Silicosis and Chronic Renal Disease

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Background *Silica has been associated with end stage kidney disease and kidney dysfunction.*
Methods *Calculated glomerular filtration rate, history of kidney disease or chronic dialysis, elevated serum creatinine, and stages of chronic kidney disease among silicotics identified in Michigan's Silicosis Surveillance System from 1987 to 2009 were reviewed to determine the prevalence of kidney disease in confirmed cases of silicosis.*
Results *Twenty-four percent of 1,072 silicotics had a measure of kidney dysfunction (32.3% if diabetes or hypertension present vs. 20.2% if not). Sixty-nine percent of silicotics had Stage I or greater chronic kidney dysfunction versus 38.8% of the U.S. general population ≥60 years. No association was found between kidney function and measures of silica exposure.*
Conclusions *Individuals with silicosis have an increased prevalence of kidney disease. More work to define the pathological changes associated with silica exposure is needed to understand the cause of silica's adverse effect on the kidney.* Am. J. Ind. Med. 58:730–736, 2015. © 2015 Wiley Periodicals, Inc.

KEY WORDS: silicosis; renal disease; silica

INTRODUCTION

Silicosis, a type of interstitial pulmonary fibrosis, is the disease most commonly associated with silica exposure. Workers with exposure to silica are at risk of developing other conditions besides silicosis including COPD, lung cancer, tuberculosis, connective tissue disease, and kidney disease [OSHA, 2010]. There is no single renal pathology; silica-induced nephropathy has been associated with both glomerular and tubular dysfunction. The hypotheses for the pathophysiology of silica's effect on the kidney include either a direct toxic effect on the kidney or as an adjuvant to enhance an immunologic mechanism [Ghahramani, 2010]. Data on kidney disease among individuals in Michigan's population-based silicosis registry for the years 1987–1995 have previously been reported [Rosenman et al., 2000]. This paper extends the observations from the previous publication by reporting on kidney disease among individuals in the registry through 2009.

METHODS

Michigan has had a surveillance program for silicosis since 1987. The system has been based on the state's public health code that requires employers, hospitals, clinics, and physicians to report all known or suspected occupational diseases. Other sources used to identify individuals with silicosis were death certificates and claims awarded by the State Silicosis, Dust Disease, and Logging Industry Compensation Fund.

When a report was received, a standard telephone questionnaire was administered by a trained interviewer to the individual, or if deceased, to the next-of-kin. The interview took approximately 30–45 min and consisted of a

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lifetime work history, cigarette smoking history, medical history, medication history, and symptom history limited to respiratory conditions. Medical records obtained include the history and physical at time of hospital admission, discharge summaries, pulmonary function testing results, laboratory data, the most recent chest radiograph, and outpatient progress notes. A physician who was board-certified in both internal and occupational medicine reviewed each patient's information. All chest X-rays were reviewed by the same physician who is a NIOSH certified "B" reader, and therefore, has special training and accreditation to interpret chest radiographs for all pneumoconioses, including silicosis. A person was considered to have silicosis if there was: (i) a history of exposure to silica; and (ii) a chest radiograph interpretation showing rounded opacities of 1/0 or greater profusion involving at least one upper lung zone per the International Labor Office (ILO) classification system for pneumoconiosis, or a biopsy report of lung tissue showing the characteristic silicotic nodule.

Kidney disease was identified and recorded as present if the medical records indicated: history of renal failure, chronic kidney disease, renal insufficiency, glomerulonephritis, end-stage renal disease, or the patient was on dialysis. Kidney disease was not recorded as present if the following were mentioned: acute renal failure, nephrolithiasis, or past history of pyelonephritis. The most recent serum creatinine value (SCr) and urinalysis values were recorded if they did not occur during an episode of known acute renal failure. Albuminuria was defined as a urinalysis with protein greater than 30 mg/dl. Any value less than 30 mg/dl was considered normal. We were unable to distinguish between micro and macro albuminuria since the definition requires the calculation of the urinary albumin-to-creatinine ratio and we did not routinely have urine creatinine values. The presence of hypertension and/or diabetes was noted if either diagnosis was recorded in the available medical records.

Glomerular filtration rate (GFR) is considered the best overall index of kidney function. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend using creatinine-based equations for estimating GFR to identify patients with potential kidney disease [National Kidney Foundation, 2002; Poggio et al., 2005]. We calculated GFR in all of the cases with an available serum creatinine and age value. The equation utilized to estimate the GFR was the abbreviated Modification of Diet in Renal Disease (MDRD) equation [Levey et al., 1999]:

$GFR = 186 \text{ X } [SCr]^{-1.154} \text{ x } [Age]^{-0.203} \text{ x } [0.742$ if patient is female] x [1.212 if patient is black] Age = age the SCr was recorded, SCr = serum creatinine (mg/dl)

We considered using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as there is data indicating it is a more accurate predictor of creatinine clearance than the MDRD [Stevens et al., 2010]. However, the GFR data in NHANES, which we used as our referent data, were calculated using the MDRD equation [Levey et al., 1999].

The calculated GFR was used to define stages of Chronic Kidney Disease (CKD) according to the classification system established by the National Kidney Foundation KDOQI as follows: stage 1, persistent albuminuria with estimated GFR >90 ml/min/1.73 m^2; stage 2, persistent albuminuria with estimated GFR of 60–89 ml/min/1.73 m^2; stage 3, estimated GFR 30–59 ml/min/1.73 m^2; stage 4, estimated GFR 14–29 ml/min/1.73/m^2 [Stevens et al., 2006]. Presence of persistent albuminuria is required to classify individuals in stage 1 or stage 2. Since we generally had urine results from a single urine specimen, we used the same approach as used for the NHANES data to estimate that 50.9% of all individuals with albuminuria at a single visit had persistent albuminuria for those with an estimated GFR of ≥90 ml/min/1.73 m^2; and 75% of those with albuminuria at a single visit had persistent albuminuria at an estimated GFR of 60–89 ml/min/1.73 m^2 [Coresh et al., 2007]. The resulting proportion with estimated persistent albuminuria was used in combination with GFR ≥90 ml/min/1.73 m^2 to define CKD stage 1 and with GFR 60–89 to define those with CKD stage 2. Additionally, the estimated GFR was stratified on GFR alone using the following qualifiers: normal (>90), mildly reduced (60–89), moderately reduced (30–59), and severely reduced (15–29) since this was the procedure used in the NHANES data, which were used as the reference population [Castro et al., 2009].

Renal dysfunction was defined as an abnormal result on at least one of the following four parameters: an estimated GFR less than 60 ml/min/1.73 m^2; a serum creatinine value greater than 1.5 mg/dl; chronic dialysis treatment; or a diagnosis of prior kidney disease in the medical record.

We evaluated kidney function in those with and without diabetes and hypertension. We assessed whether there was a relationship between renal dysfunction and surrogate measures of silica exposure: duration of silica exposure; history of sandblasting; and radiographic profusion.

Logistic regression procedures were used to determine the effects of risk factors that include age, smoking, diabetes, hypertension, and duration of silica exposure on renal dysfunction and CKD stage as defined previously. Tests were conducted for a single binomial proportion in order to compare our study population to three reference populations limited to individuals ≥70 years of age.

The SAS statistical package (version 9.4) and EpiInFo were used to calculate Chi squares, odds ratios, and the presence of statistical trends.

This activity was approved by the Michigan State University Human Research Protection Program, which determined signed informed consent was not required.

RESULTS

Data was abstracted from 1,072 confirmed cases of silicosis identified from 1987 to 2009. This includes 583 individuals with confirmed silicosis from our original report and 497 confirmed cases from the more recent time period. The demographics of this study population are recorded in Table I. Serum creatinine values were available for 564 cases. The only statistical difference between individuals with and without a serum creatinine (SCr) value was that more individuals with a SCr value had progressive massive fibrosis. The calculated GFR values are categorized in Table II. Only 22.6% of the cohort had a normal GFR, 21.0% if they had diabetes or hypertension and 25.5% if they had neither (Normal GFR; diabetes or hypertension vs. those without, $P = 0.24$). A total of 159 (28.2%) individuals had elevated SCr values ($\geq$1.5 mg/dl). Of the total 1,072 confirmed silicosis cases, 121 (11.3%) of the medical records mentioned the presence of kidney disease. This included eight (0.7%) individuals who were on dialysis. There were a total of 207 (19.3%) individuals who either had medical records that indicated kidney disease or had an elevated serum creatinine and 253 individuals who either had medical records that indicated kidney disease, an elevated serum creatinine, or had a GFR <60 ml/min/1.73 m^2 (Table III). Individuals with diabetes or hypertension were more likely to have some indication of kidney dysfunction (32.3% vs. 20.2%, $P = 0.00002$) and were more likely to have a GFR <60 ml/min/1.73 m^2 ($P = 0.004$). Analysis of risk factors (age, smoking status, diabetes, hypertension, and duration of exposure) for the aforementioned indicators of renal dysfunction revealed increasing age as being significant ($P < 0.01$, OR 2.07, 95%CI 1.23–3.50).

The stages of CKD are reported in Table IV in comparison to the general population 60 years of age or older. Of those with GFR $\geq$90 ml/min/1.73/m^2, 7.8% were estimated to have persistent albuminuria and therefore categorized as CKD stage 1. Of those with GFR 60–89 ml/min/1.73/m^2, 12.8% were estimated to have persistent albuminuria and categorized as CKD stage 2. In comparison to the general population sample, individuals with silicosis were more likely to have CKD stage 3, 4, or 5 whether or not they had diabetes or hypertension (Table IV). Since the mean age of those with silicosis who had creatinine levels to calculate CKD was 73.4 years, we compared the prevalence of CKD stages 3–5 among those with silicosis versus three reference populations limited to $\geq$70 year olds (Table V). As with indicators of renal dysfunction mentioned above, increasing age was the only risk factor significantly associated with CKD (normal vs. stages 3–5 combined) stage in this population ($P < 0.01$, OR 2.45, 95%CI 1.26–4.94).

Table VI shows the summary measure of kidney dysfunction by our three surrogate measures of silica

TABLE I. Characteristics of Total Study Population (n = 1,072) and Those With a Serum Creatinine Value (n = 564)

Characteristics*	Total study population (n = 1,072)	With serum Cr value (n = 564)
Age mean (STD), range	72.3 (11.5), 35–100	73.4 (10.8), 37–97
Duration of silica exposure mean (STD), range	27.4 (11.1), 1–60	27.4 (11.4), 1–60
	# (%)	# (%)
Male—Yes	1049 (97.9)	551 (97.7)
African American—Yes	433 (40.4)	233 (41.6)
Exposure in foundry—Yes	785 (73.2)	414 (73.4)
Exposure-sandblasting—Yes	289 (35.7)	137 (33.5)
Radiograph profusion		
Category 0 (biopsy)	30 (2.9)	14 (2.5)
Category 1	381 (36.6)	161 (29.2)
Category 2	264 (25.4)	148 (26.8)
Category 3	106 (10.2)	55 (10.0)
Progressive massive fbrosis	260 (25.0)	174 (31.5)
Diabetes mellitus (DM) Yes	171 (20.6)	119 (22.4)
Hypertension (HTN) Yes	400 (47.5)	259 (48.2)
DM or HTN Yes	480 (57.0)	315 (58.7)
Cigarette smoking status		
Current	150 (14.2)	74 (13.3)
Ex	620 (58.7)	329 (59.3)
Never	286 (27.1)	152 (27.4)

TABLE II. Stratification by Estimated GFR(Glomerular Filtration Rate) Using the MDRD (Modification of Diet in Renal Disease) Equation Among all Individuals With Silicosis and Those With and Without Diabetes Mellitus (DM) or Hypertension (HTN)

GFR, ml/min/1.73 m^2	All # (%)	HTN or DM # (%)	No HTN or DM # (%)
Normal, $\geq$90	124 (22.6)	65 (21.0)	54 (25.5)
Mildly reduced, 60–89	224 (40.9)	116 (37.5)	96 (45.3)
Moderately reduced, 30–59	160 (29.2)	96 (31.1)	57 (26.9)
Severely reduced, 30–59	30 (5.5)	23 (7.4)	4 (1.9)
ESRD*, <30	10 (1.8)	9 (2.9)	1 (0.5)
Total	548	309	212

*ESRD, end stage renal disease.

exposure. There was no association between increased duration, more severe radiograph findings or history of sandblasting, and the occurrence of kidney dysfunction.

DISCUSSION

In this cohort of individuals with silicosis, 23.6% had an indication of renal dysfunction based on an elevated serum creatinine, listing of kidney disease in the medical record, or a GFR less than 60 ml/min/1.73 m^2 (Table III). Based on creatinine levels and presence of albuminuria, 69% were classified as having chronic kidney disease stage 1 through 5 as compared to 38.8% ($P < 0.0001$) of a random sample of the general population $\geq$60 years (Table IV). Hypertension and diabetes are both risk factors for renal dysfunction. The prevalence of chronic kidney disease was greater if the individual with silicosis also had hypertension or diabetes (32.3 vs. 20.2%, OR = 1.89, 95%CI 1.37–2.58, $P = 7 \times 10^{-5}$, Table III and 73.4% vs. 61.1%, OR = 1.67, 95%CI 1.01–2.74, $P = 0.04$, Table IV). Even accounting for the presence of DM and HTN, individuals with silicosis were found to have a higher prevalence of renal dysfunction compared to the general population (60.1% vs. 38.8%, $P <$ 0.0001, Table IV). This difference was due to individuals with silicosis having a greater prevalence of severe kidney dysfunction, chronic kidney disease Stage 3, 4, or 5, as compared to a sample of the general population $\geq$60 years. These findings are consistent with our previous publication based on individuals identified with silicosis from 1987 to 1995 [Rosenman et al., 2000]. In our previous analysis, we used a serum creatinine $\geq$1.5 mg/dl rather than stage of chronic kidney disease as the measure of kidney dysfunction. This update with 14 years' worth of new data shows that individuals more recently diagnosed with silicosis continue to have an increased risk of renal dysfunction. This updated analysis used stages of chronic kidney disease, a more reliable measure of kidney dysfunction than the previous report which used serum creatinine levels. Also in this update both hypertension and diabetes, two of the most common causes of chronic renal disease, were controlled for in the analysis. Case reports, cases series, cohort mortality studies, and case–control studies have found end stage kidney disease and kidney dysfunction to be associated with both silica exposure and silicosis [OSHA 2010; Vupputuri et al., 2012].

As with the analysis of silicosis cases from 1987 to 1995, duration of silica exposure, severity of silicosis, and history of abrasive blasting were not associated with renal dysfunction (Table V). We did know levels of exposure to silica and used these surrogate measures as markers of cumulative exposure (i.e., duration and severity of silicosis) and a marker of cumulative and peak exposure (i.e., sandblasting). The lack of association with severity of silicosis is consistent with studies that have reported an association between chronic kidney disease and silica

TABLE III. Prevalence of Renal Dysfunction by Various Indices/Measures Among all Individuals With Silicosis and Those With and Without Diabetes Mellitus (DM) or Hypertension (HTN)

Measure of renal dysfunction	All # (%)	HTN or DM # (%)	No HTN or DM # (%)
Serum creatinine $\geq$1.5 mg/dl	159 (28.2)	107 (34.0)	45 (28.3)
Renal disease noted in medical record	121 (21.0)	90 (30.7)	20 (12.8)
Dialysis	9 (0.8)	8 (1.0)	1 (0.6)
Renal disease or serum creatinine $\geq$1.5 mg/dl	207 (19.3)	139 (29.0)	53 (14.3)
Renal disease or serum creatinine >1.5 mg/dl or GFR* <60 ml/min/1.73 m^2	253 (23.6)	160 (32.3)	75 (20.2)

*GFR, glomerular filtration rate.

TABLE IV. Calculated Chronic Kidney Disease (CKD) Stage Among all Individuals in Study Population With Silicosis and Those With and Without Diabetes Mellitus (DM) or Hypertension (HTN) versus General Population (National Health and Nutrition Examination Survey [NHANES])

CKD stage	All # (%)	HTN or DM # (%)	No HTN or DM # (%)	NHANES* 1999–2006 > 60 years (%)
Normal	97 (31)	54 (26.6)	43 (38.9)	61.2
1	2.5 (0.8)	1.5 (0.8)	1.5 (1.4)	2.3
2	13.5 (4.3)	8.3 (4.4)	2.5 (2.3)	8.4
3	160 (51.1)	96 (51.6)	57 (51.8)	26.3
4 and 5	40 (12.8)	32 (17.2)	5 (4.6)	1.8

All versus NHANES, $\chi^2 = 389, P < 0.0001$; HTN or DM, $\chi^2 = 361, P < 0.0001$; No HTN or DM, $\chi^2 = 45, P < 0.0001$.
*The data reported here have been supplied by the United States Renal Data System (USRDS).

exposure in the absence of the radiographic changes of silicosis [Vupputuri et al., 2012]. In this recent case–control study of individuals with chronic renal disease, however, there was a dose-response to silica exposure estimates based on industrial hygiene evaluation of lifetime work histories [Vupputuri et al., 2012]. In contrast, the absence of an association with years of exposure to silica in our cohort of individuals with silicosis suggests that above an undefined/as-yet undetermined threshold exposure to silica for which radiographic changes occur, there is no dose-response effect. Other relevant studies that have not shown a dose-response effect to silica exposure include those on the occurrence of auto immune antibodies [Sanchez-Roman et al., 1993], those on the increased risk for connective tissue disease [Makol et al., 2011] and those on the increased risk for p-ANCA vasculitis in silica-exposed individuals [Gomez-Puerta et al., 2013]. We have previously reported the prevalence of ANCA vasculitis in this cohort was 0.8% based on six cases. The relative risk was 25.3 (95%CL 6.3–101.0) in comparison to a reference population [Makol et al., 2011]. Anti-nuclear cytoplasmic antibody (p-ANCA) as well as ANCA-associated vasculitis has been reported to be elevated in individuals with silica exposure in the absence of silicosis [Gomez-Puerta et al., 2013]. Further work evaluating particular genes may prove useful for identifying individuals who are at increased risk of adverse renal and/or autoimmune effect from silica exposure. Also, other than ANCA-associated vasculitis, there are no specific clinical or pathological changes that have been associated with silica exposure. Further work to either identify specific changes in urine parameters [Ibraham KS et al., 2010] or pathology is needed to better understand the epidemiologic association noted between silica and kidney dysfunction.

The limitations of this study include the lack of complete medical records, lack of serial laboratory values, and lack of calibration among the serum creatinine values, which were obtained from medical records from multiple hospitals. The medical records were collected over 20 years from Michigan's 136 hospitals. Over half the medical records we reviewed were missing serum creatinine levels. Hospitals are required to submit the discharge summary, chest radiograph, radiograph report, and breathing test results. Many hospitals submit additional records including results of laboratory tests. Creatinine values were obtained either from copies of the laboratory results or the discharge summary. It is possible that a creatinine value was more likely to be recorded in the discharge summary if it was elevated. A second factor that may limit the generalizeability of our results to all individuals with silicosis is that our data source for identifying individuals with silicosis was mainly hospital discharge data (77%), and morbidity from kidney disease may have increased the likelihood of hospitalization. Previous capture–recapture analysis of the Michigan surveillance system has estimated the system misses from 59–81% of the cases of silicosis that occur in the state [Rosenman et al., 2003]. These missed cases would be non-

TABLE V. Calculated Chronic Kidney Disease (CKD) Stages 3–5 Among all Individuals With Silicosis and Those With and Without Diabetes Mellitus (DM) or Hypertension (HTN) versus Three References Populations of Individuals ≥70 years in a 5% Sample of Veteran's Administration Patients, Enrollees in a Michigan Managed Care Group and NHANES, 2005–2006

CKD stage	All # (%)	HTN or DM # (%)	No HTN or DM # (%)	5% VA sample ≥70 (%) (95%CI)	MI managed care group ≥70 (%) (95%CI)	NHANES 2005–2006 ≥70 (%) (95%CI)
3–5	200 (63.9)	128 (68.8)	62 (56.4)	29.9 (29.6–30.2)	13.2 (8.1–18.3)	38.9 (34.7–43.1)

All versus 5% VA Sample >70, $P < 0.0001$; All versus MI Managed Care Group >70, $P < 0.0001$; All versus NHANES, $P < 0.0001$; HTN or DM versus 5% VA Sample >70, $P < 0.0001$; HTN or DM versus MI Managed Care Group >70, $P < 0.0001$; HTN or DM versus NHANES, $P < 0.0001$; No HTN or DM versus 5% VA Sample >70, $P < 0.0001$; No HTN or DM versus MI Managed Care Group >70, $P < 0.0001$; No HTN or DM versus NHANES, $P < 0.0001$.

TABLE VI. Number/Percent With Renal Disease or Serum Creatinine >1.5 mg/dl or GFR (Glomerular Filtration Rate) <60 ml/min/1.73 m^3 Among all Individuals With Silicosis and Those With and Without Diabetes Mellitus (DM) or Hypertension (HTN) by Measures of Silica Exposure or Severity of Silicosis

Renal disease or serum creatinine >1.5 mg/dl or GFR <60 ml/min/1.73 m^3

	No DM or HTN		DM or HTN		All	
Duration of silica exposure (years)	#	%	#	%	#	%
1–9	9	23.1	7	23.3	18	21.7
10–19	6	13.0	19	30.0	28	20.1
>20	58	21.2	118	33.9	188	23.7
Radiograph profusion	#	%	#	%	#	%
Category 0, biopsy positive	2	25.0	5	55.6	6	37.5
Category 1	22	19.6	60	35.9	70	25.8
Category 2	19	20.7	40	33.9	58	28.6
Category 3	6	15.8	19	36.5	25	28.1
PMF	24	22.4	33	26.7	56	24.8‘
History of sandblasting	#	%	#	%	#	%
No	42	22.0	86	37.6	132	25.3
Yes	19	19.4	28	24.6	53	18.3

hospitalized cases. A final limitation is that this is a cross-sectional study and we cannot determine if the diagnosis of hypertension was a risk factor or a consequence of renal dysfunction.

The results of this study continue to support the findings that the adverse effects of silica are not limited to the respiratory system. This study does not directly address the effects of silica on kidney function since all individuals in this cohort by definition had been diagnosed with silicosis. However, proposals to reduce the allowable workplace silica exposure level should have the effect of reducing kidney dysfunction by reducing both silica exposure and the future incidence of silicosis.

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Conflict of Interest: Melissa L. Millerick-May, Sarah Schrauben, and Mary Jo Reilly declare no competing interests/conflicts of interest. Kenneth D. Rosenman has been an expert witness for patients applying for worker compensation.

Author Contributions: KD Rosenman and MJ Reilly participated in the design of the study. S. Schrauben collected/abstracted data. ML Millerick-May, KD Rosenman analyzed and interpreted the data. All authors participated in the development of initial and subsequent drafts of the manuscript, including approval of the final version to be published.

Ethics Review/Approval: This investigation was approved by the Michigan State University Human Research Protection Program (Biomedical and Health IRB).