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# Non-Malignant Respiratory Diseases and Lung Cancer Among Chinese Workers Exposed to Silica

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## **Abstract   Author Information   Article Outline**

The objective of this study was to explore whether a medical history for non-malignant respiratory disease contributes to an increased lung cancer risk among workers exposed to silica. We analyzed data from a nested case-control study in 29 dusty workplaces in China. The study population consisted of 316 lung cancer cases and 1356 controls matched to cases by facility type and decade of birth who were alive at the time of diagnosis of the index case and who were identified in a follow-up study of about 68,000 workers. Age at first exposure and cigarette smoking were accounted for in the analysis. Smoking was the main risk factor for both lung cancer and chronic bronchitis. Lung cancer risk showed a modest association with silicosis and with cumulative silica exposure, which did not vary by history of previous pulmonary tuberculosis. Among subjects without a medical history for chronic bronchitis or asthma, lung cancer risk was associated with silicosis (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.1 to 2.2), and it was increased in each quartile of cumulative silica exposure. However, risk was not elevated in the highest quartile (OR, 1.3, 1.6, 1.8, 1.4). Among subjects with a medical history for chronic bronchitis or asthma, lung cancer risk was associated with neither silicosis (subjects with chronic bronchitis: OR, 0.6; subjects with asthma: OR, 0.4) nor with silica exposure. In this study population, we observed a modest association of both silicosis and cumulative exposure to silica with lung cancer among subjects who were not previously diagnosed with chronic bronchitis or asthma, but not among subjects who had a medical history for either disease. Risk of lung cancer associated with silicosis or cumulative exposure to silica did not vary by previous medical history of pulmonary tuberculosis.

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Previous diagnoses of chronic obstructive pulmonary disease <sup>1,2</sup> and obstructive impairment of ventilatory function <sup>3</sup> have shown these conditions to be independent risk factors for lung cancer. Clinical symptoms and functional signs of chronic obstructive pulmonary disease frequently accompany silicosis. <sup>4</sup> Indeed, inhaled particles, including crystalline silica, either alone or in association with smoking or workplace exposure to nitrogen or sulfur oxides, may cause airways obstruction. <sup>5</sup> When airways obstruction occurs, mucociliary clearance is slowed, which may prolong contact between the bronchoalveolar mucosa and inhaled particles. Also, inhaled particles themselves and/or particles carrying workplace carcinogens, such as benzo(a)pyrene and  $\alpha$ -radiation from radon and its decay products, might more easily penetrate into the deep lung. A longer retention time of inhaled carcinogens close to the target cells is likely to result in an increase of their effective dose. <sup>6</sup> In a recent follow-up of 724 silicosis patients, airway obstruction accounted for the small excess lung cancer risk observed in the study population. <sup>7</sup> Also, risk was highest among metal miners with low-level exposure to radon-daughters and obstructive impairment of ventilatory function, compared with metal miners exposed to radon-daughters but not suffering from airways obstruction or vice versa, whereas it was lowest among metal miners with neither condition. <sup>8</sup> However, deposition studies have shown that among subjects with chronic bronchitis or asthma, particle deposition is increased in the proximal airways compared with the peripheral airways. <sup>9,10</sup> This indicates that a smaller proportion of inhaled particles penetrates into the deep lung, which might actually decrease the risk of silicosis and lung cancer among these subjects compared with their coworkers having normal respiratory function and similar occupational and non-occupational exposures.

Numerous clinical reports have described concurrent lung cancer and pulmonary tuberculosis in the same study subjects, whereas analytic epidemiologic studies have yielded conflicting results. <sup>11–13</sup> A recent report described an excess lung cancer risk among subjects with a previous history of tuberculosis when the lung cancer occurred before 55 years of age, but risk was not elevated when lung cancer occurred after 55 years of age. <sup>14</sup> Risk of lung cancer was also elevated when the diagnosis of tuberculosis occurred within 10 years of the lung cancer diagnosis. On the other hand, tuberculosis frequently complicates silicosis, probably as a consequence of the associated immunologic impairment. <sup>4</sup> Whether it contributes to or confounds the association between silicosis and lung cancer is not yet clear.

To explore the association between non-malignant respiratory diseases and lung cancer risk among workers exposed to silica, we analyzed data from a collaborative study conducted in the late 1980s in numerous dusty trades in China. <sup>15–17</sup> Lung cancer risk was not increased in this study population in the cohort analysis. <sup>15</sup> However, a nested case-control study showed that lung cancer risk associated with either cumulative silica exposure or with silicosis varied by type of mine and industry. <sup>16</sup> The availability of information on medical history and radiologic staging of silicosis in this data set provides the opportunity to investigate whether occurrence of non-malignant respiratory diseases may influence the association between silica and lung cancer and between silicosis and lung cancer.

## Methods

Details of the study have been published elsewhere.<sup>15-17</sup> Briefly, a collaborative study between the US National Cancer Institute, the US National Institute for Occupational Safety and Health, and the Chinese Tongji Medical University was undertaken in the late 1980s in 29 Chinese mines and factories (10 tungsten mines located in the Jaingxi, Henan, and Hunan provinces; 6 copper and iron mines located in the Hubei province; 4 tin mines located in the Guangxi province; and 8 pottery factories and 1 clay mine also located in the Jiangxi and Hunan provinces). Personnel records, rosters, and files of these factories and mines were used to compile the complete job history of all employees with at least 1 year of employment from 1972 to 1974. The total number of cohort members was approximately 68,000. Industrial hygiene data, available from the 1950s for total dust, particle size, and percentage of free silica, were used to estimate an exposure level for each job by calendar-year periods. Measurements of current concentrations for total dust, respirable dust, thoracic dust, percentage of free silica, radon-daughters, arsenic, polycyclic aromatic hydrocarbons, cadmium, nickel, talc, and asbestos were taken in each of the 29 mines and factories by both American and Chinese industrial hygienists. This information allowed estimation of historical exposure to each occupational hazard for each of the 1392 facility/job title combinations over fourteen 3-year calendar periods starting from 1950.<sup>15</sup>

Chinese workplaces with silica exposure are required by law to have registries of employees with silicosis. Chest x-ray examinations must be given yearly to dust-exposed workers. This information identified cases of silicosis with dates of diagnosis, the silicosis stage at first diagnosis, and subsequent changes in silicosis stage. Vital status of cohort members was followed up through December 31, 1989. A total of 319 men were diagnosed with lung cancer; they were matched by decade of birth and facility type with 1358 control subjects who were alive at the time of diagnosis of the index case. Further information on demographic background, medical history, and personal habits such as smoking was acquired by questionnaire from next-of-kin of patients and control subjects. The medical history focused on whether and when the individual was diagnosed with chronic bronchitis, asthma, or pulmonary tuberculosis, and whether and when the individual was ever hospitalized for these diseases. No attempts were made to obtain information from medical records.

For the present analysis, we included 316 cases and 1356 controls after exclusion of five subjects (three cases and two controls lacking questionnaire information). Historical data, retrospective exposure estimates, and more recent workplace surveys were used to estimate cumulative exposure to various lung cancer risk factors for each study subject.<sup>17</sup> Only estimates of total and respirable dust and silica exposure were used in this analysis. Cumulative exposure to occupational risk factors for lung cancer among matched controls was truncated at the age of diagnosis of lung cancer in the index case.

Odds ratios (ORs) and 95% confidence intervals (CI) were generated by logistic regression with the GMBO program in the Epicure software.<sup>18</sup> All risk estimates were adjusted by age at first exposure (continuous) and cigarettes per day (never smoker,  $\leq 15$  cigarettes/day, 16 to 25 cigarettes/day, and  $\geq 26$  cigarettes/day). Stratified analysis and logistic regression modeling were also used to analyze interaction and effect modification.

## Results

Exposure data were previously described by facility type.<sup>15–17</sup> Total dust exposure was highest among pottery factories, whereas exposure estimates of respirable dust and respirable silica were highest among tungsten mines and tin mines. Exposure in all workplaces was high; however, even in iron and copper mines, where average exposure to silica was the lowest, in 1981 to 1987 it was still twice as high as the current US standard. Silica exposure was highest in the 1950s, and it subsequently declined in all workplaces except pottery factories. Average silica exposure throughout all of the facilities from 1950 to 1987 was 1.22 mg/m<sup>3</sup>.<sup>17</sup> Quartiles of cumulative silica exposure were defined by the following cut points of mg/m<sup>3</sup>-year: 0.01, 3.7, 10.7, and 26.9, with subjects exposed to <0.01 mg/m<sup>3</sup>-year defined as unexposed. Silicosis was more prevalent in tungsten mines and tin mines, where exposure to silica was highest. The strong association between exposure to silica and risk of silicosis in this study population and its linear increase by cumulative exposure level was considered to be a validation of the retrospective exposure assessment procedure.<sup>17</sup>

A diagnosis of asthma was reported for 4.6% of study subjects (77 of 1668). A medical history for chronic bronchitis was reported for 20.5% of study subjects (342 of 1668), and pulmonary tuberculosis was reported in 20% of study subjects (333 of 1667); no information was available for one subject. Asthma and chronic bronchitis, but not pulmonary tuberculosis, showed a significant upward trend with cigarette smoking (Table 1). The test for trend in asthma risk was also significant with quartiles of cumulative exposure to total, thoracic, and respirable dust, but not respirable silica. Total dust showed the strongest association. However, risk in the upper exposure level was smaller than in the lower levels, particularly for thoracic and respirable dust. Risk of chronic bronchitis was not related to any indicator of dust exposure. Risk of pulmonary tuberculosis was elevated in the highest quartile of cumulative exposure to total, thoracic, and respirable dust and respirable silica. The latter showed the most significant trend.

TABLE 1  
Cigarette Smoking, Chronic Bronchitis, and Pulmonary Tuberculosis Among Study Subjects by Age, Sex, and Quartile of Cumulative Exposure to Total Dust, Thoracic Dust, Respirable Dust, and Silica

Exposure	Age	Sex	Chronic Bronchitis	Pulmonary Tuberculosis
Total Dust	100	100	100	100
Thoracic Dust	100	100	100	100
Respirable Dust	100	100	100	100
Silica	100	100	100	100

Table 1

Lung cancer risk was not elevated among subjects with previous diagnosis of chronic bronchitis (OR, 0.6; 95% CI, 0.4 to 1.9), asthma (OR, 1.0; 95% CI, 0.6 to 2.0), or pulmonary tuberculosis (OR, 1.1; 95% CI, 0.8 to 1.9). However, risk associated with pulmonary tuberculosis was elevated within the subgroup of participants with a medical history of chronic bronchitis or asthma (OR, 1.8; 95% CI, 1.0 to 3.3). To explore the effect modification related to non-malignant respiratory diseases, we evaluated lung cancer risk associated with silicosis within the strata of positive or negative medical history for each of the three non-malignant respiratory diseases considered in this study (Table 2). Lung cancer risk was not elevated among silicosis patients with a medical history for chronic bronchitis or asthma, whereas silicosis patients who did not have a medical history for either of these two diseases had a significantly elevated lung cancer risk. The modest association between silicosis and lung cancer did not vary substantially in relation to a medical history for pulmonary tuberculosis.

TABLE 2  
Effect Modification on Lung Cancer Risk Associated With Silicosis and Non-Malignant Respiratory Diseases\*

Non-Malignant Respiratory Disease	Cases	Controls	OR	95% CI
Chronic bronchitis	7	62	0.6	0.2–1.8
Asthma	4	18	0.4	0.05–6.6
Pulmonary tuberculosis	77	289	1.8	1.1–3.2
Yes	23	100	1.7	0.9–3.1
No	54	189	1.4	1.0–2.0

\*OR, odds ratio; CI, confidence interval.

Table 2

Among subjects without a medical history for chronic bronchitis, lung cancer risk increased by cumulative exposure to respirable silica, although the trend was not significant. Also, risk decreased and was no longer statistically significant in the highest quartile (Table 3). Among subjects with a medical history of chronic bronchitis, lung cancer risk was not increased in any cumulative exposure category. The modest association between lung cancer risk and cumulative silica persisted regardless of medical history for pulmonary tuberculosis. Only 29 study participants (7 patients and 22 control subjects) had a medical history for asthma but not for chronic bronchitis. Therefore, the numbers were too small to explore asthma-related effect modification of lung cancer risk.

TABLE 3  
Risk Associated With Duration of Cumulative Silica Exposure by Medical History of Chronic Bronchitis and Pulmonary Tuberculosis

		Duration of Cumulative Exposure to Respirable Silica (years)					
		0-10	11-20	21-30	>30	OR	95% CI
Respiratory Disease	N						
Chronic Bronchitis	10	1	0	0	0		
No	10	1	0	0	0		
Yes	10	0	0	0	0		
Pulmonary Tuberculosis	10	1	0	0	0		
No	10	1	0	0	0		
Yes	10	0	0	0	0		

OR, Odds Ratio; CI, Confidence Interval.

## Table 3

The average number of years between diagnosis of non-malignant pulmonary diseases and death from lung cancer was 6.7 years (standard deviation, 6.2) for asthma, 11.2 years (standard deviation, 8.9) for chronic bronchitis, and 11.3 years (standard deviation, 9.7) for pulmonary tuberculosis. The average number of years before death did not vary by smoking status among lung cancer cases affected by chronic bronchitis. Among 10 non-smoking patients with a medical history for pulmonary tuberculosis, death from lung cancer occurred  $6.2 \pm 3.8$  years after diagnosis of pulmonary tuberculosis, significantly earlier than among 50 smokers ( $12.4 \pm 10.2$ ;  $P < 0.01$ ). Among patients with silicosis, a shorter period separated the diagnosis of asthma ( $4.7 \pm 4.9$  years vs  $7.6 \pm 6.8$  years;  $P = \text{NS}$ ), chronic bronchitis ( $5.0 \pm 4.1$  vs  $12.5 \pm 9.1$  years;  $P < 0.01$ ), and tuberculosis ( $7.8 \pm 7.4$  vs  $13.5 \pm 10.4$  years;  $P < 0.01$ ) from lung cancer death compared with lung cancer patients without silicosis. The average number of years since first exposure among patients with lung cancer was  $29.3 \pm 8.9$ ; this did not vary among patients with asthma, chronic bronchitis, or pulmonary tuberculosis. Patients with silicosis and lung cancer died an average of  $33.8 \pm 9.1$  years after the onset of exposure, a period 4.9 years longer than among lung cancer patients without silicosis ( $P < 0.05$ ). Similarly, among lung cancer patients with silicosis, the average number of years separating onset of exposure from death did not vary by medical history of tuberculosis, asthma, or chronic bronchitis.

## Discussion

Among this highly silica-exposed Chinese working population, a previous diagnosis of a non-malignant respiratory disease was not a risk factor for lung cancer. We found a modest association of lung cancer with both cumulative silica exposure and silicosis among participants who had no medical history of chronic bronchitis. Among participants who had a medical history of chronic bronchitis or asthma, lung cancer risk was not associated with silicosis or cumulative silica exposure. However, subjects with a medical history for asthma but not chronic bronchitis were too few (7 cases and 22 controls) for a separate analysis of the two disease subgroups.

The present results do not confirm reports that previous non-malignant lung disease predicts lung cancer <sup>1,3,6,2,14</sup> independently of active or passive smoking. <sup>1,7,14</sup> Also, in a study of 1500 lead and zinc miners, lung cancer deaths exceeded the expectation only among workers with airways obstruction who also had low-level exposure to silica and radon-daughters. <sup>8</sup>

A possible explanation for the differences across studies is that, at high exposure levels such as in dusty trades in China, particles deposition among subjects with chronic bronchitis or asthma would shift to the proximal airways instead of the peripheral lung.<sup>10</sup> Under these conditions, one would expect a smaller proportion of inhaled particles to penetrate into the deep lung, which might actually decrease the risk of silicosis and lung cancer among these subjects compared with their coworkers who have normal respiratory function and similar occupational and non-occupational exposures. Indeed, among uranium miners a greater proportion of small-cell and squamous-cell tumors were located centrally rather than peripherally in the airways compared with the general population.<sup>19</sup> In our study, the risk of silicosis associated with quartiles of silica exposure was higher among subjects who did not have chronic bronchitis or asthma (OR, 24.5, 50.3, 111, and 532, respectively), compared with subjects having a medical history of either of these diseases (OR, 8.0, 23.1, 30.0, and 83.1, respectively) (data not shown in the tables).

In our study, pulmonary tuberculosis did not confound or modify the modest association of lung cancer with silicosis and cumulative silica exposure. In addition, our results do not confirm reports of an increased lung cancer risk associated with pulmonary tuberculosis.<sup>11–14</sup> In a study of non-smoking women, the association between tuberculosis and lung cancer was weakened after adjusting by other non-malignant lung diseases.<sup>14</sup> Our study did not include women because of the small number of lung cancer cases among them ( $n = 11$ ). Among Chinese male workers exposed to silica, a medical history of pulmonary tuberculosis was a lung cancer risk factor only within the subgroup of subjects with chronic bronchitis or asthma. Further research is warranted to understand whether the excess lung cancer risk associated with pulmonary tuberculosis is limited to subjects who also suffer from other non-malignant respiratory diseases.

Caution in interpreting our findings is advised because next-of-kin reporting of medical history of study subjects may have not been as accurate as self-reports or clinical records. However, the proportion of reported hospitalization for asthma and chronic bronchitis was similar between cases and controls (asthma: 6 of 14 cases vs 30 of 63 controls; chronic bronchitis: 17 of 49 cases vs 86 of 293 controls), which suggests that this is not likely to be a major source of error in our study. Yet not all subjects who report a diagnosis of chronic bronchitis show functional abnormalities of the airways, and vice versa. In addition, subjects with asthma may have normal airflow between attacks. Further validation of next-of-kin reports in this data set is not feasible. Therefore, the present results might not be directly comparable with results using information from respiratory function tests.

Further research might profit from screening programs for respiratory diseases, including data gathering on medical history of non-malignant respiratory diseases and spirometries for an earlier and more specific diagnosis of airways obstruction. This information is warranted for a better understanding of conflicting results in the epidemiology of silica, silicosis, and risk of lung cancer. The longer duration from first exposure to death among patients with silicosis and lung cancer also requires further study. Additional exposure modeling may assist in understanding whether silicosis lesions contribute to risk of lung cancer in some individuals.

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