Silicosis in Lymph Nodes: The Canary in the Miner?

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Objectives: *To investigate evidence that lymph node silicosis can precede parenchymal silicosis.* ***Methods:*** *The study population was comprised of 264 deceased male uranium miners for whom two or more of four pathologists agreed on the presence or absence of silicosis in lymph nodes and lung parenchyma. We had work histories and silica exposure estimates.* ***Results:*** *Twenty percent of the miners had lymph node silicosis only, 4% had parenchymal silicosis only, and 39% had both. Silica exposure was lower for miners with lymph node silicosis only than for those with both lymph node and parenchymal silicosis. Lymph node silicosis was associated with parenchymal silicosis after adjustment for silica exposure.* ***Conclusions:*** *Our results are consistent with silicosis potentially occurring in lymph nodes before the parenchyma. Lymph node damage could impair silica clearance and increase the risk for parenchymal silicosis.* (J Occup Environ Med. *2009;51:164–169*)

Silicosis has long been recognized as an untreatable yet preventable occupational lung disease caused by exposure to airborne silica dust.[1,2] Silica exposure occurs in a variety of occupations including sandblasting, mining, tunneling, milling, glass making, as well as among foundry, quarry, abrasives, and pottery workers.[1] The pathologic features of silicosis have been extensively reviewed by an international panel of pathologists.[3]

It has been suggested that fibrotic changes in lymph nodes in the lungs play a role in the development of lung parenchymal silicosis.[4,5] Using information from a pilot study on silicosis and lung cancer using archived autopsy tissue and exposure data from German uranium miners, we investigated this possibility by analyzing the relationships among silica exposure, silicosis of hilar/peribronchial lymph nodes, and pulmonary parenchymal silicosis in a cross-sectional sample. Although the question of whether or not lymph node silicosis precedes the development of parenchymal silicosis cannot be answered directly with a cross-sectional study, we looked for indirect evidence by determining: 1) if lymph node silicosis occurred alone more often than did parenchymal silicosis; 2) if lymph node silicosis occurred at lower exposures to silica than parenchymal silicosis; 3) if lymph node silicosis was a risk factor for the presence of parenchymal silicosis after taking into account silica exposure itself; and 4) if silicosis grade was worse in lymph nodes than in the lung parenchyma.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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Methods

With the collaboration of the German authorities responsible for maintenance of the materials and data, we identified a sample of 302 males, former East German uranium miners included in a histo-pathologic autopsy archive for ~30,000 individuals who had died in East Germany during the period 1957 to 1992 held at the German Center for Research on Cancer in Heidelberg, Germany. Because the investigation initially focused on silica exposure and risk of lung cancer, we had chosen 205 miners listed as dying of lung cancer, but included 97 miners listed as dying of other causes.[6] Only individuals who died in 1971 or later were selected, as information on cigarette smoking was not available from company medical records before this time. More than 2700 histology slides, for 292 of the 302 miners sampled, were examined by four pathologists. The present study population consists of 264 miners for whom two or more of the pathologists agreed on the presence or absence of lymph node and parenchymal silicosis.

Histopathology

The slides were examined independently by four pathologists in the United States using a standardized protocol. We defined silicosis in hilar/peribronchial lymph nodes or parenchyma as the presence of rounded nodules with concentric, eosinophilic hyalinization, and polarizable crystals, either with or without accompanying granulomatous inflammation. The degree of silicosis was assessed for the parenchyma and lymph nodes and graded using the profusion of nodules categorized as mild, moderate, severe, or progressive massive fibrosis. Progressive massive fibrosis was defined as either confluent fibrosis >1 cm in greatest dimension, or obliteration and matting of the hilar lymph nodes. For the 264 subjects, the pathologists read: 2 to 32 slides with lung sections (median = 7), 1 to 11 slides with lymph nodes (median = 2), and a total of 1 to 15 (median = 2) lymph nodes, per subject. For consensus grade assignment, when two or more pathologists assigned the same degree of silicosis that grade was used. When all the pathologists assigned a different degree of silicosis, the lowest grade was used.

Exposure Indices and Smoking Categories

We estimated cumulative exposures to silica dust, by intergrating detailed occupational histories of the study subjects with assessments of the mine environment by three German occupational hygienists familiar with undergound conditions at the mines over the years. The three experts used historical konimetric data to assign levels of concentrations of respirable dusts in particles per cubic centimeter (ppcc), as well as the percentage of silica in corresponding total dust for the sampled occupational histories. Their assignments were made on ordinal scales, with respirable dust categorized as <250, 250 to 500, 500 to 2000, and >2000 ppcc, and the proportion of silica in total dust categorized as <1%, 1% to 5%, 5% to 20%, and >20%. For each miner, we multiplied segments of time worked in distinct mine-, job- and calendar-time–specific periods by 250, 375, 1250, and 2000 ppcc dust concentrations for the four corresponding categories. These segments were multiplied by the assigned proportion of silica in the dust, which we approximated as 1%, 3%, 12.5%, and 20% for the four categories, respectively. These products were then summed. Cumulative silica exposure was divided into quartiles for one analysis.

Smoking history was available for 139 of the 264 cases (53%) from company medical records. We condensed the data to two categories: never, former, or occasional smoker and moderate or heavy smoker of cigarettes.

Statistical Methods

Two-way frequency tables were analyzed using Fisher exact two-tailed test. Analysis of variance and Duncan's multiple range test were used for comparisons of age at death, years since last exposure and other silica exposure characteristics between silicosis groups.[7] The SAS (Cary, NC) procedure, GENMOD, was used to provide generalized estimating equations to examine the association between lymph node silicosis and parenchymal silicosis (as the outcome variable). This approach allowed parenchymal silicosis to vary by pathologist for each subject. Lymph node silicosis was included in these models as an explanatory variable based on consensus among the pathologists. We also used generalized estimating equation models to investigate whether lymph node silicosis was associated with parenchymal silicosis after adjusting for silica exposure, time since last exposure, death from lung cancer, and smoking category.[8] Models including smoking category were run on the subset of 139 cases with smoking information. A P value of 0.05 was used to indicate statistical significance, and SAS 8.0 was used for data analysis.[9]

Results

For the 264 male miners the average age of death was 54, and they had worked for 17 years in the mining industry, with 15 years worked in silica-exposed jobs (Table 1). Based on agreement of presence of silicosis by two or more pathologists, prevalence of lymph node silicosis was 59% and prevalence of parenchymal silicosis was 43% (Table 2). In the 114 subjects with parenchymal silicosis, 90% also had lymph node silicosis, whereas in the 155 subjects with lymph node silicosis, 66% also had parenchymal silicosis. Calculated as percentages of the total number of subjects, 11 of 264 (4%) had parenchymal silicosis alone, whereas a larger percentage, 52 of 264 (20%)

TABLE 1
Characteristics of 264 German Uranium Miners

Characteristic	Values*
Age at death, yr	53.5 (9.5)
Total years worked in mining, yr	16.6 (11.1)
Years worked in silica exposed jobs, yr	15.3 (10.7)
Years from last exposure to death, yr	13.4 (13.1)
Average silica exposure, ppcc	159.9 (123.0)
Cumulative silica exposure, ppcc-yr	1861 (1566)
Moderate or heavy cigarette smoking†	112 (80.6)
Subjects with lung cancer as cause of death, *n* (%)	192 (72.7)
Subjects with other cause of death, *n* (%)	72 (27.3)

*Values are means (SD) or number of subjects (%).

†Based on 139 subjects with smoking information available.

ppcc indicates particles per cubic centimeter of air.

had lymph node silicosis alone. There was a statistically significant, positive association between the presence of lymph node silicosis and parenchymal silicosis (odds ratio [OR] = 17.6, 95% CI = 8.7 to 35.8). When analyzed separately for each of the four pathologists, ORs ranged from 8.7 to 19.3. Using the more conservative generalized estimating equation approach, the association remained strong (OR = 10.0, 95% CI = 6.3 to 15.7).

The relationship between the proportion of subjects with both lymph node and parenchymal silicosis compared with the proportion with lymph node silicosis only, changed as cumulative silica exposure increased (Fig. 1). In the two lower quartiles of cumulative exposure there was a higher proportion of miners with lymph node silicosis only, but in the two highest quartiles of exposure there was a higher proportion of miners with both lymph node and parenchymal silicosis.

Cumulative silica exposure and average intensity of silica exposure were significantly lower for the subjects with lymph node silicosis only, when compared with those with lymph node silicosis accompanied by parenchymal silicosis (Table 3).

We found statistically significant positive associations between presence of parenchymal silicosis and silica exposure measured either as cumulative exposure or as average intensity of exposure together with tenure in silica exposed jobs and years since last exposure (models 1 to 4) (Table 4). After adjustment for these silica exposure and duration variables, the presence of lymph node silicosis was significantly associated with parenchymal silicosis with ORs of 5.6 and 6.3. Death from lung cancer was not associated with parenchymal silicosis and its inclusion in the model did not alter associations involving silica exposure or lymph node silicosis (models 3 and 4). When smoking history was included in a model for the smaller subset of 139 miners for whom we had a smoking history, associations between lymph node silicosis and parenchymal silicosis remained elevated (OR = 12.8, 95% CI = 5.5 to 30.1) after adjustment for cumulative silica exposure and years since last exposure. Smoking was not significantly associated with the presence of parenchymal silicosis (OR = 1.54, 95% CI = 0.3 to 7.3).

We assessed the correlation among the four pathologists for grades of lymph node silicosis and parenchymal silicosis. Spearman correlation coefficients ranged from 0.57 to 0.76 for lymph node silicosis and 0.67 to 0.83 for parenchymal silicosis showing reasonable agreement. The distribution of silicosis grades showed that severity tended to be highest in those with silicosis in both locations, intermediate in those with lymph node silicosis only and

TABLE 2
Association of Lymph Node Silicosis With Parenchymal Silicosis*

Lymph Node Silicosis	Parenchymal Silicosis			
	Present	Absent	Total	OR (95% CI)
Present	103	52	155	17.6 (8.7–35.8)
Absent	11	98	109	
Total	114	150	264	

*Classification of silicosis was based on agreement between two or more of four pathologists assessed separately for lymph node and parenchymal location.

OR indicates odds ratio.

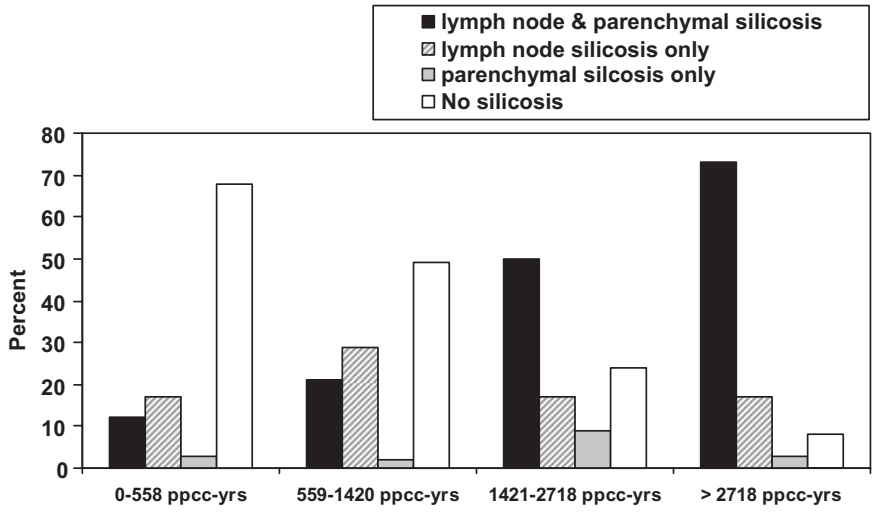

Fig. 1. Comparison of proportions of silicosis in the lymph nodes and in the parenchyma in relation to quartiles of cumulative silica exposure.

TABLE 3
Mean (±SD) Exposure and Other Characteristics by Silicosis Location

Characteristic	Silicosis*			
	None (n = 98)	Lymph Node Only (n = 52)	Parenchymal Only (n = 11)	Both Lymph Node and Parenchymal (n = 103)
Cumulative silica exposure, ppcc-yr	1000† ± 985	1769‡ ± 1597	2290‡§ ± 1461	2681§ ± 1583
Average intensity silica exposure, ppcc	91† ± 92	164‡ ± 124	152‡ ± 99	224§ ± 117
Years of silica job exposure	15.5† ± 10.0	15.1† ± 12.0	17.0† ± 10.6	15.0† ± 10.8
Years since last exposure	9.0† ± 12.8	13.8†‡ ± 13.6	10.9†‡ ± 8.7	17.5‡ ± 12.3
Age at death, yr	49.0† ± 8.9	54.3‡ ± 9.8	53.6‡ ± 8.3	57.4‡ ± 8.3

*Classification of silicosis was based on agreement between at least two of four pathologists assessed separately for lymph node and parenchymal locations.

†‡§Across the rows, means with the same symbols are not significantly different based on Duncan's multiple range test, [α] of 0.05.

ppcc indicates particles per cubic centimeter of air.

TABLE 4
Association of Lymph Node Silicosis With Parenchymal Silicosis Adjusting for Silica Exposure and Lung Cancer

	OR (95% CI)
Model 1	
Lymph node silicosis	5.62 (3.46–9.13)
Cumulative silica exposure, ppcc-yr*	1.46 (1.23–1.73)
Years since last exposure*	1.52 (1.27–1.80)
Model 2	
Lymph node silicosis	6.29 (3.91–10.12)
Average silica exposure, ppcc*	1.44 (1.12–1.85)
Years of silica job exposure*	1.50 (1.09–2.06)
Years since last exposure	1.42 (1.05–1.92)
Model 3	
Lymph node silicosis	5.57 (3.44–9.01)
Cumulative silica exposure, ppcc-yr*	1.47 (1.23–1.74)
Years since last exposure*	1.51 (1.27–1.80)
Lung cancer	0.92 (0.55–1.54)
Model 4	
Lymph node silicosis	6.28 (3.93–10.04)
Average silica exposure, ppcc*	1.44 (1.12–1.85)
Years of silica job exposure*	1.50 (1.09–2.07)
Years since last exposure	1.42 (1.05–1.92)
Lung cancer	0.98 (0.58–1.69)

*Odds ratios are for an increase of 10 yr since last exposure, 10 yr of silica exposure, 1000 ppcc-yr of cumulative exposure and 100 ppcc of average silica exposure.

OR indicates odds ratio; ppcc, particles per cubic centimeter of air.

least severe in those with parenchymal silicosis only (Table 5).

Discussion

As pointed out by Murray et al[4] and Seaton and Cherrie,[5] it is biologically plausible that the presence of lymph node fibrosis impairs the elimination of silica dust from the lungs, leading to higher lung burdens of silica and thereby increasing the likelihood of lung damage and parenchymal silicosis. In Seaton and Cherrie's[5] two case reports, both developed silicosis in the hilar lymph nodes before silicosis of the lung parenchyma. One case had a low level exposure for 30 years, which led to silicotic fibrosis of the hilar lymph nodes. He then had high silica exposure for about 6 years and died of rapidly progressive diffuse silicotic fibrosis. The other case had the same high silica exposures as case 1 for 6 years, which led to fibrosis and calcification of his hilar nodes, at which point early massive parenchymal fibrosis developed.

In a cross-sectional study, evidence suggesting that lymph node silicosis may precede parenchymal silicosis in individuals may be revealed by comparing the distribution of the two types of silicosis in the sample. Murray et al[4] found 88% of their subjects with parenchymal silicosis had accompanying lymph node fibrosis. In our sample of subjects, we found a very similar relationship, with 90% of subjects with parenchymal silicosis having accompanying lymph node fibrosis. Stated another way, Murray et al[4] found that prevalence of parenchymal silicosis was over five times more common in those with lymph node silicosis (43.3%) than in those without lymph node silicosis (7.9%), whereas our results showed a comparable six-fold difference (66.4% and 10.1%, respectively). In our study, isolated parenchymal silicosis was much less prevalent than isolated lymph node silicosis (4% and 20%, respectively), consistent with findings reported by Murray et al[4] where 3% and 32% had isolated parenchymal and isolated lymph node silicosis, respectively. Consistent with these findings, silicosis grade for both parenchymal and lymph node silicosis tended to be most severe, those with lymph node silicosis only tended to be intermediate, and those with parenchymal silicosis were least severe. Although the temporal sequence cannot be elucidated in a cross-sectional study, these patterns of distribution between the two sites of silicosis are consistent with lymph node silicosis in general preceding parenchymal silicosis.

Because we had silica exposure estimates, we could extend the work of Murray et al.[4] We found that subjects with lymph node silicosis only had lower cumulative and average silica exposures than those with both lymph node and parenchymal silicosis. Furthermore, comparing

TABLE 5
Distribution of Lymph Node and Parenchymal Silicosis Grade by Silicosis Location

	Silicosis*							
	No Silicosis (n = 98) Lymph Node	Parenchymal	Lymph Node Only (n = 52) Lymph Node	Parenchymal	Parenchymal Only (n = 11) Lymph Node	Parenchymal	Both Lymph Node and Parenchymal (n =103) Lymph Node	Parenchymal
Silicosis Grade	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
None (1)	98 (100)	98 (100)	0 (0)	52 (100)	11 (100)	0 (0)	0 (0)	0 (0)
Mild (2)			45 (86.5)			11 (100)	49 (47.6)	73 (70.9)
Moderate (3)			4 (7.7)				35 (34.0)	22 (21.4)
Severe (4)			3 (5.8)				19 (18.4)	6 (5.8)
PMF (5)			0 (0)				0 (0)	2 (1.9)

*Classification of silicosis was based on agreement between at least two of four pathologists assessed separately for lymph node and parenchymal locations.

PMBF indicates progressive massive fibrosis.

the proportions of miners with lymph node silicosis only with those with both lymph node and parenchymal silicosis, we found a higher proportion of miners with lymph node silicosis only in the two lower quartiles of cumulative silica exposure and a higher proportion of miners with both lymph node and parenchymal silicosis in the two higher quartiles of cumulative silica exposure. These results were consistent with those of Murray et al,[4] who showed similar trends for these two groups with increasing duration of silica exposure. This result also is consistent with lymph node silicosis preceding the development of parenchymal silicosis.

Finally, assuming this temporal relationship, in models with parenchymal silicosis as the outcome variable, we found that the presence of lymph node silicosis was a risk for the presence of parenchymal silicosis over and above the risk because of silica exposure. This may point to the importance of the hilar lymph nodes in the clearance of silica from the lungs and the additional risk for parenchymal silicosis when this mechanism is impaired.

Strengths of this study include 1) use of detailed exposure information from work histories and industrial hygiene data, interpreted by three industrial hygienists who were familiar with the mining conditions; 2) availability of pathologic tissue specimens from a relatively large number of silica-exposed miners; and 3) incorporation of independent histopathologic assessments of lymph node and parenchymal silicosis by four pathologists using agreed upon criteria. Limitations of this study include its cross-sectional design, the limited number of subjects in particular subgroups, possible imprecision or inaccuracy in measures of silica exposure, and having smoking information on only about half of the miners. The cross-sectional study design precludes inferences regarding causality. It is also possible that the processes involved in lymph node and parenchymal silicosis are separate and independent. If development of lymph node silicosis is a more acute response to silica dust exposure and parenchymal silicosis develops after a longer duration of exposure, one could also expect lymph node silicosis to predict parenchymal silicosis. It could also be that the lymph nodes demonstrate a higher prevalence of silicosis because they either receive a higher concentration of the dust or are more sensitive to it than the parenchyma. It is clear that a cross-sectional study design cannot discern the reason for a higher prevalence of lymph node silicosis than parenchymal silicosis. The unusually low prevalence of isolated parenchymal silicosis in our study subjects contributes to some statistical instability of the estimates involved and yet is also consistent with the occurrence of parenchymal silicosis after lymph node silicosis has already developed. Respirable particles count data derived from the use of the konimeter has limitations. Only short-term air samples can be taken; and the samples must be examined using optical microscopy, which may be unreliable, especially with high dust concentrations. If silica exposure estimates were imprecise or inaccurate, it is possible that adjustment for exposure could be incomplete; however, silica exposure levels were notably different in the expected direction across the four groups of individuals with and without lymph node and parenchymal silicosis. Although smoking history was only available in a subset (53%), when analyses were restricted to those with smoking habits and adjustment for smoking was performed, associations were essentially unchanged.

An interesting aspect of our models was that the years since last exposure was significantly and positively associated with the presence of parenchymal silicosis, as was found by Kreiss and Zhen[10] in their cross-sectional study on the risk of silicosis in a Colorado mining community. Our ORs for years since last exposure in the various models were 1.4

and 1.5 for an increase in 10 years, whereas Kreiss and Zhen[10] found comparable yet slightly higher ORs of 1.7 to 2.4. These similarities are remarkable considering the differences in the study populations, and that we used histologic evidence of silicosis whereas Kreiss and Zhen[10] used radiologic evidence. Although prospective studies on onset of silicosis in silica-exposed workers after leaving employment would be useful, our findings further support the suggestion that lifetime follow-up is necessary to assess the full health burden of silica dust exposure.

If indeed lymph node silicosis can precede parenchymal silicosis and occur at lower silica exposures, as is suggested by our results, current methods of surveillance for silicosis, which concentrate primarily on parenchymal silicosis might miss early cases of silicosis in which the lymph nodes alone are affected. In the two cases reported by Seaton and Cherrie,[5] early chest radiographs had shown hilar lymph node enlargement or fibrosis and calcification before lung involvement. Baldwin et al[11] also reported on five workers exposed to silica who had chest radiographs showing enlarged hilar lymph nodes without radiographic evidence of parenchymal silicosis. They discuss that sarcoidosis is a major differential diagnosis to be considered. Thus, signs of enlarged hilar lymph nodes on chest radiographs during surveillance for silicosis should raise the level of suspicion of possible early signs of effects of silica exposure. In addition, epidemiologic studies of silicosis and lung cancer may underestimate the risk of lung cancer if parenchymal silicosis alone is considered. This is particularly true if, as hypothesized, lymph node silicosis impedes not only the clearance of silica from the lung, but other carcinogens as well.

In summary, we found that the presence of lymph node silicosis was associated with the presence of parenchymal silicosis over and above the association with silica exposure. Findings from the current study indicated that the likelihood of parenchymal silicosis was 10 times greater in those with lymph node silicosis than in those without, and this likelihood was reduced to approximately six times greater after adjusting for silica exposure. Results from Murray et al[4] showed a similar yet slightly greater reduction in ORs from 8.9 to 2.6 with adjustment for duration of silica exposure. These results are consistent with the potentially important role of hilar lymph nodes in the clearance of silica from the lungs and may also reflect an additional risk for parenchymal silicosis when this mechanism is impaired.

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