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Connective Tissue Disease and Silicosis

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Background: *To determine the prevalence of connective tissue disease in a cohort of individuals with silicosis, we reviewed the medical records and questionnaires from individuals reported from 1987 to 1995 to a state surveillance system for silicosis. Reporting of individuals with silicosis is required by state law. Cases were reported by hospitals, physicians, the state workers' compensation bureau, or from death certificates. Only individuals who met the criteria for silicosis developed by the National Institute for Occupational Safety and Health (NIOSH) were included in the analysis.*

Results: *A questionnaire was completed for all 583 cases. Medical records were available for 463. There were 24 people with rheumatoid arthritis, one with scleroderma, and one with systemic lupus erythematosus. All were men. The prevalence of rheumatoid arthritis was 5.2% (relative risk (RR) 2.73, 95% confidence limit (CL) 1.75–4.06). The prevalence of scleroderma was 0.2% (RR 15.65, 95% CL 0.21–87.03) and the prevalence of systemic lupus erythematosus was 0.2% (RR 11.37, 95% CL 0.15–63.23). This is an approximately 2.5–15-fold increased risk for these connective tissue diseases compared to estimated prevalences in the general population. Individuals with silicosis and connective tissue disease did not differ from individuals with silicosis but without connective tissue disease by race, age, type of industry where exposed to silica, history of tuberculosis, whether or not they had applied for workers' compensation, and whether or not they had progressive massive fibrosis on chest x-ray.*

Conclusion: *Although the association between scleroderma and silicosis has been more widely reported in the literature, the prevalence of rheumatoid arthritis was greater than the prevalence of scleroderma or systemic lupus erythematosus among a cohort of individuals with silicosis.* Am. J. Ind. Med. 35:375–381, 1999. *© 1999 Wiley-Liss, Inc.*

KEY WORDS: rheumatoid arthritis; scleroderma; silicosis; systemic lupus erythematosus

INTRODUCTION

Exposure to silica has been associated with humoral immunological changes, including positive antinuclear antibodies (ANA), positive rheumatoid factor (RF), and elevation in immunoglobulins (IgA and IgG). ANA and RF have been reported to be present in 20–40% of patients with silicosis [Doll et al., 1981; Kang et al., 1973]. The risk of developing clinical connective tissue disease has been reported to be greater among individuals with both silica exposure and silicosis. The best evidence of this association is for rheumatoid arthritis and scleroderma [Bramwell, 1914; Erasmus, 1957; Rodnan et al., 1967; Sluis-Cremer et al., 1985, 1986; Haustein and Ziegler, 1985; Cowie, 1987; Koeger et al., 1995; Bovenzi et al., 1995; Silman and Jones, 1992; Haustein et al., 1990; Caplan, 1953; Caplan et al., 1958; Williams, 1991; Klockars et al., 1987; Steenland et al., 1992; Steenland and Brown 1995]. In addition, there are a limited number of reports of systemic lupus erythematosus in individuals with silicosis [Koeger et al., 1995; Sanchez-Roman et al., 1993; Conrad et al., 1996; Masson et al., 1997].

We reviewed the medical records of individuals with silicosis reported to a state surveillance system for silicosis

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to determine the prevalence of connective tissue disease among individuals with silicosis in Michigan.

METHODS

As part of the Sentinel Event Notification System for Occupational Risks (SENSOR) the State of Michigan, with financial assistance from the National Institute for Occupational Safety and Health (NIOSH), instituted a surveillance/investigation program for silicosis in 1987 [Rosenman et al., 1997]. Sources used to identify persons with silicosis were: 1) reports from hospitals, 2) reports from physicians, 3) death certificates, and 4) claims awarded by the Michigan Silicosis, Dust Disease, and Logging Industry Compensation Fund.

Reports from hospitals were requested once per year. Hospital discharge summaries for individuals with a primary or secondary diagnosis of silicosis (ICD 502) or pneumoconiosis not otherwise specified (ICD 505) were obtained from all acute care hospitals in Michigan including Veteran's Administration hospitals. Reporting by both Michigan practitioners and hospitals was required under part 56 of Public Act 368 of 1978, which requires the reporting of all known or suspected occupational disease. Physicians reported known or suspected cases as they were identified. Death certificates and workers' compensation data were reviewed on a yearly basis.

When a report was received, the individual was interviewed by a trained interviewer over the telephone. If the individual was deceased, a next-of-kin was interviewed. For 87 individuals where an interview could not be completed, the questionnaire was completed from medical records. A standard questionnaire was used as part of the process to confirm the diagnosis of silicosis. The interview took approximately 30–45 min and consisted of a lifetime work history, cigarette smoking history, medical care history, medication history, and medical and symptom history limited to respiratory conditions.

Medical records including pulmonary function testing, and a recent chest x-ray on the reported patients were also collected. A fourth-year medical student reviewed the medical records for any mention of connective tissue disease in general, as well as specific diseases including rheumatoid arthritis, systemic lupus erythematosus, and scleroderma. When medical records were available they were typically the discharge summary from hospitalization, x-ray reports, and assorted laboratory data. All of the charts identified by the student were reviewed by a physician board certified both in internal medicine and occupational medicine; he made the final determination if the chart indicated a connective tissue disease. Typically, there were insufficient records available to determine if the patient met the diagnostic criteria of the American College of Rheumatology.

Due to delays in receiving reports and the availability of databases, the most complete data available were for 1987–1993. Only preliminary data were available for 1994 and 1995. Partial data were also available for the years 1985 and 1986.

A person is considered to have silicosis if there is: 1) a history of exposure to silica, and 2) a chest x-ray interpretation showing rounded opacities of 1/0 or greater profusion per the International Labour Office's (ILO) classification system for pneumoconiosis, or a biopsy report of lung tissue showing the characteristic silicotic nodule. All chest x-rays are reviewed by a physician who is NIOSH certified ''B'' reader, and therefore has special training and accreditation to interpret chest x-rays for all pneumoconioses, including silicosis.

Relative risks and 95% confidence limits were calculated. Published information was used to determine rates in the general population [Lawrence et al., 1989; Johnson-Davis, 1996].

RESULTS

We reviewed 583 confirmed cases of silicosis reported to the state from 1985 to 1995. For 120 of the reports, there was no discharge summary available for review. Among the 463 silicotics with medical records, there were 24 people with rheumatoid arthritis, one person with scleroderma, and one person with systemic lupus erythematosus. In the group with informative medical records, therefore, there is a prevalence of 5.2% for rheumatoid arthritis (relative risk (RR) 2.73, 95% confidence limit (CL) 1.75–4.06), 0.2% for scleroderma (RR 15.65, 95% CL 0.21–87.03), and 0.2% for systemic lupus erythematosus (RR 11.37, 95% CL 0.15–63.23). All 26 silicotics with connective tissue disease were men. In the general population, however, these conditions are more common in women than in men. The individuals with silicosis who had connective tissue disease did not differ significantly from the individuals with silicosis without connective tissue disease by race, age, type of industry where exposed to silica, whether or not they had done sandblasting, years of exposure to silica, whether they ever had tuberculosis, whether they had applied for workers' compensation, and whether they had progressive massive fibrosis on their chest radiograph (Table I). The estimated prevalence in the general population, which is less than found in this group of individuals with silicosis, is shown in Table II [Johnson-Davis, 1996; Lawrence et al., 1989].

The individual with silicosis and scleroderma, the individual with silicosis and systemic lupus erythematosus, and 17 of the individuals with silicosis and rheumatoid arthritis were reported through the hospital discharge system. The prevalence of rheumatoid arthritis among men with silicosis reported by a hospital was 4.8% (RR 2.52, 95% CL 1.47–4.04) and the prevalence of rheumatoid arthritis among men with silicosis reported from other sources was 3.1% (RR 1.6, 95% CL 0.65–3.33).

TABLE I. Comparison of Silicotics With and Without Connective Tissue Disease, Michigan 1985–1995

	Connective tissue disease (26)*		No connective tissue disease (463)*			
	#	%	#	%	O.R.	(95% C.L.)
White	14	(53.8)	236	(54.3)	0.98	(0.39–2.20)
Black	12	(46.2)	188	(43.2)**		
Year of birth <1930	21	(80.8)	384	(87.9)	0.58	(0.20–1.84)
Worked in a foundry	21	(84.0)	329	(75.5)	1.71	(0.54–7.17)
Had done sand-blasting	8	(40.0)	102	(32.6)	1.38	(0.50–3.76)
Exposure to silica >20 years	16	(61.5)	309	(72.4)	0.61	(0.25–1.49)
Smoked cigarettes	17	(68.0)	316	(73.0)	0.79	(0.31–2.05)
Tuberculosis	5	(22.7)	72	(19.6)	1.21	(0.37–3.63)
Applied for workers' compensation	6	(60.0)	94	(55.6)	1.20	(0.29–5.27)
Progressive massive fibrosis on chest x-ray	12	(46.2)	138	(31.6)	1.8	(0.77–4.31)

*Denominator varies because information is missing on some individuals.
**Eleven (2.5%) were not reported either white or black.

Among the 583 silicotics with a completed questionnaire, 124 (21.3%) self-reported they had arthritis. The self-reported prevalence is similar to that reported in the general population (21%), even though the general population data are from a younger age group (men and women ≥ 18 years of age) [Johnson-Davis, 1996] compared to the more elderly individuals with silicosis.

SAMPLE CASE REPORTS

Scleroderma

A 60-year-old white male died of silicosis and scleroderma. He had cleaned up the sand and other debris for sandblasters at a shipyard for 14 years. He had begun this work in the mid-1960s. He never smoked cigarettes. He was skin-test negative for tuberculosis. Sixteen years after first exposure to silica at the shipyard, his x-ray showed progressive massive fibrosis (3/3 and a large opacity category A using the ILO classification system).

An open lung biopsy was consistent with the presence of both silicosis and scleroderma (classical silicotic nodule as well as alveolar wall fibrosis with mild inflammation and proliferation of alveolar lung cells). A skin biopsy showed scleroderma. SSA antibody and antitopoisomerase antibody were positive. Pulmonary function tests showed severe restriction.

He was treated with steroids, but had slowly progressive disease and died 8 years after his initial diagnosis, in respiratory failure.

Systemic Lupus Erythematosus

A 61-year-old African-American male with silicosis had weakness and pain in his muscles and swelling of his knees and wrists. His ANA titer was >1:640. Anti-double-stranded DNA IgM was 116.6 (nml <100 units); anti-double-stranded DNA IgG was 68.4 (nml <70 units); single-stranded IgG was 109 (nml <100 units); and C_3 complement was 79 (nml 95–186). He was treated with oral corticosteroids and hydroxychloroquinone. His pulmonary function tests showed mild restrictive lung disease and chest radiograph showed simple silicosis (2/2 on the ILO classification system). Silicosis was confirmed by an open lung biopsy.

He had worked for 38 years as a chipper and grinder in a foundry. He was first exposed to silica in the 1940s. He developed lupus 42 years after his first exposure to silica. He had averaged 2 packs of cigarettes a day for 36 years and quit 4 years before the lupus was diagnosed. He was skin-test negative for tuberculosis.

Rheumatoid Arthritis With Sjogren Syndrome

A 50-year-old African-American man presented with shortness of breath. His x-ray showed simple silicosis (2/1 on the ILO classification system). He had smoked less than 2 packs of cigarettes a day for 27 years, quitting at the age of 42. He had a negative skin test for tuberculosis. He had symptoms of chronic dry mouth, morning joint stiffness lasting an hour or more, and swelling of his knees. His rheumatoid factor was positive; the titer was >1,280. His ANA was homogenous with a titer >1:640. His sedimentation rate was elevated, at 121.

He had worked for 12 years as a chipper and grinder at a foundry. He began work there in the late 1960s. He was diagnosed with silicosis 23 years after his first exposure to silica.

DISCUSSION

Although the literature most commonly cites an association between scleroderma and silicosis than with other connective tissue diseases, rheumatoid arthritis was more common in this population of individuals with silicosis; 5.2% had rheumatoid arthritis (RR 2.73) versus 0.2% with scleroderma (RR 15.65). The relative risk for rheumatoid arthritis was statistically significant, while that for scleroderma was not. A similarly statistically nonsignificant in-

TABLE II. Prevalence of Connective Tissue Disease Among 583 Individuals With Silicosis, Michigan, 1985–1996

Information from medical records**	Michigan data		Relative risk (95% C.L.)	General population
	Number	Prevalence		
Rheumatoid arthritis	24	5.2%	2.73 (1.75–4.06)	2% of white and black men ≥55 years [Lawrence et al., 1989]
Scleroderma	1	0.2%	15.65 (0.21–87.03)	0.014% [Lawrence et al., 1989]
Systemic lupus erythematosus	1	0.2%	11.37 (0.15–63.23)	0.02% of men [Lawrence et al., 1989]
Self-reports**				
Any type of arthritis	124	21.3%		21.0% of white and black men and women ≥18 years [Johnson Davis, 1996]

*Medical records were available on 463 individuals.
**Questionnaires were completed on 583 individuals.

creased relative risk was found for systemic lupus erythematosus (Table II). There were no demographic, exposure, or radiographic characteristics that distinguished the silicotics with connective tissue disease from those without connective tissue disease (Table I).

Our report differs from most previous reports in the literature because we estimated the prevalence of connective tissue disease in individuals with confirmed silicosis. Most previous reports either studied silicosis and silica exposure among individuals with connective tissue disease or examined connective tissue disease among individuals with silica exposure, of whom only a small percentage would have had silicosis.

Scleroderma

The first association between scleroderma and a job with silica exposure was described in 1914 among Scottish stonemasons, although in the first report the disease was attributed to the stonemasons' use of cold chisels [Bramwell, 1914]. A study of South African gold miners in 1957 first suggested that silica was the etiologic agent [Erasmus, 1957]. Subsequent to this report, there have been case series and case-control studies which supported an associated between silica exposure and scleroderma [Bramwell, 1914; Erasmus, 1957; Rodnan et al., 1967; Sluis-Cremer et al., 1985; Haustein and Ziegler, 1985; Cowie, 1987; Koeger et al., 1995; Bovenzi et al., 1995]. Generally, the association has only been seen among men with scleroderma. The association has been reported with silica exposure even in the absence of silicosis. One report from Pittsburgh, Pennsylvania, showed that 43 of 60 men (72%) with scleroderma had silica exposure [Rodnan et al., 1967]. Another report found that 79 South African white male gold miners with scleroderma had increased cumulative dust exposure, but no increase in the prevalence of silicosis as compared to a reference group of miners [Sluis-Cremer et al., 1985]. Sixty-six of 86 men (77%) with scleroderma from Leipzig, Germany, had silica exposure and 39 (45%) had silicosis in comparison to women with scleroderma, where 7 of 151 (4.6%) and 1 of 151 (.7%) had silica exposure or silicosis [Haustein and Ziegler, 1985]. Case series of individuals with scleroderma have been reported among South African black male gold miners [Cowie, 1987] and from Paris, France [Koeger et al., 1995]. There was a 5-fold increased risk of scleroderma among silica-exposed men in the province of Trento, Italy [Bovenzi et al., 1995]. There is one report of no association with silica exposure among 56 men with scleroderma from the United Kingdom [Silman and Jones, 1992].

Silica presumably acts as a fibrogenic stimulus wherever it is deposited. Silica particles are widely disseminated in the body after inhalation. Silica deposition, as well as nodule formation, has been reported in the abdominal peritoneum, bone marrow, extrathoracic lymph nodes, liver, and spleen [Miranda et al., 1996]. Deposition without nodule formation has been reported in the brain, kidney, and skin [Haustein et al., 1990; SSDC, 1988].

Patients who develop scleroderma after silica exposure typically have antitopoisomerase antibodies and cannot be distinguished immunologically from patients with idiopathic scleroderma [McHugh et al., 1994].

A committee that recently reviewed the adverse effects of crystalline silica concluded there was ''persuasive evidence relating scleroderma to occupational silica exposures. . . .'' [ATS, 1997].

Rheumatoid Arthritis

An association between rheumatoid arthritis and exposure to coal (Caplan's Syndrome) was first described in 1953 [Caplan, 1953]. The French had described a similar syndrome among silica-exposed workers in 1950 and Caplan in

subsequent reports also described the syndrome in silica-exposed workers [Caplan et al., 1958]. No association between the severity of the joint lesions and radiological findings has been found and the lung lesions can either precede or follow the joint disease [Williams, 1991]. The classical picture of the radiographic changes is one of multiple rounded large nodules that appear rapidly throughout the lungs. In comparison, progressive massive fibrosis classically shows solitary, irregular, slowly enlarging nodules in the upper lobes.

An increased risk (odds ratios of 4–5) of rheumatoid arthritis among individuals with silicosis has been reported among Finnish granite miners [Klockars et al., 1987] and white South African gold miners [Sluis-Cremer et al., 1986]. Further, arthritis without reference to type was more frequently mentioned (proportionate mortality ratios of 2.00) on the death certificates of granite workers [Steenland et al., 1992] and South Dakota gold miners [Steenland and Brown, 1995] than on death certificates of the reference population.

Because of the prevalence of arthritis in the elderly population that develops silicosis and the high prevalence of positive serum tests for rheumatoid factor, the committee that recently reviewed the adverse effects of silica concluded that ''a causal association between rheumatoid arthritis and silica exposure is thus plausible but unproved'' [ATS, 1997]. Examination using the standardized criteria for the diagnosis of rheumatoid arthritis of a cohort of patients with silicosis such as the patients identified in our surveillance system should be able to resolve this issue.

Systemic Lupus Erythematosus

A case series of silica-associated connective tissue disease from France reported four patients with systemic lupus and one with discoid lupus [Koeger et al., 1995]. A second case series also from France reported seven patients with systemic lupus erythematosus and one with cutaneous lupus erythematosus [Masson et al., 1997]. A cross-sectional study of 50 workers from a scouring powder factory of 300 employees identified three workers with systemic lupus erythematosus and five with a mixed connective tissue disorder of systemic lupus and scleroderma, and five with scleroderma [Sanchez-Roman et al., 1993]. If one assumed all 250 nonparticipating workers had no connective tissue disease, then the prevalence of systemic lupus was 1%, mixed connective tissue disease 1.7%, and scleroderma 1.6%. Examination of a cohort of 15,000 heavily exposed uranium miners from the former East Germany identified 28 definite and 15 probable cases of systemic lupus erythematosus. The authors estimated the prevalence was up to 0.09% [Conrad et al., 1996]. Exposure to silica was from 1–42 years, with an average duration of about 10 years. The committee that reviewed the adverse effects of crystalline silica exposure suggested that systemic lupus should only be suspected as being caused by silica in patients with acute or accelerated silicosis [ATS, 1997]. However, the case identified in our surveillance system, the report of East German uranium miners, seven of the nine cases from one series in France, and one of the four cases in the other series from France were among patients with chronic silicosis.

Potential Sources of Bias

Certain aspects of the methodology of this study would be expected to underestimate the prevalence of connective tissue disease, while others would be expected to overestimate the prevalence.

This was a retrospective review of available medical records and a telephone-administered questionnaire. We were not able to clinically examine the patients included in this study. Rather, we relied solely on the available reports we received from hospitals and doctors, and further relied on an individual physician diagnosis of a connective tissue disease without being able to assess whether each physician applied standardized criteria for diagnosing these conditions. If the treating physician did not evaluate their patient for connective tissue disease, or we did not have the complete medical records, we would have underestimated the prevalence. For 21% of the individuals with silicosis, we were unable to obtain medical records. If the treating physician did not use standard criteria and/or was unaware that silicosis may cause a positive rheumatoid factor in the absence of rheumatoid arthritis, then we would have overestimated the prevalence.

Despite the relatively large number of individuals with silicosis, scleroderma and systemic lupus erythematosus were rare in this population, with only one patient with each condition. The increased risks for these conditions were not statistically significant. Also, we did not calculate age-adjusted prevalence ratios, although we used the largest published prevalence rates from studies that most closely matched the demographics of our silicotic population (elderly men) as our reference rates [Johnson-Davis, 1996].

We know the state reporting system does not receive all reports of silicosis in the state. Based on the reporting system's reliance on hospitalized individuals as the major source of our reports, we believe we received reports on individuals with more advanced silicosis. If more advanced silicotics have more connective tissue disease or the presence of two diseases (i.e., silicosis plus connective tissue disease), which is more likely to lead to hospitalization, then our reported prevalence will be an overestimate. The prevalence of rheumatoid arthritis was 4.8% (RR 2.52, 95% CL 1.47–4.04) among hospitalized individuals and 3.1% (RR 1.6; 95% CL 0.65–3.33) among individuals reported from other sources, which suggests our overall prevalence may be an overestimate. Both individuals with systemic lupus erythematosus and scleroderma had been reported after

hospitalization. We are unaware of any bias in our inability to review medical records on 120 of the cases. Finally, we used published prevalence rates of connective tissue disease to calculate relative risks [Lawrence et al., 1989; Johnson-Davis, 1996]. The methods used to determine the published rates differed from our methodology in determining the prevalence among the reported individuals with silicosis.

For rheumatoid arthritis, the published rates we used were based on the National Health Examination Survey, which evaluated clinical examinations, roentgenograms of hands and feet, and blood tests for rheumatoid factor, and then evaluated the results using the American Rheumatism Association (ARA) criteria. For systemic lupus erythematosus and scleroderma, the published rates are based on ARA criteria in the review of medical records from two geographic locations: Rochester, Minnesota, and San Francisco, California. The use of more stringent criteria in the published control groups would cause us to overestimate the risk in our silicosis population. We did not have sufficient medical records available to apply ARA criteria to our silicotic population.

SUMMARY

In summary, the majority of studies reporting an association between connective tissue disease and silicosis or silica exposure have been case reports or case series. Seven studies have been performed which provide risk estimates of approximately 5-fold increase for connective tissue disease among individuals with silicosis or silica exposure: a study in Italy [Bovenzi et al., 1995]; studies among South African [Sluis-Cremer et al., 1985, 1986] and U.S. gold miners [Steenland and Brown, 1995]; studies among Finnish [Klockars et al., 1987] and U.S. granite miners [Steenland et al., 1992]; and a study in Spanish scouring powder workers [Sanchez-Roman et al., 1993]. Using a state-based surveillance system of reported silicosis cases, we found that rheumatoid arthritis was the most common connective tissue disease among individuals with silicosis (24 individuals) (5.2% with a 2.73-fold increased risk, 95% CL 1.75–4.06). There was one individual each with systemic lupus erythematosus (0.2% with an 11.37-fold increased risk, 95% CL 0.15–63.23) and scleroderma (0.2% with a 15.65-fold increased risk, 95% CL 0.21–87.03), which yielded greater but nonsignificant relative risks.

The findings from this study highlight the importance of considering connective tissue disease as an additional complication when evaluating a patient with silicosis.

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