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BRIEF COMMUNICATION

Silica Exposure and Autoimmune Diseases

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There have long been case reports linking silica exposure to a variety of autoimmune diseases (systemic sclerosis, rheumatoid arthritis, lupus, chronic renal disease). Evidence of this association in larger epidemiologic studies has been increasing in the last decade. We summarize this evidence here, and present some plausible mechanisms which have been discussed in the literature. The link between silica exposure and autoimmune disease may have been missed in cohort mortality studies because autoimmune diseases are rarely underlying causes of death. Similarly, case-control studies of autoimmune diseases have often failed to consider occupational exposure to silica. Further research is needed in occupationally exposed populations to verify this association. The link between respirable silica exposure and autoimmune disease may have some bearing on the possible association between silicone breast implants and autoimmune disease, although the nature of the silica involved is quite different in the two situations.

Key words: silica, autoimmune, arthritis, scleroderma, systemic sclerosis, lupus, renal disease, occupational hazard

BACKGROUND

The frequent coexistence of silicosis and tuberculosis, and the occasional coexistence of silicosis and arthritis (Caplan's syndrome), have been thought to have a basis in effects of silica on the immune system [Burrell, 1982; Unge and Mellner, 1975]. There have also been case reports in the literature linking silica exposure with systemic sclerosis and other autoimmune disorders [Erasmus, 1957; Balaan and Banks, 1992]. Based on these latter reports, scleroderma among silica-exposed workers has been judged a compensable occupational disease in the former East Germany, in South Africa, and in Ontario, Canada [Industrial Disease Standards Panel, 1992].

Recently there is increasing evidence from larger epidemiologic studies supporting the hypothesis that silica exposure is linked to a wide variety of known or suspected autoimmune disorders (rheumatoid arthritis, scleroderma, lupus, renal disease). We summarize this recent evidence below in Table I.

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TABLE I. Studies of Silica-Exposed Workers and Autoimmune Disease

Autoimmune disease	Reference	Population	Design	Measure of risk (95% CI)
Rheumatoid arthritis morbidity	Klockars et al. [1987]	1,026 granite workers, incidence 1940–1991, 17 disability cases	Cohort incidence, Finnish population referent	Rate ratio 5.08 (3.31–7.79)
Rheumatoid arthritis morbidity	Sluis-Cremer et al. [1986]	Gold miners with high silica exposure, 91 "definite" disability cases	Case-control for prevalence of silicosis, pair-matched controls	Odds ratio 3.79 (1.72–8.39) for silicosis, no association with cumulative dust
Arthritis mortality	Steenland et al. [1992]	1,905 granite cutters, 17 arthritis deaths	Proportionate mortality, U.S. referent, multiple cause analysis	PMR 2.01 (1.17–3.21)
Arthritis mortality	Steenland and Brown [1995]	3,328 gold miners with high silica exposure, 17 deaths	Cohort mortality, U.S. referent, multiple cause analysis	SMR 2.29 (1.13–3.67)
Systemic sclerosis morbidity	Sluis-Cremer et al. [1985]	Gold miners with high silica exposure, 79 cases	Case-control, pair-matched controls, cases via regular exam or disability	Cases had higher cumulative silica dust ($p < .001$)
Musculoskeletal disease mortality, including sclerosis, lupus (ICD 710, 717–9, 722–9, 731–9)	Steenland and Brown [1995]	3,328 gold miners with high silica exposure, 10 deaths	Cohort mortality, U.S. referent, multiple cause analysis	SMR 2.14 (1.03–3.94)
Skin disease mortality including scleroderma (ICD9 680–86)	Steenland and Brown [1995]	3,328 gold miners with high silica exposure, 10 deaths	Cohort mortality, multiple cause analysis	SMR 2.45 (1.17–4.51)
Chronic renal disease mortality	Steenland et al. [1992]	1,905 granite cutters, 34 deaths	Proportionate mortality, U.S. referent, multiple cause analysis	PMR 2.22 (1.47–2.96)
End-stage renal disease morbidity	Steenland et al. [1990]	325 cases with end-stage renal disease, 325 matched controls	Population-based case-control, occupational exposure	Odds ratio 1.67 (1.32–2.74)
Chronic renal disease mortality	Steenland and Brown [1995]	3,328 gold miners with high silica exposure	Cohort mortality, U.S. referent	SMR for high exposure group 2.77 (1.20–5.47) and significant dose response

EPIDEMIOLOGIC STUDIES

Table I shows four studies [Klockars et al., 1987; Sluis-Cremer et al., 1986; Steenland et al., 1992; Steenland and Brown, 1995] with positive findings for arthritis among granite workers and gold miners with high silica exposure (granite is 30% silica). Two of these studies are mortality studies, and it is often impossible to differentiate between rheumatoid and osteoarthritis on death certificates. Granite workers and gold miners might suffer osteoarthritis due to chronic repetitive trauma. However, in both these mortality studies other excesses of autoimmune diseases were found, suggesting a generalized problem of autoimmunity.

Systemic sclerosis, systemic lupus, and Sjögren's syndrome have also been found in silica-exposed populations. Table I shows two studies with excesses of these diseases among workers with high exposure to silica [Steenland and Brown, 1995; Sluis-Cremer et al., 1985]. Excesses in Steenland and Brown [1995] were found using multiple cause analyses, in which all causes on the death certificate are analyzed, not just the underlying cause. Besides these analytic epidemiologic studies, there are other suggestive reports. In a series of 120 East German male scleroderma cases in the 1980s, Haustein et al. [1990] found that 93 had long-term exposure to silica dust. In a recent report from Spain, 64% of a group of 50 ex-workers from a scouring powder plant (the silica "flour" used in this process contained 70–90% quartz) were diagnosed with systemic illness of an autoimmune nature, including Sjögren's syndrome, systemic sclerosis, and systemic lupus [Sanchez-Roman et al., 1993]; 72% had antinuclear antibodies (ANA). Although this study lacked a nonexposed comparison group, the authors indicated that prevalence of autoimmune disease appeared far in excess of normal.

Chronic renal disease (especially glomerular disease) has been associated with silica exposure, and some authors [Osorio et al., 1987] have postulated an autoimmune process. Table I lists three studies indicating an association between renal disease and silica exposure [Steenland et al., 1990, 1992; Steenland and Brown, 1995]. Again, renal disease is often not listed as the underlying cause of death and excesses were detected in one of these studies (the mortality study of granite workers) only by using multiple cause analyses. The population-based case-control study cited found an excess for all workers reporting a history of regular (not occasional) exposure to silica, with the excess concentrated among those who had worked in foundries and in sandblasting, both areas with known high exposure to silica. Goldsmith and Goldsmith [1993] have recently reviewed much of the literature regarding silica and renal disease.

MECHANISMS

The mechanisms for the link between occupational silica exposure, silicosis, and autoimmune conditions are not fully understood. However, Haustein and colleagues [1990] have proposed possible pathways for silica-induced scleroderma, a process which follows or is linked to the induction of silicosis. Scleroderma is proposed to arise from exposure to respirable particle sizes (<10 μm) of quartz coming into contact with the lung. In both cases, this stimulates the production of macrophages and interleukin 1, platelet-derived growth factor, beta-transforming growth factor, and fibronectin. Production and recruitment of macrophages to engulf

silica particles lead to the destruction of macrophage cells, production of more macrophages to attack the particles, stimulation of collagen, and the hyalinization of collagen to form a silicotic network. The cycle of production and destruction of macrophages releases hydrolases and proteases leading to the generation of free oxygen radicals, and some particles bound with macrophages are transported to pulmonary lymph nodes. Macrophage production and destruction cycles and the presence of particles in the lymph system stimulate T-helper and B-cell production, and ultimately activation of the immune system [Guidotti et al., 1986]. Immune activation is linked to a variety of humoral responses: hypergammaglobulinemia, production of rheumatoid factor, ANA, and release of other immune complexes. These immunostimulatory states lead to rheumatoid arthritis and polyarthritis, connective tissue disorders such as systemic lupus, Sjögren's syndrome, polymyositis, scleroderma, and glomerulonephritis [Seaton, 1984; Haustein et al., 1990].

A silica-autoimmune disease association may also be relevant to the issue of whether silicone breast implants cause autoimmune disease (connective tissue disorders). Silicone is formed by polymerized chains of silicon oxides surrounded by simple hydrocarbons, and there is animal and some human evidence that silicone is not inert but can cause inflammatory reactions [Brautbar et al., 1994]. Shanklin [1990] reported that metabolism of silicone gel leads to the release of silica and macrophages in tissue adjacent to the implants. The link with silica has been recently suggested in a study of women with implants which showed statistically significant T-cell reactivity to silica in vitro compared with healthy volunteers without implants [Ozo-Amaize et al., 1994]. Respirable silica, in contrast to silicone, is made up of silicon oxides in crystalline form. Although the evidence cited above is suggestive, it remains unclear whether there might be any comparable human immune response to these two substances.

Existing epidemiology is still too scant to determine if silicone breast implants are related to autoimmune disorders. Gabriel et al. [1994] found no excess autoimmune disease in a cohort of 749 women with breast implants followed for 8 years, but this study had low power. McLaughlin and colleagues [1994] reported significantly increased incidence of scleroderma in Denmark among 824 women after breast implant surgery, although there were only two cases (0.07 expected), producing a standardized incidence ratio of 27.7 (95%CI 3.1–99.8).

CONCLUSIONS

We have summarized the recent epidemiologic evidence suggesting an association between silica exposure and the most commonly recognized autoimmune diseases. We are not aware of other studies which failed to find such associations; most researchers have not looked for them. Many cohort studies of silica-exposed workers have been mortality studies in which excesses of autoimmune conditions may well have been missed if only the underlying cause of death was considered. On the other hand, case-control studies of specific autoimmune diseases have not generally considered occupational silica exposure. It is possible that reanalyses of existing data sets could reveal more information about the silica-autoimmune disease association.

Of the three cohort (or PMR) studies considered here it is worth noting that two [Steenland and Brown, 1995; Steenland et al., 1992], were consistent in showing

excesses of several different autoimmune diseases, while the third was a cohort incidence study focused on arthritis alone [Klockars et al., 1987].

More than 2 million workers are currently exposed to silica in the United States [NIOSH, 1991], and many more have past exposure. Historically, workplace standards for silica have been set to prevent the occurrence of silicosis, which itself may result from the activation of immune mechanisms. Concerns have also been raised recently about the carcinogenic properties of silica [Goldsmith, 1994]; if silica does cause cancer, again it might do so via producing immune dysfunction among highly exposed individuals [Guidotti et al., 1986]. Our purpose here has been to bring attention to the increasing evidence that silica may also cause a wide variety of known and suspected autoimmune diseases. Further rigorous clinical and epidemiologic studies are needed. Workers with high past exposure to silica might be followed and studied cross-sectionally for the autoimmune diseases discussed here, along with appropriate comparison groups. Registries of silicotics could be useful sources for such studies. Longitudinal studies of newly exposed workers could also be conducted for immunologic endpoints short of frank disease, such as the presence of ANA. In addition, surveillance of currently exposed workers for autoimmune conditions might be appropriate.

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