End-stage Renal Disease Among Silica-Exposed Gold Miners

A New Method for Assessing Incidence Among Epidemiologic Cohorts

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Objective.—To examine the association between silica exposure and end-stage renal disease (ESRD).

Design.—Retrospective cohort study.

Participants.—A cohort of 2412 white male gold miners was studied. Eligible gold miners worked underground for at least 1 year between 1940 and 1965 in a South Dakota gold mine and were alive on January 1, 1977. Of primary interest was exposure to silica.

Methods.—The ESRD Program Management and Medical Information System (PMMIS) was used to identify members of the gold mine cohort who had treated ESRD and to create a US rate file for treated ESRD. The ESRD incidence among the gold miners was compared with that in the US population.

Results.—Based on the 11 cohort members identified with treated ESRD, the risk for ESRD in the cohort was elevated (standardized incidence ratio [SIR], 1.37; 95% confidence interval [CI], 0.68-2.46). The risk was greatest for nonsystemic ESRD (ESRD caused by glomerulonephritis or interstitial nephritis) for which the SIR was 4.22 (95% CI, 1.54-9.19), increasing to 7.70 (95% CI, 1.59-22.48) among workers with 10 or more years of employment underground.

Conclusions.—To our knowledge this is the first epidemiologic study to examine ESRD incidence in an occupational cohort. This study provides evidence that silica exposure is associated with an increased risk for ESRD, especially ESRD caused by glomerulonephritis. This study also demonstrates the usefulness of the ESRD PMMIS to assess ESRD risk among cohorts exposed to potential nephrotoxins.

JAMA. 1997;277:1219-1223

THE HUMAN and economic costs of end-stage renal disease (ESRD) are enormous. In 1993, approximately 57 000 new cases of treated ESRD were identified, producing an adjusted incidence rate in the United States of 21 per 100 000.[1] Since the late 1980s the incidence rate has been increasing approximately 9.8% per year.[1] In 1993, approximately 257 000 prevalent cases were being treated for ESRD under the Medicare program at an annual treatment cost of approximately $8.3 billion. Approximately 60% to 80% of ESRD patients treated with dialysis die within 5 years, and quality of life during these years is sharply diminished.

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Diabetes and hypertension are the leading causes of ESRD, and several other diseases are also recognized as causes of ESRD (eg, systemic lupus erythematosus, systemic sclerosis, amyloidosis).[1] End-stage renal disease among individuals with one of these conditions is called systemic ESRD (or secondary ESRD). End-stage renal disease caused by either glomerulonephritis or interstitial nephritis is called nonsystemic ESRD (or primary ESRD). Of all incident cases of treated ESRD, 12% are caused by glomerulonephritis and 3% are caused by interstitial nephritis.[1] In most cases, the etiology of nonsystemic ESRD is unknown.[2] Whether ESRD is systemic or nonsystemic, it is hypothesized to have a multifactorial etiology involving complex interactions between systemic diseases, toxins, nutritional status, and genetic susceptibility.[3]

Little is known about the etiologic role of occupational and environmental exposures in the development of renal disease. The only compounds widely accepted to be nephrotoxins are lead and cadmium.[3] However, the National Institute for Occupational Safety and Health (NIOSH) lists kidney damage as one of the adverse health effects associated with human exposure to 40 different compounds.[4]

To address the need for research into the etiologic role of occupational exposures for ESRD, we report the first study of ESRD incidence in an occupational cohort. The method used to assess the risk for ESRD involves the comparison of incidence rates of treated ESRD in the cohort with those of the US population. Using this new method, we examined the risk of ESRD among a cohort of gold miners exposed to silica. The workers in this study consist of a subcohort of the cohort studied by Steenland et al.[5]

The evidence for the nephrotoxicity of silica continues to mount. Case reports of workers with heavy silica exposure have described the presence of glomerulonephritis,[6-12] and case series of silicotic individuals have found high proportions with glomerular alterations.[13,14] In addition, 2 case-control studies have observed an association between silica exposure and renal failure.[15,16] Finally, 2 mortality studies of gold mine cohorts found significantly elevated risks for renal disease[5,17]; however, 4 other mortality studies of silica-exposed cohorts did not find significantly elevated risks for renal disease.[18-21]

METHODS

The ESRD PMMIS Database

The ESRD Program Management and Medical Information System (PMMIS) was used to identify which members of the NIOSH gold miners cohort had treated ESRD and to create a treated ESRD rate file for the United States. The ESRD PMMIS database is maintained by the Health Care Financing Administration (HCFA) and contains information on every individual with ESRD who received Medicare-covered renal replacement therapy (dialysis or transplant) in 1977 or later. Approximately 92% of ESRD patients have Medicare insurance and are therefore included in the ESRD

Table 1.—Major and Minor Subclassifications for End-stage Renal Disease (ESRD)

Systemic ESRD
Diabetes mellitus
Hypertension
Cystic nephropathy
Obstructive nephropathy
Collagen vascular disease
Malignancy
Metabolic disease
Hereditary and congenital nephropathy
Sickle cell disease
Acquired immune deficiency syndrome
Nonsystemic ESRD
Glomerulonephritis
Interstitial nephritis
Other
Unknown

PMMIS.[1] Individuals treated for ESRD who may not be included in the ESRD PMMIS include (1) persons or dependents not eligible under the Social Security Act; (2) persons younger than 65 years who are not otherwise covered by Medicare and who die before Medicare eligibility would begin (60 to 90 days after commencing chronic dialysis); (3) Medicare-ineligible persons who were treated by US Department of Veterans Affairs hospitals before 1990; and (4) persons who were treated by military hospitals.

Data from the ESRD PMMIS are considered complete back to January 1, 1977, and include the name of every individual who received ESRD benefits from Medicare since 1977 (ESRD cases who die are never purged from the system). Data available from the ESRD PMMIS include name, Social Security number, race, sex, date of birth, date of death, disease causing the ESRD, type of treatment received, and the first service date for ESRD (which was used as a surrogate for date of onset of ESRD).

In general, the ESRD PMMIS is available only to US government researchers in the US Department of Health and Human Services (DHHS). A similar file that contains no patient identifiers is maintained by the US Renal Data System (USRDS). Information on how to obtain USRDS data from the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease can be found in the USRDS annual report.[1]

Creation of a Rate File

To compute the expected incidence of treated ESRD in the United States, a rate file was created to establish specific ESRD incidence rates for race, sex, and 5-year age intervals and calendar time intervals, as described below. Rates were also determined for each of the major (systemic ESRD, nonsystemic ESRD, other, and unknown) and minor (specified in Table 1) subclassifications of ESRD.

Race was dichotomized into white and nonwhite (African American, Native American, and Asian American). The Native American and Asian American race categories were not used by HCFA before 1981 and are significantly underreported before 1982.[1] Therefore, the dichotomization of race into white and nonwhite was required so that race categories would be consistent from 1977.

Rate File Numerator.—For each specific group (sex, race, 5-year age intervals, and calendar time intervals), the number of incident treated ESRD cases occurring among US residents was abstracted from the ESRD PMMIS. When possible, these data were summed over 5-year calendar intervals (1980-1984, 1985-1989). Because systematic collection of data did not begin until 1977, data from 1977 to 1979 were multiplied by 1.67 to create the 5-year numerator for the period 1975 to 1979. Due to delays in reporting ESRD, complete data for a given calendar year are not available for many months after the end of that calendar year. Because our data file was obtained from HCFA in February 1994, it was considered complete through 1992. Therefore, data from 1990 to 1992 were multiplied by 1.67 to create the 5-year numerator for the period 1990 to 1994.

Rate File Denominator.—The denominators were estimates of age-specific, race-specific, and sex-specific US populations on July 1 of the midyear of the calendar period. These estimates were taken from US Census Bureau estimates (July 1977, July 1982, July 1987, and July 1992) available in the NIOSH life table program.[22]

Rate.—For each race-specific, sex-specific, and age-specific stratum, the total number of cases of treated ESRD in each time period was divided by 5 to obtain an annual average. These averages were divided by the midpoint population for the corresponding time period to obtain stratum-specific ESRD incidence rates for the US population.

The NIOSH Gold Miner Cohort

Details on the NIOSH gold miner cohort are available elsewhere.[5] In summary, the cohort was assembled from a South Dakota gold mine. White male employees who had worked underground for at least 1 year between 1940 and 1965 were eligible for the study. Only those gold miners alive as of January 1, 1977, are included in this study because it is from this date that the ESRD PMMIS data are considered to be reliable. Vital status was ascertained via the National Death Index and Social Security, with the latter source searched through December 31, 1992. Only 2% of the cohort was lost to follow-up.[5]

Most of the cohort (52%) was first employed in 1950 or earlier. Silica exposures are estimated to have exceeded the current Occupational Safety and Health Administration Permissible Exposure Limit (OSHA PEL) in the years prior to 1951 but were below the current OSHA PEL after dust controls and work-practice changes were implemented in the early 1950s.[23] The silica content of respirable dust was estimated at 13% in a survey in the mid 1970s.[23] The OSHA PEL for respirable dust is (10 mg/m^3)/[(% crystalline silica)+2], which in the gold mine under study is equivalent to 0.09 mg/m^3 respirable silica.[24] Average silica dust levels prior to 1951 ranged from 0.1 to 0.25 mg/m^3, indicating substantial silica dust levels during this time period. After 1950, average silica dust exposures ranged from 0.02 to 0.1 mg/m^3. Silica was measured in millions of particles per cubic foot (mppcf) and converted to mg/m^3 using a conversion of 10 mppcf of respirable dust=0.1 mg silica/m^3.[5]

A job-exposure matrix was created to estimate dust exposures over time for each job in the mine. All full-time underground jobs were assembled into 5 major groups (laborers, miners, motormen, supervisors, and skip loaders) based on similarity in job function and dust exposure. A sixth category grouped all jobs not considered full-time underground jobs; these jobs were considered nonexposed. Average dust exposures for the job categories were then calculated using existing measurements for each year from 1937 to 1975. The gold mine operated from the early 1900s; exposures prior to 1937 were estimated at 0.25 mg/m^3 by industrial hygienists familiar with early mine conditions. No job history data were collected after 1975. Although the mine continued to operate after 1975, exposure levels were low and only 14% of the eligible cohort was employed underground after 1975. Thus, there is little underestimation of cumulative exposure by ignoring exposures after 1975.

The estimated daily dust exposures (constant over yearly intervals) for each of the 5 job categories were weighted (multiplied) by a factor estimating how much daily time was spent underground by workers in these jobs; a factor of 1 was assigned to work done in the 1920s, decreasing in later years.[23] For each underground worker, estimated dust levels were summed over time, and the resulting measure was used as the estimate of cumulative exposure.

Underground exposures also included nonasbestiform mineral fibers, low levels of arsenic, and low levels of radon.[5] There is no evidence that exposure to nonasbestiform minerals is associated with renal damage in humans. As for arsenic, acute poisoning with this element is associated with renal injury (acute tubular

necrosis[25,26]); however, there is no evidence that chronic, low-level arsenic exposure, as experienced by the gold miners, is associated with renal effects. Finally, although renal failure has been observed among patients receiving therapeutic radiation,[27] there is no evidence that chronic, low-level radon exposure is associated with renal effects. Other airborne contaminants such as carbon monoxide, methane, nitrogen dioxide, total hydrocarbons, benzo(a)pyrene, and total aldehydes were identified in the mine but only in negligible quantities.[28]

The mine also had an aboveground metallurgical department where the gold was extracted from the ore. Approximately 10% to 15% of all mine employees worked in this department. Some of the metallurgical department workers had the potential for exposure to inorganic lead (approximately 25%) and metallic mercury (approximately 5%).[29] Because the study cohort was originally assembled to examine mortality in the cohort of underground miners, work histories for the metallurgical department were not obtained.

Standardized Incidence Ratio Analyses

The NIOSH gold miner cohort was linked to the ESRD PMMIS to identify cohort members with treated ESRD. The linkage was by name, Social Security number, and date of birth.

The person-years at risk (PYAR) in the cohort were tallied into 5-year calendar time and age intervals. PYAR measurement combines persons and years of observation. Each cohort member contributes only as many years of observation as the cohort member is observed. The criteria for calculating PYAR was the same as in the original standardized mortality ratio (SMR) study of the cohort,[5] except PYAR did not begin accumulating until January 1, 1977. Miners contributed PYAR until the first service date for those with ESRD, the date of death for deceased miners, the date last observed for those lost to follow-up, or the ending date of the study (December 31, 1992) for miners known to be alive.

The PYAR of persons with ESRD should cease on the date their ESRD began. However, the ESRD PMMIS does not have the date ESRD began. Instead, ESRD PMMIS has a "first service date for ESRD," which generally represents the date on which treatment for ESRD began. Since ESRD is fatal without prompt treatment, the first service date is a reasonable surrogate for the date of onset of ESRD. The ESRD PMMIS derives this date from the first recorded dialysis or transplant date.

The PYAR were stratified into 5-year intervals by age and calendar time and were then multiplied by the appropriate US ESRD incidence rate to calculate the expected number of cases for that stratum. The expected number of ESRD cases in all strata were summed to yield the total expected number. The ratio of observed to expected number of treated ESRD cases is the standardized incidence ratio (SIR). This statistic and its confidence interval (CI) were derived according to the methods of Rothman and Boice.[30] Overall SIRs, as well as SIRs by duration of underground employment and by cumulative silica dust exposure, were calculated employing the modified life table system developed by NIOSH.[22] The tertiles for duration of underground employment and cumulative silica dust exposure were determined a priori and were based on intervals used in the mortality analyses.[5]

Table 2.—Composition of the Gold Miner Cohort as of December 31, 1992

Characteristic	Entire Cohort (n=3332)
Excluded from analysis, No. (%)*	920 (28)
White males, No. (%)	2412 (72)
Year of birth, mean±SD	1923±10.9
Year of first underground employment, mean±SD	1949±9.5
Age at first underground employment, mean±SD, y	25.5±5.9
Duration of underground employment,† mean±SD, y	8.0±8.0
Person-years at risk	30623
Latency <20 y	1945
Latency ≥20 y	28678
1-5 y exposure	17001
≥5 y exposure	13622
<0.22 mg/m³ silica dust exposure‡	18513
≥0.22 mg/m³ silica dust exposure‡	12110

*A total of 919 men died before the study start date (January 1, 1977) and 1 had a missing date of birth.
†Through 1975.
‡Cumulative silica dust exposure.

RESULTS

Of the 3332 white male members of the gold miner cohort, 2412 (72%) were determined to be eligible for this study, providing 30623 PYAR. A total of 920 were excluded because they died before the study start date (January 1, 1977), and 1 was excluded because of missing date of birth. Table 2 provides information on the cohort eligible for analysis. The mean duration of employment underground was 8.0 years, the average year of first underground employment was 1946, and 94% of the PYAR in the study had 20 or more years of latency since first employment underground. The median cumulative silica dust exposure was 0.18 mg/m³-years, the mean was 0.39 mg/m³-years, and the range was 0.008 to 4.32 mg/m³-years. The median intensity of exposure to silica dust was 0.04 mg/m³, and the mean was 0.05 mg/m³ (the current OSHA PEL is 0.09 mg/m³ respirable silica).[24]

Table 3.—Treated ESRD Incidence Among Gold Miners*

Type of Treated ESRD	Observed	SIR (95% CI)
Systemic ESRD	4	0.80 (0.22-2.06)
Diabetes mellitus	2	1.07 (0.13-3.85)
Hypertension	0	. . .
Obstructive nephropathy	1	3.18 (0.08-17.64)
Metabolic disease	1	14.60 (0.37-81.10)
Nonsystemic ESRD†	6	4.22 (1.54-9.18)
Glomerulonephritis†	5	4.27 (1.38-9.98)
Interstitial nephritis	1	3.96 (0.10-22.02)
Unknown	1	1.54 (0.04-8.57)
Total	11	1.37 (0.68-2.45)

*Incidence through December 31, 1992. ESRD indicates end-stage renal disease; SIR, standardized incidence ratio; and CI, confidence interval.
†95% CI excludes the null value.

Table 3 provides the risk for treated ESRD among the gold miner cohort. The risk for treated ESRD in the entire cohort was elevated (SIR, 1.37; 95% CI, 0.68-2.46) and is based on a total of 11 cohort members who were identified with treated ESRD. The risk was greatest for nonsystemic ESRD (ESRD caused by glomerulonephritis or interstitial nephritis) for which the SIR was 4.22 (95% CI, 1.54-9.19) (Table 3). A similar SIR was found when ESRD caused by glomerulonephritis was examined separately (SIR, 4.28; 95% CI, 1.38-10.00). Those with the longest duration of underground employment (10 or more years) had the highest risk for nonsystemic ESRD (SIR, 7.70; 95% CI, 1.59-22.48) (Table 4). We also examined risk associated with cumulative silica dust exposure. A total of 4 cases of nonsystemic ESRD were observed among those with 0.22 to 0.54 mg/m³-years (SIR, 11.05; 95% CI, 3.01-28.30) (Table 4). However, only 1 case of nonsystemic ESRD was observed among those with the highest cumulative silica dust exposures (>0.55 mg/m³-years) (SIR, 3.68; 95% CI, 0.09-28.30).

Of the 11 workers with treated ESRD, 7 died before the end of the study (December 31, 1992). Of the 7 workers who died, only 4 (57%) had renal problems mentioned on the death certificate. On the other hand, when we examined the death certificates of all deceased cohort members who were eligible for this study, we found an additional 28 miners whose death certificate contained a cause of death coded as "chronic renal disease" (chronic glomerulonephritis, nephritis, chronic renal failure, renal failure unspecified, or renal sclerosis), but who were not present in the ESRD PMMIS. To determine if any of these 28 miners had ESRD missed by the ESRD PMMIS, medical records were sought and were successfully obtained for 19 miners (68%). The records for 2 of these miners supported a diagnosis of ESRD. One of these miners with ESRD apparently never received renal replacement therapy and died approximately 3 months

Table 4.—Risk for Treated Nonsystemic ESRD Among Gold Miners by Duration of Employment and Cumulative Silica Dust Exposure*

	No. Observed With Nonsystemic ESRD	SIR (95% CI)
Total duration of underground employment, y		
<5	2	2.59 (0.31-9.36)
5-9.9	1	3.86 (0.10-21.50)
≥10†	3	7.70 (1.59-22.48)
Cumulative silica dust exposure, mg/m³-year		
<0.22	1	1.27 (0.03-7.08)
0.22-<0.55†	4	11.05 (3.01-28.30)
≥0.55	1	3.68 (0.09-20.52)

*ESRD indicates end-stage renal disease; SIR, standardized incidence ratio; and CI, confidence interval.
†95% CI excludes the null value.

after ESRD was detected. He was not identified by the ESRD PMMIS because the ESRD PMMIS only captures individuals who are treated for ESRD. His medical records suggest that his ESRD was caused by recurrent episodes of pyelonephritis. The other individual was diagnosed 1 month before his death with renal systemic sclerosis that rapidly progressed to ESRD. This eldery individual was not identified by the ESRD PMMIS because his hemodialysis was provided in a military hospital. Patients treated in military hospitals are not captured by the ESRD PMMIS. Of the remaining 17 miners for whom medical records were obtained, 12 had chronic renal failure not requiring renal replacement therapy and 5 had acute renal failure.

COMMENT

Little is known about the contribution of toxins in the development of ESRD. There are several reasons for the difficulty in identifying nephrotoxins[3]: the long latency between exposure and onset of chronic renal failure and ESRD (the mean latency observed in this cohort was 36 years), the nonspecific appearance of renal disease once it has become symptomatic, and the occurrence of ESRD in a toxin-exposed individual often being modulated by a complex interaction involving other toxins, diseases, nutritional factors and genetic susceptibility.

To our knowledge, this is the first epidemiologic study to examine ESRD incidence in an occupational cohort, and as such, it is one of the initial efforts in assessing the contribution of toxins in the development of ESRD. The ESRD PMMIS represents a national disease registry for treated ESRD because it is estimated to contain over 90% of the US population treated for ESRD. There are no other diseases for which there is a nationwide registry of cases. This article demonstrates the utility of the ESRD PMMIS in assessing the incidence of treated ESRD among populations exposed to potential nephrotoxins.

This study provides evidence that occupational silica exposure is associated with an increased risk for ESRD. The risk was greatest for nonsystemic ESRD, especially ESRD caused by glomerulonephritis. Cohort members had an average duration of silica exposure of 8 years. Because the median intensity of exposure to silica dust was 0.04 mg/m³, the current OSHA standard of 0.09 mg/m³ may not provide adequate protection against the nephrotoxic effects of silica exposure. Furthermore, although silica exposure was reduced after 1950, the risk for nonsystemic ESRD remained elevated even when only workers first employed underground after 1950 were included in the analysis (SIR, 5.00; 95% CI, 1.03-14.61). The median intensity of silica exposure among this subgroup of workers was 0.02 mg/m³.

Our findings take on additional importance as silica continues to be a highly prevalent exposure among workers in the United States and worldwide. NIOSH estimates that approximately 3 million US workers are exposed to crystalline silica (unpublished data, July 1990). Industries and occupations having the potential for silica exposure include mining, quarrying, tunneling, foundry work, glass manufacture, abrasive blasting, ceramic and pottery production, and cement production. The primary source of silica is quartz. The pervasive distribution of quartz is the primary reason workers are exposed to silica in various occupations.

The mortality study of the gold miner cohort from which our subcohort was drawn also found an association between silica exposure and renal disease.[5] The mortality study (which also included workers who died before 1977) found 11 miners with an underlying cause of death of chronic renal disease (SMR, 1.25; 95% CI, 0.62-2.23).[16] The excess was confined to those hired before 1930 (SMR, 2.91; 95% CI, 1.17-6.00) and among those whose cumulative silica dust exposure exceeded 1.31 mg/m³-years (SMR, 2.77; 95% CI, 1.20-5.46). In contrast, the current study of ESRD incidence was able to detect an increased risk for renal disease among miners with more recent and lower silica exposures. Among the 11 miners with treated ESRD, the earliest year of underground employment was 1937, and the highest cumulative silica dust exposure was 0.77 mg/m³-years. In addition, an increased risk for glomerulonephritis was not identified in the mortality study because this level of detail is not usually present on the death certificate and because any renal diseases that are present on the death certificate are coded into broad, nonspecific renal disease categories. The absence of ESRD subclassification information is an additional limitation of using mortality data to examine ESRD risk. Therefore, the ESRD PMMIS provides investigators with a new, powerful tool to examine the risk of ESRD and its subclassifications in occupational cohorts.

Our study suggests that silica exposure is most associated with ESRD caused by glomerulonephritis. The pathogenesis of this glomerulonephritis is unclear. Several case reports of silica-exposed individuals with glomerulonephritis provide evidence that immunologic injury by immune complex formation may be involved.[6-8,11,12] However, others speculate that the structural alterations present in the glomeruli are due to a direct toxic effect of silica.[9,31] Two other studies provide evidence that silica exposure is associated with glomerulonephritis, but shed little light on the mechanism of the damage.[14,32]

Studies of the subclinical renal alterations present in silica-exposed workers suggest that renal tubular dysfunction appears initially and is followed by glomerular injury.[33,34] This information may be useful for selecting markers of renal injury to be used when screening silica-exposed workers.

It is of interest that of the 7 miners with treated ESRD who were deceased, none had silicosis or any other chronic lung disease listed on the death certificate (the only lung condition listed was *Klebsiella* pneumonitis present on 1 death certificate). The absence of pulmonary involvement has also been observed in other individuals whose renal disease developed after extensive silica exposure.[10] This evidence suggests that renal disease may be the dominant adverse effect among some silica-exposed individuals.

Although there was the potential for lead and mercury exposure in the metallurgical department of the mine, for several reasons it is doubtful that these exposures were responsible for our findings. First, the study cohort was originally assembled to examine mortality in the cohort of underground miners. Although work history information is unavailable for the metallurgical department, it is estimated that only approximately 4% and 1% of the mine employees had the potential for exposure to lead and mercury, respectively. Conversely, all cohort members had exposure to silica dust. Furthermore, hypertensive renal disease and interstitial nephritis are the types of renal disease usually associated with lead exposure.[3] None of the gold miners was found to have ESRD caused by hypertension, and only 1 was found to have ESRD caused by interstitial nephritis. There is little evidence that chronic, low-

level mercury exposure is associated with permanent renal effects. Mortality studies of mercury-exposed cohorts have not found significant elevations for renal disease mortality.[35,36] In addition, in many cases the renal effects from mercury exposure appear to be self-limited and to disappear after removal from exposure.[3,37]

Some limitations of this method should be noted. One possible limitation is that the expected incidence rates generated from the ESRD PMMIS will underestimate the true ESRD incidence rates because the ERSD PMMIS does not include 2 types of ESRD patients: (1) those who do not receive renal replacement therapy, and (2) some non-Medicare patients who receive renal replacement therapy for ESRD. However, because we have no data to suggest that the gold miners differ from the general population with respect to these factors, we would expect the risk estimates from this study to be unbiased.

Another limitation is that the ESRD PMMIS is considered complete only from January 1, 1977. Cohort members who died before this date were excluded from analysis. Because the gold miner cohort is relatively old, approximately 28% of the cohort had to be excluded, thereby reducing the statistical power of the study. Those excluded had a higher mean duration of underground employment (11.6 years) and a higher mean cumulative dust exposure (1.32 mg/m^3-years). Excluding these workers reduced our power to detect elevated risks among those with high cumulative silica dust exposures. This may explain why the greatest risk for nonsystemic ESRD was not found in the group with the highest cumulative silica dust exposures. To circumvent this problem, we redefined the tertiles of cumulative silica dust exposure so that each of the tertiles had a similar number of expected cases of nonsystemic ESRD. When we did this we found that the tertile with the highest cumulative silica dust exposure (cumulative silica dust exposures of 0.30 mg/m^3-years or more) had the highest risk of nonsystemic ESRD (SIR, 8.11; 95% CI, 2.20-20.77; based on 4 cases). The median intensity of silica dust exposure in this tertile was 0.04 mg/m^3.

An additional limitation is that the ESRD PMMIS only identifies individuals with ESRD. This method is not useful for investigating less severe chronic renal failure. Although chronic renal failure involves a progressive and generally irreversible decline in renal function, not all cases of chronic renal failure proceed to ESRD. Chronic renal disease is more common than ESRD (as evidenced in our findings from death certificates). Studies using a less severe outcome (chronic renal disease vs ESRD) may in some instances offer an advantage for uncovering etiologic relationships. Many published case-control studies of glomerulonephritis, for example, have used chronic renal disease as an outcome instead of ESRD.

In conclusion, this study provides evidence that occupational exposure to silica is associated with an increased risk for ESRD. The risk elevation was strongest for ESRD caused by glomerulonephritis. Furthermore, this study found that the current OSHA PEL may not provide adequate protection against the nephrotoxic effects of silica since the median level of exposure of this cohort was below the OSHA PEL. However, small numbers and wide confidence intervals do not allow strong conclusions in this regard. This study also demonstrates the usefulness of the ESRD PMMIS in assessing the incidence of treated ESRD among cohorts exposed to potential nephrotoxins. As such, we plan to use this method to examine the risk of treated ESRD in a number of occupational cohorts previously investigated by NIOSH.

The authors are indebted to David P. Brown, MPH, for his efforts in assembling the original gold miner cohort from which our subcohort was drawn. The authors thank Chris Gersic for her assistance with obtaining medical records on the gold miners.

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