End stage renal disease among ceramic workers exposed to silica

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Abstract

***Objectives*—To evaluate whether ceramic workers exposed to silica experience an excess of end stage renal disease.**

***Methods*—On the basis of a health surveillance programme, a cohort of 2980 male ceramic workers has been enrolled during the period 1974–91 in Civitacastellana, Lazio, Italy. For each worker, employment history, smoking data, and *x* ray film readings were available. The vital status was ascertained for all cohort members. All 2820 people still alive and resident in the Lazio region as in June 1994 were searched for a match in the regional end stage renal diseases registry, which records (since June, 1994) all patients undergoing dialysis treatment in public and private facilities of the region. Expected numbers of prevalent cases from the cohort were computed by applying the rate of patients on dialysis treatment by the age distribution of the cohort.**

***Results*—A total of six cases was detected when 1.87 were expected (observed/expected (O/E)=3.21; 95% confidence interval (95% CI) 1.17 to 6.98). The excess risk was present among non-smokers (O=2; O/E=4.34) and smokers (O=4; O/E=2.83), as well as among workers without silicosis (O=4; O/E=2.78) and workers with silicosis (O=2; O/E=4.54). The risk was higher among subjects with <20 years since first employment (O=4; O/E=4.65) than among those employed >20 years.**

***Conclusion*—These results provide further evidence that exposure to silica dust among ceramic workers is associated with nephrotoxic effects.**

(*Occup Environ Med* 1999;**56**:559–561)

Keywords: ceramics; end stage renal disease; silica; surveillance

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Accepted 8 March 1999

An association between inhalation of silica dust and renal diseases was first suggested on the basis of clinical observations,[1 2] and subclinical signs of nephrotoxicity have been detected both among workers exposed to silica[3 4] and in patients with silicosis.[5] Two mortality studies conducted among granite cutters exposed to silica[6] and gold miners in the United States[7] have indicated an increased risk of death for chronic renal diseases. Two case-control studies have also suggested an association between exposure to silica and end stage renal disease.[8 9] Calvert *et al*[10] have recently reported the results of the first incidence study of gold miners based on the end stage renal disease programme management and medical information system in the United States. They found an association between chronic exposure to silica and development of end stage renal disease in the whole cohort and among workers with the longest duration of underground employment.

The present investigation was specifically designed to replicate the results obtained by Calvert *et al*[10] in a cohort of Italian ceramic workers. As in the gold miners' study, we linked personal data of the cohort members with a population register of patients with end stage renal diseases.

Methods

The ceramic industry located in Civitacastellana (about 16 000 inhabitants, in the Lazio region near Rome) has been one of the leading ceramic production sites in central Italy during recent decades. It employs about 3000 workers in more than 100 factories. Exposure to silica dust has been associated with a high incidence of radiological signs of silicosis among ceramic workers employed in the manufacture of sanitary ware and crockery,[11] with risk estimates consistent with findings of incidence of silicosis among South African[12] and American gold miners.[13]

A programme of health surveillance was set up in 1974 by the Local Health Unit of Civitacastellana. The programme included an annual medical examination and a standard posterioanterior chest *x* ray film for all exposed workers. The films had been classified during the years by a reader at the radiology department according to the International Labour Organisation (ILO) method available at the time of the *x* ray film.[14 15] A total of 231 people in the cohort developed radiological signs of silicosis, at a critical profusion level of 1/1 or more.[11] Employment history and information on smoking was obtained for each subject. The present cohort consists of all 2980 male workers who entered the health surveillance programme during the period 1974–87. Vital status was ascertained from the last municipality of residence and through record linkage with the regional mortality files: 75 subjects died before June 1994, six subjects were lost to follow up, and 79 workers had migrated outside the Lazio region. The remaining 2820 subjects were eligible for the study of end stage renal disease.

In 1994, the Department of Epidemiology, Lazio Regional Health Authority, established a regional end stage renal disease registry to

Table 1 Characteristics of six male ceramic workers with end stage renal disease

Case	Age at first employment	Job	Cumulative exposure to silica (mg/m³/y)	Smoking	x Ray status	Age at diagnosis	Age at start of dialysis	Primary renal disease
1	19	Molder, furnace operator	1.12	Smoker	1/1p-s	52	52	Polycystic kidney
2	24	Furnace operator	0.24	Non smoker	0/0	30	36	Glomerulonephritis
3	31	Moulder	1.04	Former smoker	0/0	45	52	Chronic renal failure, unknown aetiology
4	39	Moulder	3.84	Non smoker	0/1p	50	51	Polycystic kidney
5	39	Moulder	0.50	Smoker	1/1p-s	56	56	Glomerulonephritis in generalised vasculitis
6	40	Sprinkler	0.90	Smoker	0/0	51	51	Glomerulonephritis

monitor occurrence of disease in the Lazio region (an area which includes the city of Rome, with five million inhabitants).[16] A census of prevalent cases being treated by all dialysis units (60 public and private regional centres) on 30 June 1994 was made; the registry is considered to be a complete population based assessment of end stage renal disease because all sources of kidney dialysis treatment report to this authority. The prevalence data of the registry include both demographic (name, sex, dialysis centre, date and place of birth, residence, educational level, job activity before and after dialysis) and clinical information (primary nephropathy, co-morbidity, year of starting treatment, type of dialysis) for 2834 subjects (58.8% men). The male population prevalence of patients undergoing a dialysis treatment has been estimated as 66.8 per 100 000, of which 28.1% have glomerulonephritis. However, only 23% of all the cases of glomerulonephritis have had a pathological confirmation. The prevalences of end stage renal disease are consistent with data from other countries.[17] The 2820 ceramic workers still alive in June 1994, and resident in the Lazio region, were searched in the registry to match prevalent cases of end stage renal disease among cohort members.

The data of the regional registry were used to create regional end stage renal disease sex, age, (five year classes) specific disease rates with population denominators from the 1991 census. Expected numbers among ceramic workers were computed by applying these rates to the age distribution of the cohort. Observed/expected ratios (and 95% confidence intervals (95% CIs)) were computed according to findings from chest *x* rays films, and latency since first exposure to silica. The association between smoking and end stage renal disease was also considered in the analysis because smoking directly and indirectly affects normal kidney function.[18] A retrospective assessment of the effect of cumulative exposure to silica on end stage renal disease was done with information on the quartz content in the raw material (22%–33%), industrial hygiene data of respirable exposure to silica in different jobs during the 1980s, and historical information about main change in the working process since the 1950s.[11]

Table 2 Cohort of male ceramic workers and risk of end stage renal disease

Variable	Subjects (n)	O	E	O/E	95% CI
Total cohort	2820	6	1.87	3.21*	1.17 to 6.98
Glomerulonephritis		3	0.94	3.19	0.65 to 9.32
Smoking:					
Non-smokers	741	2	0.46	4.34	0.52 to 15.7
Smokers	2076	4	1.41	2.83	0.77 to 7.26
x Ray status:					
0/0 to 1/0	2393	4	1.44	2.78	0.72 to 7.18
1/1+	421	2	0.44	4.54	0.55 to 16.4
Latency since first exposure (y):					
<10	116	1	0.04	25.0	0.65 to 139
10 to 19	1568	4	0.86	4.65*	1.26 to 11.9
20 to 29	841	0	0.62	—	—
≥30	295	1	0.35	2.85	0.07 to 15.9

*p<0.05.
O=observed; E=expected.

Results

Six male ceramic workers were detected in the regional end stage renal disease registry. Table 1 shows some characteristics of these cases. Cumulative exposure to silica among cases ranged from 0.2 to 3.8 mg/m³/years. Two workers had had a diagnosis of silicosis (1/1; cases 1 and 5). Glomerulonephritis was the leading cause of the renal failure in three cases. More specifically, case 5, a worker with silicosis, had a diagnosis of necrotising glomerulonephritis in systemic vasculitis with perinuclear antineutrophil cytoplasmic antibodies.

Table 2 shows the risk for end stage renal disease among the members of the cohort. The number of cases expected on the basis of the regional rates was 1.87. The observed (O) over expected (E) ratio for end stage renal disease was 3.21 (95% CI 1.17 to 6.98), and the corresponding risk for only glomerulonephritis was 3.19 (95% CI 0.65 to 9.32). The excess risk was present among non-smokers (O/E=4.34; 95% CI 0.52 to 15.7) and smokers (O/E=2.83; 95% CI 0.77 to 7.26) as well as among workers without silicosis (O/E=2.78; 95% CI 0.72 to 7.18) and with silicosis (O/E=4.54; 95% CI 0.55–16.4). The risk was higher among subjects with <20 years since first employment, with O/E=25 for latency <10 years, and O/E=4.65 for a latency 10–19 years (95% CI 1.26 to 11.9). After excluding from the analysis the cases with a diagnosis of polycystic kidney disease, the risk did not change, although it was no longer significant (O=4; E=1.62; O/E=2.47; 95% CI 0.67 to 6.32).

Discussion

Our data confirm the results by Calvert *et al*[10] and indicate that exposure to silica is associated with an increased risk for end stage renal disease. Because there seems to be an increased risk of end stage renal disease among those with and without silicosis, this suggests that kidney damage related to silica does not always show fibrosis. Our analysis by latency, although based on small numbers, showed that most of the cases appeared after a short or medium latency period. This is by contrast with the findings from Calvert *et al*.[10]

A direct toxic action of silica on the glomerulus and proximal tube is a possible mechanism leading to renal damage.[1] Haustein *et al*,[19] however, proposed a possible immune pathway for silica induced scleroderma, and this seems to be a relevant mechanism for other autoimmune conditions, including end stage renal disease. As the precise mechanisms of silica toxicity, and the direct toxic effects or immunological injury, are not clear,[20] future studies should consider the issue of the pathological potential of the chemical and surface characteristics of silica.[21] Mechanistic studies have suggested that fresh surface is highly reactive with hydrogen, oxygen, and carbon, driving oxidant production.[22] In vitro studies have shown that recently crushed quartz is more cytotoxic than aged quartz.[23 24] The raw material used in the ceramic production contains a variable proportion of so called "chamotte", sanitary ware failing at final inspection and recycled after fine grounding. This material has shown increased ability to produce free radicals in vivo, even higher than freshly ground quartz (B Fubini, personal communication).

Several reports have linked exposed to silica and silicosis with autoimmune disorders, including rheumatoid arthritis, systemic sclerosis (scleroderma), and systemic lupus.[25] It is worth noting that two linked papers on Spanish workers who cleaned silica flour showed extraordinarily high risks of autoimmune diseases, and two workers (of 50 examined) had glomerulonephritis—one with systemic lupus erythematosus, and the other without anyautoimmunedisease.[26 27]Inthiscontext,polyarteritis and necrotising glomelonephritis associated with silicosis has already been reported,[28] a condition similar to that which was found for patient 5 in our study.

There are limitations in our findings. We could only trace the more severe form of renal damage requiring dialysis; the registry covered only prevalence data, and we cannot describe long term incidence of the disease. We were not able to carry on an analysis relating cumulative exposure to silica with end stage renal disease, as detailed occupational histories were not available for all the cohort members. There are other possible risk factors for renal damage in the ceramic industry that may have acted as confounders—for example, lead, chromium, and cadmium. However, they usually contaminate the decorating process in the ceramic industry, whereas our cases were mainly employed in the moulding department, an area with the highest level of exposure to silica.[11]

In conclusion, these results provide further evidence that exposure to silica dust among ceramic workers is associated with nephrotoxic effects. Although additional research is needed to characterise the risks among other types of workers exposed to silica, we think that renal function should be monitored among workers exposed to silica, and a thorough occupational history should be used in evaluating otherwise unexplained renal insufficiency.

This study was supported by a grant of the Public Health Institute (Project No 639A). FF has been partially supported from the UICC Yamagiwa-Yoshida Grant.

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