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Is There an Increased Risk of Lung Cancer among the Chinese Silica Cohort? - The Influence of Occupational Confounders

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Abstract

To evaluate a possible influence of confounding in risk estimation for lung cancer in relation to silica dust exposure, we re-analyze a recently published exposure-response relationship using a sub-cohort of Chinese tungsten miners which has no relevant occupational confounders.

The cohort of tungsten miners consisted of 19,007 workers in six tungsten mines with a follow-up period from January 1, 1960 to December 31, 2003. Cumulative silica dust exposure was estimated by linking the work history to the job-exposure matrix. The time-dependent Cox proportional hazards model was used for exposure-response analysis.

Analysis of the cohort of tungsten miners does not deliver a clear exposure-response relationship between silica dust exposure and lung cancer deaths. The Chinese silica cohort fails as yet to provide clear evidence of a dose-response relationship between silica dust exposure and lung cancer risk in the absence of occupational confounding factors.

Keywords

Silica dust, Lung cancer, Occupational confounders, Risk assessment, Epidemiology

Introduction

The Chinese silica cohort is one of the largest silica cohorts worldwide with a sample size of some 74,000 employees from 4 industrial facilities (tungsten mines, tin mines, iron/copper mines and pottery factories) [1,2]. Since the establishment of this cohort in the late 1980s, a series of analysis have been carried out to address the association between silica dust exposure and lung cancer deaths (Table 1). Although early analyses [3-8], indicate the importance of occupational confounders (arsenic, polycyclic aromatic hydrocarbon (PAH) and radon) in risk estimation for lung cancer due to silica dust exposure, no adjustment of these confounders can be carried out for the entire cohort due to some technical difficulties.

In 2007, Chen, et al. published a nested case-control study, in which the occupational confounders were for the first time systematically controlled [9]. In this analysis, the authors indicate that, the tungsten mines are the only facility which has no relevant occupational confounders. There is no exposure-response relationship between silica dust exposure and lung cancer deaths among the tungsten miners. In other facilities, same findings were reported only if the occupational confounders were controlled in the analysis.

Six years later, Liu, et al. reported an increased risk of lung cancer among the Chinese silica cohort based on the extended follow-up [2]. In this analysis, the authors excluded facilities with severe occupational confounders (tin mines and copper mines), but still left iron mines and pottery factories in the analysis data set. Since early reports indicate the influence of occupational confounders not only in tin and copper mines, but also in iron mines and pottery factories [4,6,9], this raises the question whether the results of Liu, et al. [2] were biased by residual confounders that were not adjusted for in the analysis.

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Table 1: Previous analysis on the association between silica dust exposure and lung cancer deaths among the Chinese silica cohort.

Analyses methods	Follow-up periods		
	1960-1989	1960-1994	1960-2003
SMR	Chen J, et al. [3]		
Internal comparison[1]		Steenland K, et al. [5]	Chen W, et al. [1]
Internal comparison[2]	Mc Laughlin JK [4]	Cocco P, et al. [6] Chen W, et al. [7] Chen W, et al. [8] Chen W, et al. [9]	Liu, et al. [2]

[1]Without consideration of occupational confounders; [2]With consideration of occupational confounders.

In order to answer this question, we reanalyzed the data of Liu, using only the sub-cohort of workers in tungsten mines which has no relevant occupational confounders.

Methods

Design and study population

Details of the study design and methods, including case identification, exposure monitoring methods and follow-up information, have been described previously [1,2]. Briefly, a cohort of 34,018 employees (active employment between January 1, 1960 and December 31, 1974) in four pottery factories, six tungsten mines and one iron mine was followed for all-cause mortality from January 1, 1960 to December 31, 2003 with an average of 34.5 years of follow-up. In this paper, we transferred the previous analysis strategy only to the cohort in the six tungsten mines, with the following cohort definitions:

1. All cohort members in the six tungsten mines.
2. Cohort members in the six tungsten mines who were hired after January 1, 1950 and were over 15 and under 45 years of age at the beginning of employment.

Historical exposure monitoring data in this study is only available since the early 1950s. For workers employed before 1950, exposure assessment based mainly on the assumption that the working conditions before 1950 were consistent over time, and thus may be imprecise. The exclusion of workers hired before 1950 minimizes the exposure misclassification, particularly systematic underestimation of silica exposure for workers hired before 1950 [5]. According to a previous analysis [10], exposure information for workers who began to work before the age of 15 is often poor in the early ages, and the external exposure among workers who began employment aged over 45 is likely to be unknown. Therefore, the exclusion of workers who began employment aged before 15 and over 45 may increase the quality of data.

Ascertainment of lung cancer deaths

All participants were traced for their vital status during the follow-up period. Information on underlying causes of death was obtained by medical records, employment registers, accident records or death certificates. Where participants died of lung cancer, the diagnostic information was reconfirmed by hospital records [1,2].

Silica exposure assessment

More than 4 million historical industrial hygiene data dating back to the 1950s are available for total dust particle size and percentage of free silica in the related mines and pottery factories studied. These data were used to create a job exposure matrix (JEM) for average total dust for each calendar year. Approximately 1,100 facility/job title combinations over 50 calendar periods, starting in 1950, are available.

For estimation of the respirable silica dust exposures, monitoring programs were designed to compare the Chinese total dust with the US respirable crystalline silica dust concentrations based on side-by-side measurements during 1988-1989 and 2003-2009. Conversion factors between Chinese total dust and US respirable crystalline silica dust exposure were developed [2,11]. Respirable crystalline silica dust exposures were calculated by multiplying the total dust exposures with the corresponding conversion factors.

To estimate cumulative silica dust exposures, complete individual work histories for each study subject were assessed using employment records in the personnel files of the mining companies and factories involved.

Smoking information

Detailed lifetime smoking data (pack-years) were collected in 1986, 1995 and 2004. Overall, smoking data from next-of-kin or colleagues accounted for 11% of the study subjects. Smoking data correlate strongly (93.6%) between self-reported data and those obtained from next-of-kin of living subjects [1].

Statistical analysis

Exposure-response relationships between cumulative silica dust exposure and lung cancer deaths were estimated by Cox proportional hazard model. Age was used as the time variable to define the risk set for each lung cancer death.

Table 2: Description of the study population

	All tungsten mines	Miners hired[1] after 1950
N	19,007	17,847
Total person-years (PY)	635,962	602,695
Lung cancer cases (N)	240	209
Follow-up duration (year): Median (range)	34.6 (0.8-43.9)	34.6 (0.8-43.9)
Age at starting work: Median (range)	22.6 (9.8-62.6)	22.7 (15-44.9)
Age at beginning of follow-up: Median (range)	25.6 (10.3-62.6)	25.3 (15 -54.3)
Cumulative silica dust exposure (mg/m^3-year)[2]:		
Total (Median, range)	**2.23 (0.01-34.1)**	**2.05 (0.01-31.4)**
Lung cancer cases (Median, range)	**3.28 (0.1-27.9)**	**2.90 (0.1-24.9)**
Non-cases (Median, range)	**2.22 (0.01-34.1)**	**2.03 (0.01-31.4)**
Cumulative silicosis cases (N, %)	4228 (28.9%)	3686 (26.0%)

[1]Miners starting employment after January 1, 1950 and aged over 15 and under 45 years.

[2]Values given for dust exposed employees

The association was quantified by hazard ratios (HR) and their 95% confidence intervals (95% CI) with adjustment for the potential confounders including facility, sex, year of birth, and smoking amount (five categories in the model: nonsmoker, quartile categorization of smoking amount in pack-years).

Cumulative silica dust exposure was treated both as categorical (quartile) and continuous variables (unlogged or logged, no lag or lag for 15, 25 years) in separate models. Both cumulative silica exposure and smoking amount were considered as a function of time in the analysis. All analyses were conducted using SAS 9.3.

Results

Table 2 gives a description of the study population. In total, 19,007 employees were involved in this analysis. The median follow-up duration is about 35 years, with a crude lung cancer mortality rate of about 38/100,000 person-years and a cumulative silicosis incidence of 28.9%. Cumulative silica dust exposure varied between 0.01 and 34.1, with a median value 2.23 mg/m^3-year. In the comparison of all tungsten miners with miners hired after 1950 (and aged over 15 and under 45 years at the beginning of employment), there is nearly no difference regarding follow-up duration, age at starting work, age at the beginning of follow-up, cumulative silica dust exposure, crude lung cancer mortality rate and cumulative silicosis incidence rate.

Table 3 presents the estimated exposure-response relationship between silica dust exposure and lung cancer deaths by using different exposure models and cohort definitions. No clear exposure-response trend between silica dust exposure and lung cancer deaths can be observed in either continuous or categorical analysis. These findings do not change when a 15 or 25-year lag is considered in the analysis.

The use of logged cumulative exposure models tends to produce higher effect estimates than use of the conventional Cox-model. However, the effect estimates are still around 1.

Discussion

The role of silica in the causation of lung cancer is an ongoing debate. Although the exposure-response relationships and excess risk estimations published up to now have resulted in advanced risk communication for regulatory discussions, methodological limitations and uncertainties in published studies have still given rise to much debate within the scientific community.

The purpose of the present analysis is to evaluate the methodological uncertainties associated with risk estimation for lung cancer due to silica dust exposure among the Chinese silica cohort. In a former comprehensive analysis of Chen, et al. [9], no exposure-response relationship between silica dust exposure and lung cancer deaths can be demonstrated. Although occupational confounders were systematically controlled in this analysis, some methodological limitations have been intensively discussed within the working group. Besides the relative short follow-up time period, imprecise assessment of occupational co-exposures, one important limitation is the strong collinearity between silica dust exposure und the occupational confounders (arsenic, PAH, and radon daughter). This makes the interpretation of the study findings difficult. Therefore the working group decided to extend the follow-up for another 10 years. During this time, the JEM for silica dust exposure were improved and the smoking information was assessed for all cohort members.

In order to acquire a valid analysis data basis and to avoid the problem of collinearity in the analysis, Liu, et al. exclude in his newly published exposure-response analyses about 54% of cohort participants with either low data quality or strong occupational confounders. An exposure-response relationship between silica dust exposure and lung cancer

Table 3: Hazard ratio[1] (HR) for lung cancer mortality associated with cumulative silica dust exposure.

Cumulative silica exposure (mg/m^3-year)	All tungsten miners (N = 19,007)			Tungsten miners hired after 1950[2] (N = 17,841)		
	Cases	HR	95% CI	Cases	HR	95% CI
No lag						
Non-exposed	37	reference	-	34	reference	-
Quartile (0.01-1.65)	51	0.82	0.53-1.27	44	0.81	0.51-1.29
Quartile (1.65-3.30)	51	1.16	0.75-1.78	44	1.22	0.77-1.93
Quartile (3.30-6.20)	50	1.09	0.71-1.68	43	1.15	0.73-1.81
Quartile (≥ 6.20)	51	0.98	0.64-1.55	44	0.76	0.47-1.21
1 mg/m^3-year increase		1.00	0.97-1.03		0.97	0.93-1.01
ln (1 mg/m^3-year + 1)		1.06	0.90-1.24		0.95	0.80-1.14
15-Year lag						
Non-exposed	45	reference	-	41	reference	-
Quartile (0.01-1.65)	58	0.87	0.58-1.32	50	0.86	0.56-1.33
Quartile (1.65-3.30)	42	1.00	0.65-1.55	38	1.15	0.72-1.82
Quartile (3.30-6.20)	48	1.06	0.70-1.62	38	1.05	0.66-1.66
Quartile (≥ 6.20)	47	0.96	0.62-1.48	42	0.78	0.49-1.23
1 mg/m^3-year increase		1.00	0.97-1.04		0.98	0.94-1.02
ln (1 mg/m^3-year + 1)		1.00	0.85-1.16		0.90	0.76-1.07
25-Year lag						
Non-exposed	62	reference	-	58	reference	-
Quartile (0.01-1.65)	53	0.88	0.58-1.32	46	0.83	0.54-1.27
Quartile (1.65-3.30)	38	1.17	0.76-1.82	35	1.30	0.82-2.06
Quartile (3.30-6.20)	43	1.21	0.79-1.85	31	1.04	0.65-1.67
Quartile (≥ 6.20)	44	1.23	0.80-1.90	39	0.94	0.59-1.49
1 mg/m^3-year increase		1.02	0.98-1.05		0.99	0.95-1.04
ln (1 mg/m^3-year + 1)		1.14	0.97-1.35		1.02	0.85-1.23

[1]HR was estimated by time-dependent Cox model adjusted for sex, facility, year of birth and smoking amount; [2]Tungsten miners starting employment after January 1, 1950 and aged over 15 and under 45 years (quartile categories of cumulative silica dust exposure: 0.01-1.56, 1.56-2.90, 2.90-5.22, ≥ 5.22).

deaths was clearly demonstrated in this analysis. However, since the occupational cofounders were not considered at all in this analysis a valid interpretation of the study findings are difficult.

In the present analysis, we only want to know whether the extended follow-up provides a clear evidence of an association between silica dust exposure and lung cancer deaths among the Chinese silica cohort. Therefore, we repeated the previous analysis of Liu only among the cohort in tungsten mines which has no relevant occupational confounders.

To ensure a valid risk estimation sensitivity analyses were carried out by using different cohort definition, exposure models and lag-years. The descriptive analysis in Table 2 indicates that, there is hardly any difference between the two cohort definitions regarding age, follow-up duration, cumulative silica dust exposure and the incidence of lung cancer death and silicosis. In the multivariate analyses, no matter which method was used, no exposure-response relationship between silica dust exposure and lung cancer deaths can be demonstrated. The findings in tungsten mines did not provide an evidence of an association between silica dust exposure and lung cancer deaths even after the extended follow-up.

The Chinese silica cohort is a large industrial cohort, which composed of employees from 29 metal mines and pottery factories. The findings in tungsten mines may not be representative for the whole industrial sectors involved in this study. Toxicological studies indicate that free silica particles from different geographical area or industrial facilities may lead to different biological responses [12]. Therefore, an increased risk of lung cancer due to silica dust exposure in facilities other than tungsten mines cannot be ruled out. However, the co-existence of the occupational confounders, do not allow a valid interpretation of the study findings in these facilities.

Overall, the Chinese silica cohort still fails as yet to provide clear evidence that exposure to silica causes lung cancer in the absence of relevant occupational confounding factors.

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