	1.8 (0.57 – 5.48)
4. quintile (5.4–10.1)	0.8 (0.42 – 1.51)	1.5 (0.71 – 3.21)	2.1 (1.14 – 3.80)	– –
5. quintile (10.1–72.4)	1.0 (0.55 – 1.66)	3.5 (1.45 – 8.66)	3.3 (1.66 – 6.61)	– –
But typical confounder	no	PAH	Arsenic	PAH, Radon

*adjusted for smoking only

Table 3: Effect estimates (OR) after adjusting for occupational confounders

Respirable silica (mg/m³-year)	Tungsten (OR*, 95% CI)	Potteries (OR*, 95% CI)	Tin (OR*, 95% CI)	Iron/copper (OR*, 95% CI)
Non-exposed	Reference	Reference	Reference	Reference
1. quintile (0.1–1.1)	2.0 (0.97 – 4.19)	0.7 (0.25 – 1.98)	–	0.7 (0.24 – 2.08)
2. quintile (1.1– 2.6)	1.4 (0.64 – 2.81)	0.7 (0.29 – 1.81)	–	1.0 (0.31 – 3.28)
3. quintile (2.6 – 5.4)	0.6 (0.32 – 1.30)	0.7 (0.25 – 2.19)	–	1.4 (0.33 – 5.50)
4. quintile (5.4–10.1)	0.8 (0.42 – 1.51)	0.5 (0.15 – 1.84)	–	– –
5. quintile (10.1–72.4)	1.0 (0.55 – 1.66)	0.9 (0.19 – 4.32)	–	– –
Additionally adjusted for	no	PAH	Arsenic	PAH, Radon

*adjusted for smoking

Table 4: Effect estimates in a pooled analysis of all facilities

	OR*	95% CI
Arsenic (mg/m³-year)	1.69	1.07 – 2.68
Carcinogenic-PAH (per 100 µg/m³-year)	1.06	0.97 – 1.17
Radon (yes vs. no)	0.81	0.48 – 1.39
Respirable silica (mg/m³-year)		
per mg/m³-year	1.01	0.98 – 1.02
Non-exposed	Reference	–
1. quintile (0.1 –1.1)	1.40	0.81 – 2.43
2. quintile (1.1 – 2.6)	1.54	0.90 – 2.63
3. quintile (2.6 – 5.4)	1.30	0.75 – 2.24
4. quintile (5.4 – 10.1)	1.18	0.68 – 2.06
5. quintile (10.1 – 72.4)	1.50	0.83 – 2.72
	Trend-Test: p>0.64	

*Adjusted for smoking, arsenic, PAH and radon

Results

- Description of the study population and exposure to relevant occupational and non-occupational risk factors are given in table 1.
- In a crude analysis adjusted for smoking only, a significant trend of increasing risk of lung cancer with exposure to silica was found for tin, iron/copper miners, and pottery workers, but not among tungsten miners (table 2).
- However, the observed dose-response relationship disappeared after the relevant occupational confounders were adjusted (table 3).
- Among tin miners, adjustment of relevant occupational confounder can not produce reliable results in the analysis due to the strong correlation (co-linearity) between the cumulative exposure to respirable silica and arsenic (table 3).
- In a pooled analysis of all facilities (table 4), no effect of silica on the mortality of lung cancer can be observed. Instead, there is a statistical significant association between lung cancer mortality and cumulative exposure to inorganic arsenic and carcinogenic PAHs.

Conclusion

In the present case-control analysis of the largest industrial silica cohort world wide, relevant occupational and non-occupational confounders are for the first time systematically assessed and quantitatively considered on the evaluation of the association between crystalline silica exposure and lung cancer. The analysis of this study does not provide any evidence that exposure to silica causes lung cancer in the absence of confounding factors.

To confirm our study results, further analysis is needed in which not only the exposure doses, but also the exposure patterns (various combination of exposure level and duration) are also considered.

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