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Silicosis and end-stage renal disease

by Steenland K, Rosenman K, Socie E, Valiante D

Affiliation: School of Public Health, Emory University, 1518 Clifton Road, Atlanta 30322, Georgia, United States. nsteenl@sph.emory.edu

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Silicosis and end-stage renal disease

by Kyle Steenland, PhD,[1,2] Ken Rosenman, MD,[3] Ed Socie, MS,[4] Dave Valiante, CIH[5]

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Objectives The objective of this study was to determine the incidence of renal disease among workers with silicosis.

Methods A population of 1328 workers with definite silicosis and adequate work history information, drawn from three states with silicosis surveillance systems, was followed. Renal disease was ascertained via linkage of the cohort with a United States register (which has existed since 1977) of end-stage renal disease.

Results In the first analysis, it was assumed that the risk of end-stage renal disease began upon exposure to silica. In this analysis 12 cases of end-stage renal disease were found versus 15.6 expected, for a rate ratio of 0.77. Four cases of glomerular end-stage renal disease were found (standardized incidence ratio 2.65, 95% confidence interval 0.56–5.25). It is possible that some persons with end-stage renal disease died before being entered into the silicosis registers. In a second analysis, person-time at risk was assumed to begin at the date of entry into the silicosis register. A rate ratio of 1.67 (95% confidence interval 0.76–3.17) was found for end-stage renal disease on the basis of nine observed cases.

Conclusions The results do not clearly show that patients with silicosis have an excess of end-state renal disease, although they do suggest an excess of glomerular end-stage renal disease. Analyses were limited by small numbers and possible selection biases.

Key terms kidney, linkage study, silica.

Evidence has accumulated over the last decade that workers with crystalline silica exposure have an increased incidence of renal disease (1–8), particularly glomerular disease. However, this association has not been shown conclusively. The mechanism by which silica may damage the kidney could be either direct toxicity (silica particles in kidney) or indirect (systemic) toxicity, including glomerular damage caused by an autoimmune process (9, 10).

Patients with silicosis have usually been exposed to appreciable amounts of silica and may also represent a population particularly susceptible to silica toxicity. It is of interest to determine whether they show an increased incidence of renal disease.

To investigate this issue, we linked data from three state registers of silicotic patients with the national register of end-stage renal disease, which covers most patients treated for end-stage renal disease (ESRD) in the United States in 1977–1998. Treated ESRD patients are either on dialysis or have received a kidney transplant. The national ESRD register includes all ESRD cases which receive dialysis or transplant via Medicare (about 92% of all treated ESRD cases) (1).

Material and methods

Subjects of the study were patients with definite silicosis from three states (New Jersey, Michigan, Ohio). Silicosis cases were identified by physician reporting, hospital discharge data, workers' compensation claims, death certificate data, and workplace data. All three states have silicosis registers that are part of the

1 National Institute for Occupational Safety and Health (NIOSH), Cincinnati, Ohio, United States.
2 Current address: School of Public Health, Emory University, Atlanta, Georgia, United States.
3 Michigan State University, East Lansing, Michigan, United States.
4 Ohio Department of Health, Columbus, Ohio, United States.
5 New Jersey Department of Health, Trenton, New Jersey, United States.

Correspondence to: Dr Kyle Steenland, School of Public Health, Emory University, 1518 Clifton Road, Atlanta 30322, Georgia, United States. [E-mail: nsteenl@sph.emory.edu]

SENSOR (Sentinel Event Notification System for Occupational Risks) program developed by the National Institute for Occupational Safety and Health (NIOSH) in the United States in collaboration with the states to identify occupational disease (11). Silicosis has been a reportable disease in all three states during the years that collected data have been entered into the registers. The Michigan register includes cases diagnosed from 1987 to 1998, the corresponding years for New Jersey and Ohio being 1984–1998 and 1989–1998, respectively. According to death certificate data, all three registers include a few silicotic decedents who were entered into the registers before the aforementioned years (ie, in the early to mid-1980s) (5% of total cases).

All silicosis cases fulfilled the SENSOR criteria for a definite case, namely, (i) a history of occupational exposure to airborne silica and (ii) a chest radiograph, lung histopathology, or both interpreted as characteristic of silicosis. Chest radiographs were considered positive for silicosis on the basis of either a review by a clinical radiologist or by a NIOSH-certified "B" reader (ie, a physician with special training and accreditation to interpret chest radiographs for pneumoconiosis); in Michigan all the cases were confirmed by B readers. A chest radiograph had to have a profusion of rounded opacities of 1/0 or greater according to the classification system of the International Labour Office (ILO) to be considered indicative of silicosis.

The ESRD cases were identified among the silicotics by matching the cohort of silicotics with the national ESRD register. The national ESRD register is called the End-Stage Renal Disease Program Management and Information System, which is available for 1977–1998. The cases first receiving treatment before 1977 are not included. Data for the End-Stage Renal Disease Program Management and Information System is maintained by the Health Care Financing Administration and includes all persons who received Medicare-covered treatment for ESRD (dialysis and transplant) (12). The data include the date of first treatment, which we used as a surrogate date of diagnosis, and a diagnostic category for the type of ESRD. Approximately 92% of the patients treated for ESRD have Medicare coverage and are therefore included in the database. Noncovered ESRD cases may include those treated by Veterans Administration hospitals before 1990, those treated in military hospitals, and those under 65 years of age and not covered by Medicare who die before Medicare coverage can begin (60–90 days after beginning of dialysis). The treatment policy for ESRD candidates in the United States is relatively liberal; all patients except those with other fatal diseases are likely to be treated. Therefore, with the exception of silicotics whose disease was recognized as imminently fatal, we would expect that silicotics whose kidneys had failed would have received ESRD treatment.

The principal variables used to match the silicosis cases with the cases in the ESRD register were social security number, name, and date of birth. A match was accepted if the data for these three variables either matched exactly or matched exactly for two and closely for the third.

The observed number of ESRD cases among the silicotic patients was compared with the expected number, after adjustment for age (5-year categories), race (white or nonwhite), gender, and calendar time (5-year intervals). The ratio of observed to expected numbers, the standardized incidence ratio (SIR), was calculated. The expected number of ESRD cases among the silicotic patients was derived by multiplying their person-time at risk by the ESRD rates for the national population, using the NIOSH life-table analysis system (13). NIOSH has developed national ESRD incidence rates using numerator data from the ESRD register data stratified by age, race, gender, and calendar time for the period 1977–1998, and the US population as the denominator.

We used ESRD rates from the entire United States for our comparison rates for convenience, because the overall United States rates were readily available. The rates for the three states in question, New Jersey, Ohio, and Michigan, did not differ greatly from each other or from the overall United States rates, and therefore this procedure was justified. New Jersey, Ohio, and Michigan had 1977 ESRD rates of 326, 303, and 293 per million, respectively, while the 1997 ESRD rate for the United States as a whole was 296 per million. A population-weighted average of the rates of the three states in 1997 was 306 per million, a number similar to the overall United States rate.

In the life-table analyses, person-time ended on 31 December 1998, date of death, or date of ESRD diagnosis, whichever was earlier; 1998 was the last date for which the silicosis registers were considered complete. Death data for the cohort were available from the silicosis registers and were presumed to be relatively complete. In the Michigan and Ohio registers the national death index was used to ascertain vital status, while New Jersey linked its silicosis register records with New Jersey death certificates. Persons not found to have died via these methods were assumed to be alive at the end of the follow-up.

Two different methods of choosing dates on which to begin person-time calculations were used. The hypothesis of this study was that silicotics had relatively high exposure to silica and were thought to be at risk of renal disease as of their date of first exposure to silica (not date of silicosis diagnosis). Therefore, in our first method of analysis, person-time at risk began after either (i) 1 January 1977, the beginning of

the ESRD register, or (ii) the date of first exposure, whichever came later — 97% of the workers had begun work involving silica exposure prior to 1977. Workers were included only if they had a work history with valid dates of beginning and ending exposure. This criterion led to the exclusion of 20% of the cases (336 of 1664).

Some subjects with silicosis may have died from renal disease before they had a chance to be entered into a silicosis register and, thereby, were ineligible for the study — possibly resulting in a type of "survivor" selection bias that would underestimate the ESRD risk for silicotics. Therefore, we also conducted a second analysis assuming that person-time began at the time of entry into the silicosis register, rather than on the date of first exposure to silica. All three registers had computerized data for only the year of entry, rather than the exact date of entry, although exact dates were available in the raw data. For the purposes of this analysis we assumed a date of January 1 for entry into the silicosis register. The average year of entry into a silicosis register was 1991. For several ESRD cases that occurred in the same year as entry into a silicosis register, we sought the exact date of entry into the silicosis register by manually searching the database and included or excluded the cases in the second analysis based on whether their ESRD data was subsequent to or preceded by entry into the silicosis register.

Table 1 gives the number of silicotic patients by state with some descriptive statistics. This is an older cohort with high mortality (58%). Workers had an average of 27 years of exposure. However, the cohort as a whole had relatively few person-years at risk (23 945), largely because person-time could not begin before the ESRD registry data in 1977 (analysis method 1).

Most (79%) of the cases in the Michigan register had been exposed in iron foundries, and 26% said they had done sandblasting as part of their work (11). Most had begun work in the 1930s and 1940s and had worked for over 25 years with silica exposure. Regarding severity, 69% had simple silicosis, and 25% had progressive massive fibrosis. Only 3% had normal chest radiographs with biopsy evidence. Air sampling was conducted in 48 workplaces still in operation and located in Michigan; exposure exceeded the NIOSH recommended standard (0.05 mg/m^3) in 30 (63%) of the 48.

Most of the cases in the New Jersey register were identified in the vitreous plumbing fixture industry (30%) (14). Other industries with the larger percentage of cases were the foundry industry (21%), the ceramic tile industry (11%), sand and gravel mining (11%), iron ore mining (10%), and porcelain electrical supplies (10%). Data on silicosis severity were not routinely available from New Jersey.

Ohio cases were largely comprised of people exposed while working in foundries (45%) or in the production of stone, clay, and concrete (23%); 22% indicated they had performed at least some sandblasting. Twenty of the 29 worksites where registry staff conducted air monitoring had samples that exceeded the NIOSH recommended exposure limit for silica. Data on silicosis severity were not routinely available from New Jersey.

Results

Table 2 gives the results of the life-table analysis for our first analysis in which person-time began at the time of first exposure or at the beginning of the ESRD register (1977), whichever was later. The standardized incidence ratio (SIR) for ESRD was not elevated, on the basis of 12 observed cases (SIR 0.77, 95% Cl 0.40–1.35). A separate analysis of glomerular nephropathy showed a twofold elevation, based on only four cases (SIR 2.65, 95% CI 0.56–5.25). The results of an analysis of the trend by duration of exposure for all cases of ESRD combined were not remarkable (SIR 1.06, 0.71,

Table 1. Confirmed silicosis cases from the three state registers included in the analysis [a]

	N	%	Mean	SD
Michigan	777	59	·	·
New Jersey	256	19	·	·
Ohio	295	22	·	·
Total	1328	100	·	·
Male	1288	97	·	·
White	905	68	·	·
Died during follow-up	764	58	·	·
Year first exposed	·	·	1947	13
Year last exposed	·	·	1974	15
Year of entry to silicosis registry	·	·	1991.1	6.7
Year of death for decedents	·	·	1992	5
Year of birth	·	·	1922	15
Years since first exposure to end of follow-up	·	·	48	13

[a] Workers were included only if they had a work history with valid beginning and ending dates (minimally, a valid year required); this requirement excluded 20% of the potentially eligible cohort.

Table 2. Standardized incidence ratios (SIR) for end-stage renal disease among silicotics. (95% CI = 95% confidence interval)

State	Observed (N)	Expected (N)	SIR	95% CI
New Jersey	4	2.51	1.59	0.43–4.07
Michigan	7	10.38	0.67	0.27–1.38
Ohio	1	2.74	0.36	0.01–2.00
Total	12	15.63	0.77	0.40–1.35

1.03 and 0.53 for <10 years, 10–19 years, 20–29 years, and ≥30 years of exposure, respectively). The data on glomerular ESRD were too sparse for the trends to be analyzed meaningfully.

Our second analysis, in which we assumed that person-time began at the date of entry into the silicosis register, rather than on the date of first exposure to silica or the date that the ESRD rates were first available (1977), yielded a rate ratio for all ESRD of 1.67 (95% Cl 0.76–3.17) on the basis of nine observed cases. For glomerular disease the rate ratio was 4.19 (95% Cl 0.50–15.13), on the basis of only two cases.

Discussion

Silicosis is known to be the result of high exposure to silica (15). Furthermore, high silica exposure has been linked to renal disease in some studies in recent years (1–7), including one study (8) of the same Michigan silicotics included in our study, which found excess subclinical disease (high serum creatinine in a case-referent study). Therefore it is somewhat surprising that our study of silicotics did not find an overall excess of ESRD with our first method of analysis, in which person-time began at the time of first exposure or in 1977, when the ESRD register began. The median age of death of ESRD patients in the United States is 63 years (12), but the median age of entry into the silicosis registers studied is 69 years. Therefore, some subjects with silicosis may have died due to their renal disease before they had a chance to be entered into the silicosis registers, the result being a type of selection bias. Our second analysis, in which we assumed that person-time began at the time of entry into the silicosis register, resulted in a rate ratio for all ESRD of 1.67 (95% CI 0.76–3.17).

Even using our first method of analysis, we found a twofold excess of glomerular disease (again on the basis of small numbers, only 4 cases), which has been the main type of kidney disease associated with silica exposure in the literature. In this respect our data are in fact consistent with prior reports.

In conclusion, our results do not clearly show that silicotic patients have an excess of ESRD, although they do suggest an excess of glomerular ESRD. The analyses were limited by the small numbers and possible selection biases.

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