

Occupational Exposure to Crystalline Silica and Autoimmune Disease

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Abstract

Occupational exposure to silica dust has been examined as a possible risk factor with respect to several systemic autoimmune diseases, including scleroderma, rheumatoid arthritis, systemic lupus erythematosus, and some of the small vessel vasculitides with renal involvement (e.g., Wegener granulomatosis). Crystalline silica, or quartz, is an abundant mineral found in sand, rock, and soil. High-level exposure to respirable silica dust can cause chronic inflammation and fibrosis in the lung and other organs. Studies of specific occupational groups with high-level silica exposure (e.g., miners) have shown increased rates of autoimmune diseases compared to the expected rates in the general population. However, some clinic- and population-based studies have not demonstrated an association between silica exposure and risk of autoimmune diseases. This lack of effect may be due to the limited statistical power of these studies to examine this association or because the lower- or moderate-level exposures that may be more common in the general population were not considered. Experimental studies demonstrate that silica can act as an adjuvant to nonspecifically enhance the immune response. This is one mechanism by which silica might be involved in the development of autoimmune diseases. Given that several different autoimmune diseases may be associated with silica dust exposure, silica dust may act to promote or accelerate disease development, requiring some other factor to break immune tolerance or initiate autoimmunity. The specific manifestation of this effect may depend on underlying differences in genetic susceptibility or other environmental exposures. *Key words:* antineutrophil cytoplasmic antibodies, antinuclear antibodies, nephritis, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Wegener granulomatosis. -- *Environ Health Perspect* 107(suppl 5):793-802 (1999).

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Little is known about the role of environmental agents in the development of autoimmune disease. Many studies illustrate the influence of a complex array of genetic factors on the development of autoimmunity and specific autoimmune diseases (1-3). However, the onset of disease also appears to require the occurrence of chance events in the immune system or exposure to environmental agents that may trigger or accelerate the disease process. Occupational exposure to crystalline silica dust has been examined as a possible risk factor with respect to several systemic autoimmune diseases, including rheumatoid arthritis (RA), scleroderma (SSc), systemic lupus erythematosus (SLE), and some of the small vessel vasculitides (SVV) with renal involvement (e.g., Wegener granulomatosis [WG]). This article provides a brief overview of silica dust exposure, summarizes the evidence from human studies on the possible association between silica and autoimmune diseases, and describes the evidence related to mechanisms that may account for this association. Considerations for evaluating these data and designing future studies will be discussed.

Exposure to Silica Dust

Silica or silicon dioxide (SiO_2) is an abundant mineral found in rock, sand, and soil. Silica primarily exists in its crystalline state as quartz, which is structurally and chemically different from amorphous silica (e.g., diatomaceous earth); silicates (e.g., talc or asbestos); and silicone [a polymer containing silicon ($[\text{SiO}(\text{CH}_3)_2]_n$)]. Ubiquitous in the environment, silica is part of the small particulate fraction of air pollution and may comprise a significant fraction of environmental dust levels in some geographic regions (4,5). In this review, the term silica dust exposure refers to occupational exposure to the respirable fraction of crystalline silica dust. We do not consider the literature pertaining to silicone exposure or speculate about the effects of other silicon-containing materials.

Crystalline silica can be harmful when inhaled as a dust in the respirable range (< 5- μm particles). Silicosis, a form of pulmonary fibrosis, is a well-known occupational disease that results from acute or chronic high-level exposure to silica or silica-containing dusts (6-8). Silicosis increases susceptibility to tuberculosis and other respiratory diseases (6), and silica has recently been categorized by the International Agency for Research on Cancer as a known human carcinogen (8).

Sources of Exposure

The sources of occupational exposure to silica dust are diverse and include many manufacturing and construction processes that use silica as either a tool or a raw material, as well as the mining and processing of silica-containing rock (9,10) (Table 1). Many of these industries are traditionally known as the dusty trades. Some jobs may involve regular contact with silica but are not commonly recognized as dusty trades (e.g., dental technician, chemist, or sculptor). Silica sand and gravel are used in road construction and concrete and in the manufacture of glass and ceramics, foundry castings, and abrasives such as sandpaper and sandblasting materials. Silica sand or flour is also used as a filler in detergents, paints, plastics, and cements; as a filtering agent for water, sewage, and food production; and as the primary component of some abrasive cleansers (e.g., scouring powder).

Table 1. Industries, occupations, and tasks with crystalline silica exposure.*

Industry/occupation	Specific tasks
Abrasives	Silicon carbide production; abrasive products fabrication
Agriculture	Mechanized plowing, harvesting, sorting, cleaning, grading
Agricultural chemicals	Raw material crushing, handling
Asphalt and roofing felt	Filling and granule application
Automobile repair	Abrasive blasting
Boiler coating	Chase ash and mineral deposits from coal-fired boilers
Cement	Materials processing: clay, sand, limestone, diatomaceous earth
Ceramics	Mixing, molding, glaze or enamel spraying, finishing
Construction	Abrasive blasting, highway and tunnel construction, excavation/earth moving, masonry, concrete work, demolition
Dental material	Abrasive blasting, polishing
Foundries	Casting, chills/core, abrasive blasting, fettling, furnace installation and repair
Glass, fiberglass	Raw material processing (sand, quartz); refractory installation and repair
Iron, steel mills	Refractory preparation and furnace repair
Jewelry	Cutting, grinding, polishing (gems, stones)
Metal	Abrasive blasting (structural, machinery, transportation equipment)
Mining, milling	Most occupations and mines (ores, associated rock)
Paint	Raw materials handling (filler)
Quarrying, milling	Stone, sand, gravel processing; stone cutting and abrasive blasting; slate work; diatomite calcination
Rubber and plastics	Raw materials handling (filler)
Shipbuilding, repair	Abrasive blasting
Silicon, ferro-silicon	Raw materials handling (sand)
Soap, cosmetics	Abrasive soaps, scouring powders

*Data from: the International Agency for Research on Cancer (9).

The permissible exposure limit (PEL) for respirable silica dust used by the Occupational Health and Safety Administration (OSHA) is approximately 0.10 mg/m³ (8-hr time-weighted average for quartz) (11,12), which is twice the recommended exposure limit ([REL]; 0.05 mg/m³) suggested by the National Institute of Occupational Safety and Health to minimize risk of silicosis (13). Approximately 1-3 million people in the United States work in jobs with potential exposure to silica, and at least 10% of these workers may have dangerously high exposures (at least 2-10 times the REL) (14). The National Occupational Exposure Survey (1981-1983) estimated that women comprise approximately 20% of workers in the United States with potential silica exposure (15). This number may increase as more women move into occupations traditionally held by men. Recently, the burden of silica-related disease has shifted from industrialized to developing countries (16).

The potential for silica dust exposure in agriculture was recently recognized by OSHA based on measurements in some food-processing operations (17). The levels of silica exposure in farming depend on the tasks and crops involved (18-22) and may also vary by soil characteristics and quartz content (23). Exposures as high as 0.10-0.65 mg/m³ (1-6.5 times greater than PEL for silica exposure in other industries) have been reported in mechanized and manual harvesting of some crops (18,22). Approximately 10 million people in the United States work on a farm (18). The impact of silica dust exposure in agriculture could be substantial, but relatively few studies have characterized exposure levels and associated risks in this population.

Silica Dust and Autoimmune Disease

Initial hypotheses linking silica dust exposure (or silicosis) to autoimmune diseases were based on numerous case reports and small occupationally based case series (24-26). Larger clinic-based case-series, occupational cohort, registry-linkage, and case-control studies have also been conducted, many of them published since 1995 (27-56). The diseases that have been examined most often include SSc (24,25,27-43), RA (26,31-33, 35,37,44-46), SLE (29,33,35, 37,47-52), and some of the SVV with renal involvement (53-56). The population prevalence of these diseases differs by several orders of magnitude; RA is the most common (approximately 1 case per 100) (57,58), compared to SLE (approximately 5 cases per 10,000) (58,59) and to SSc and WG (fewer than 5 cases per 100,000) (58,60-62). High-level silica exposure has also been reported in cases of autoimmune hemolytic anemia, dermatomyositis, vasculitis, Sjögren syndrome, and Graves disease (37,63-66). A strong association between silica dust exposure and sarcoidosis was recently described (67). Sarcoidosis is an inflammatory condition

and silicosis after years of recreational scouring powder inhalation (51).

Two recent studies in occupational groups suggest that high-level silica exposure may be associated with SLE (29,52) (Table 2). This includes three cases of SLE and five SLE/SSc overlap cases in the study of 50 scouring powder factory workers (29) and 28 SLE cases identified in a study of 30,000 male uranium miners examined for silicosis (52). Silica exposure levels were very high in these cohorts. The estimated prevalence of SLE in both these studies was at least 10 times higher than the expected sex-specific prevalence in the general population. Estimates in both of these studies require several assumptions. For instance, the prevalence estimate in the scouring powder factory is calculated based on the total number of workers (300) rather than the number in the volunteer sample, assuming that there are no cases among the nonparticipants. In the uranium miner cohort, disease prevalence is based on rough estimates of the numbers of employees and work histories because of high turnover rates of employees and limited access to records in a Soviet-German company during the cold war. However, this was a time with high production rates and extremely high exposures (estimated at 200-1000 times the current OSHA PEL) (30).

One registry-linkage study in Sweden and Denmark also reported a strong association between silica dust exposure and SLE (33) (Table 3); SLE was more frequently diagnosed in patients with silicosis compared to all other hospitalized patients (RR = 23.8; 95% CI, 10.3-47.0). To date, no case-control studies have examined the role of silica dust exposure in the development of SLE.

Diseases with Renal Involvement

Some of the SVV are associated with the production of antineutrophil cytoplasmic autoantibodies (ANCA) (e.g., WG and microscopic polyangitis) and can involve both systemic effects and organ-specific pathology, including the kidney. Evidence suggesting an association between silica exposure and ANCA-associated SVV has been recently reviewed by Gregorini et al. (53). Three case-control studies show strong and statistically significant associations between silica exposure and ANCA-associated SVV with renal involvement (54-56) (Table 5). Silica exposure may also be linked with ANCA reactivity in uranium miners (68). Nearly 10% of 243 miners with proteinuria had elevated ANCA levels, compared to 5% of 1,527 miners without proteinuria. Antibodies against myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA) were detected in 3.3% of the group with proteinuria compared to 0.07% of those without proteinuria. In another study, MPO-ANCA were detected in 27% of silica-exposed individuals with and without autoimmune disease (69). The association between ANCA reactivity and silica exposure, as well as its relation to the development and pathology of autoimmune diseases, will require further elucidation.

An association between silica exposure and nephritis has been suggested by registry-linkage and occupational cohort studies (70-72), including one that describes dose-response association of silica with end-stage nonmalignant renal disease in gold miners (72). None of these studies specifically focused on autoimmune diseases. There are case reports of lupus nephritis in some patients with silicosis and cases of renal failure in silica-exposed patients who experienced clinical manifestations of connective tissue disease (73,74). However, one clinic-based case-control study found no association between silica exposure and lupus nephritis (56). Other silica-exposed cases of renal disease show negative or nonspecific immunologic findings (74). In sum, the causes of renal disease related to silica exposure appear to be diverse, and the proportion that may be associated with autoimmune diseases is unknown.

Immune Abnormalities

Silicosis and mineral dust pneumoconiosis have been linked to increased levels of autoantibodies, immune complexes, and excess production of immunoglobulins (primarily IgG) (65,75-79), even in the absence of clinical features of specific autoimmune diseases. In a study of 39 sandblasters with silicosis, 44% were positive for antinuclear antibodies (ANA) compared to 2-3% of a random sample of healthy controls (75). Similarly, 34% of 156 coal miners with pneumoconiosis from various regions of the north-central United States were ANA positive (76), and the proportion of ANA positivity was related to the silica content of the dust produced by different mines. Because these studies did not examine the relation between time of exposure and autoantibody levels, it is unclear whether autoantibody production in silica-exposed workers is predictive of the development of an autoimmune disease and if so, what threshold might exist between this process and disease onset.

Serology studies of the uranium miner cohort previously described (79,80) indicate that miners without autoimmune disease had a significantly higher frequency of autoantibodies specific to connective tissue disease (e.g., anticentromere, anti-topoisomerase, anti-double-stranded DNA (dsDNA), anti-Ro/SSA, anti-La/SSB) compared to gender- and age-matched controls from the general population. There was an association between the intensity of silica exposure and the expression of autoantibodies, but there was no apparent relation between autoantibody expression and silicosis. After 2-11 years of follow-up, miners expressing scleroderma-specific autoantibodies were more likely to develop scleroderma than autoantibody-negative miners (80). Disease progression was also observed in two miners with SLE-specific autoantibodies (both miners had dsDNA autoantibodies carrying the 16/6 idiotype) (81). Evaluating the predictive value of disease-specific autoantibodies is limited by the long latency period observed between silica exposure and the manifestation of autoimmune diseases and by loss to follow-up of workers who die of other age-related diseases.

Biologic Mechanism of Silica in Autoimmune Disease

Many cases of autoimmune disease in silica-exposed individuals have been identified during screening or treatment for silicosis. It is unclear whether silicosis is simply a marker for high-level silica dust exposure in these cases or whether it represents a pathologic process that may predispose some individuals to the development of autoimmune disease. Conversely, it is possible that autoimmune disease may predispose some individuals to develop silicosis. Because of the chronic nature of both conditions, it is difficult to establish their temporal relationship.

The development of silicosis is thought to involve the ingestion of silica particles by alveolar macrophages that become stimulated, resulting in inflammation and the activation of fibroblasts (7). Crystalline silica is extremely toxic to cells, and silica particles cannot be broken down by lysosomal enzymes. Thus, macrophages can be destroyed by internalized silica, and the process may repeat itself, resulting in a focal point of immune activity and fibrosis. In this way, silicosis can be thought of as a chronic process of immune stimulation.

In humans with high-level exposure, there is evidence that silica can be mobilized from the lung to other organs, including lymph nodes, spleen, and kidney (82). A recent study in rats demonstrated profound pathologic changes in the pulmonary lymph nodes after silica dust exposure, including the development of macrophage granulomas without fibrosis (83). The early impact on lymphoid organs reported in this study may in part explain the immune abnormalities associated with silica dust exposure.

Adjuvant Effect

Silica has long been known to have an adjuvant effect on antibody production (84). An adjuvant is a substance that nonspecifically enhances or potentiates an immune response to an antigen. Although the mechanism by which silica acts as an adjuvant is not fully understood, it appears to be related to the inflammatory response (85). One theory is that the activation of macrophages at the site of silica deposition may lead to increased antigen processing and accelerated antibody production. Macrophages respond to internalized silica by up regulating cytokine production (including interleukin (IL)-1 and tumor necrosis factor [TNF]) (86,87), which stimulates other cells and enhances the inflammatory response. IL-1 can activate the T-helper cells that facilitate B-cell production of antibodies. In one study, silica was reported to stimulate the polyclonal (nonspecific) activation of human T cells *in vitro* (88), suggesting the potential of silica to act as a superantigen *in vivo*. Silica may also activate immune processes through the release of reactive oxygen and nitrogen species (89,90).

An adjuvant effect is consistent with the hypothesis that silica may act to promote the development of autoimmune diseases, requiring some other event or process to break tolerance and initiate autoimmunity. In experimental models, an immunologic adjuvant is often mixed with antigen to produce autoimmune disease. One study reported that silica enhanced the effects of neural antigen in an animal model of multiple sclerosis (allergic encephalomyelitis); silica increased the incidence and severity of disease and advanced the onset of disease when administered both concurrent and 1 month prior to injection of the autoantigen (91). In this study, silica had both immediate and latent effects, suggesting that future studies of silica and autoimmune diseases may need to consider a wide range of opportunities for exposure.

We know of no published studies that describe a dose-response or threshold effect for silica as an adjuvant. However, the inflammatory response to silica in models of silicosis are clearly dose dependent, as observed in a recently developed murine model of silicosis (92). In this study, the characteristics of the immune response were strain dependent. Of the four strains chosen for experimentation, two (NZB and MRL/MpJ) have a propensity to develop autoimmune pathology resembling SLE. Both of these strains showed strong inflammatory responses to silica exposure, especially the NZB strain, but response characteristics varied between the strains. These results suggest that genetic differences and susceptibility to autoimmune disease can modify the features and extent of inflammatory pathology due to silica dust exposure.

Other Effects

Silica can cause cell death by apoptosis as well as necrosis (93). Apoptosis is an active process involving genetic regulation. Three experimental studies provide evidence that apoptosis may be enhanced by silica (94-96), possibly at levels where no acute toxicity may be detected (96). However, one human study found that soluble Fas mRNA was dominantly expressed by peripheral blood mononucleocytes compared to membranous Fas in silicosis patients who were free of the clinical symptoms of autoimmune disease (97). Although membranous Fas is required for a Fas-Fas ligand interaction to induce apoptosis, soluble Fas can block apoptosis. Understanding the effects of silica on the complex processes regulating apoptosis will require further research.

TNF- α is one possible mediator of long-lasting immune response modifications through its activity as a cytokine with a broad range of proinflammatory, catabolic, and immunostimulatory activities. Microsatellite polymorphisms of TNF- α have been reported that correspond to variation in secretion patterns (98); the TNFa2 allele increased secretion of TNF- α by monocytes stimulated with lipopolysaccharide. In uranium miners with SSc, the TNFa2 allele was significantly more prevalent compared to controls and to idiopathic SSc cases (99). This suggests a hypothesis that differential regulation of TNF- α production by macrophages ingesting silica could be involved in the relation between silica exposure and SSc.

Renal and Vascular Effects

The mechanisms of immune-mediated kidney diseases are diverse (100), and their relation to the other features of autoimmune diseases is not fully understood. Silica particles can accumulate in the kidney and lead to immune stimulation and fibrotic processes similar to those seen in pulmonary silicosis (82). Silica also has direct toxic effects on the kidneys in both animals and humans (101). Thus, the inflammatory and toxic effects of silica may both be involved in the development of renal pathology in autoimmune diseases.

The mechanisms of renal pathology appear to differ among the various autoimmune diseases that may be associated with silica exposure. In WG, inflammation often starts in the upper and lower airways but in most instances leads to the development of glomerulonephritis (70-80% of cases experience kidney involvement) (102). Excessive exposure to silica dust may play a role in this process through mechanisms described previously (74). Although autoantibodies can be detected in the serum, antibody deposition in the kidney does not appear to be involved in the pathology of WG (102). Conversely, the circulation of immune

complexes is thought to be responsible for the development of renal disease in lupus patients. These underlying differences in pathology may explain the lack of association between silica dust and lupus nephritis described in one study (56) compared to the strong associations with nephritis in ANCA-associated SVV. Renal disease also occurs in about 5-15% of SSc and RA patients (103), but no studies have systematically examined the association of silica exposure and renal involvement in these diseases.

Vasculitis is also a manifestation of many of the autoimmune diseases that may be associated with silica exposure, including ANCA-associated SVV, SLE, RA, and sometimes SSc (103). Vascular pathology in these diseases appears to involve the interaction of white blood cells (including macrophages) with the vascular endothelium (104), but it is not known whether silica plays a direct role in this process.

Endothelial leukocyte adhesion molecule-1 (ELAM-1) and intercellular adhesion molecule-1 (ICAM-1) may be biomarkers of vascular injury in silica-exposed uranium miners with SSc. ELAM-1 levels were elevated in silica-exposed uranium miners compared to those in age- and gender-matched population controls, and the highest levels occurred in miners with SSc. Up to 25% of miners with SSc showed strong elevations of this molecule in the serum compared to 11% of miners without symptoms (105). ELAM-1 is expressed on vascular endothelial cells in response to cytokines (IL-1, TNF- α). It can be elevated in serum when these cells are strongly activated or destroyed (106), as occurs in several inflammatory and disease conditions (e.g., sepsis, malignancies, autoimmune diseases). ICAM-1 can be induced on dermal vascular endothelial cells by silica dust (107). There is no evidence that either ELAM-1 or ICAM-1 is responsible for the hypothesized effects of silica on vascular pathology. Future studies should investigate whether these molecules may act as disease mediators and explore their use as biomarkers to study the role of silica on vascular pathology in autoimmune diseases.

Considerations for Future Research

Common Threads among Silica-Associated Diseases

Silica dust exposure may be associated with a wide range of autoimmune diseases and immune abnormalities. Although some studies have explicitly focused on only one disease, several indicate an increased occurrence of several different diseases in the same study population (27,29,30,33,35,45,52) (Tables 2, 3). Many clinical features and some autoantibodies overlap between these diseases (108). Most share a common systemic component, as well as more specific manifestations in organs such as the skin, lung, and kidney. Vascular disease may be a common underlying pathology. Future research may benefit from studies that examine the effects of silica dust exposure across these various diseases and investigate the potential for shared mechanisms.

Comparing Silica-Exposed and Idiopathic Cases of Autoimmune Disease

Many of the studies described in this review have compared the clinical features and autoantibodies of silica-exposed cases of autoimmune disease with idiopathic cases. However, it is important to account for differences in disease characteristics that might be related to age and sex. The demographics of cases may be related to both disease characteristics and the likelihood of silica dust exposure, making it more difficult to assess whether certain features or autoantibodies are related to silica dust exposure.

One study compared the autoantibodies and clinical features of 28 silica-exposed uranium miners with SLE (all men) with 102 idiopathic SLE cases (~90% women) from the general population (52) (Table 2). All the silica-exposed cases in this study were men with late-onset disease, so the differences in autoantibodies or clinical features might be related to age or gender. Compared to idiopathic cases, the uranium miners with SLE showed similar frequencies of Ro/SSA, La/SSB, and Cardiolipin antibodies, but less frequently expressed antibodies to single- and double-stranded DNA; none expressed antibodies to snRNP proteins (BB', D, E, F, G or U1-RNP). Miners with SLE were also significantly less likely to experience arthritis or photosensitivity than the idiopathic cases. Studies comparing the serological features of SLE in men with those in women suggest few significant differences (109-112). Some studies have found a lower rate of dsDNA and Sm antibodies in older-onset SLE (113-115); other studies have not, possibly because of ethnic or methodologic variation (116-118). Future comparisons of silica-exposed and idiopathic autoimmune diseases should choose an appropriate comparison group and carefully ascertain the differences in disease characteristics that may be due to age or sex.

Exposure Assessment

Obtaining exposure history by personal interview or industry records provides only a proxy for silica dust exposure, but steps can be taken to reduce exposure misclassification. Assignment to exposure groups based on standardized industrial or occupational coding is most prone to error (119). A more refined strategy is to use an expert assessment conducted by an industrial hygienist to confirm the potential for exposure (120). This procedure was used in two large population-based case-control studies of SSc in women (42,43) (Table 5). However, expert assessments were limited to jobs initially classified into standardized exposure groups and thus may have missed sources of silica exposure that are more common in women. Self-reported exposures are more likely to be influenced by differential recall in case-control studies but may sometimes provide a more accurate measure of exposures not recognized by an expert assessment (e.g., silica exposure outside the dusty trades industries).

Although there are considerable data on high-level occupational exposure to silica dust, it can be difficult to assess moderate- or lower-level exposures. Potential for high-level exposure is more easily recognized in jobs and industries required to meet regulatory standards for the prevention of silicosis. Moderate- or lower-level exposures may occur in those industries or occupations not routinely monitored for silica or in those where high rates of silicosis have not been identified. Exposure levels

in these jobs may typically fall below the regulatory limits (0.10-0.05 mg/m³), but there may be instances where higher level exposures occur. Exposure levels depend on the frequency and duration of exposure-related activities and on the concentration of silica in workplace dust. Unfortunately, there is little measurement data for many jobs and industries with potential for moderate- or lower level silica exposure.

Some common occupational sources of silica exposure are poorly characterized and will require additional data to determine the actual exposure levels. Women make up a high proportion of workers in many of these jobs. If silica exposure in these occupations is not considered, an association with autoimmune disease in female workers might be missed. These occupations include farming (silica may comprise as much as 40-50% of the respirable fraction of some types of soil), the use of scouring powder (in some cases, almost entirely silica), and other exposures to dust and dirt (e.g., textile, janitorial, laundry, refuse handling). Textile workers may be exposed to silica as a component of cotton dust (121,122), but textile work is not typically considered in assessments of silica exposure. We identified no studies measuring silica exposure in textile workers, with the exception of one study in a Chinese cotton mill reporting that ambient levels of silica dust exceeded the OSHA PEL during an early processing stage (123). In 1987, an increased rate of RA was observed in a prospective study of women in Finland who were exposed to raw cotton mill dust (124), but no subsequent studies of silica and autoimmune diseases have mentioned textile work as a source of silica exposure.

Exposure Characteristics and Confounding

Most of the published studies on silica-exposed autoimmune disease consistently describe very high levels of silica exposure. However, exposure duration among cases is more variable. One study suggests that exposure intensity may be more important than cumulative dose in the development of autoimmune disease (45) (Table 2). Several occupational cohort and registry-linkage studies used silicosis or risk of silicosis to identify exposed workers (31,33,35,52) (Tables 2,3) and thus may be limited to only the most highly exposed cases. Future research in occupational cohorts should explore the characteristics of exposure, such as cumulative dose, intensity, and timing as they relate to disease onset. It is very difficult to measure the exposure levels retrospectively, even using workplace monitoring data and employee records. At this time, the only biomarkers of silica exposure are an X-ray diagnosis of silicosis or invasive assays that measure silica in the lung or other organs.

Studying autoimmune diseases in occupational cohorts with silica exposure is limited by the rare occurrence of these diseases, especially in men. Population-based studies may be better able to reflect the effect of silica exposure in people at risk of developing autoimmune diseases, especially if they consider the occurrence of moderate- and lower-level exposures. It will remain difficult to retrospectively measure exposure in these studies for the reasons described above.

Multiple concurrent exposures are a particular problem in studying silica dust exposure and autoimmune disease. Silica rarely occurs in pure form in the environment and may be mixed with a wide range of other minerals. It may be difficult to isolate the effects of silica. Other particulates with adjuvant activity include talc, tin, and iron ore dust with relatively low silica content (85,125). Authors of a recent case-series study suggested renaming silica-dust lupus as mineral-dust lupus (50).

Variations in forms and mixtures with other minerals may impact the toxic or inflammatory effects of free silica, and quartz can contain trace impurities that affect its biologic activity (8). For instance, iron ore in quartz dust can increase the production of reactive oxygen species and several measures of immune stimulation (126). Other factors may impact the effect of silica; freshly fractured silica appears to be more reactive than aged dust (127). Surface area and ability to bind and present antigen may be related to the magnitude of adjuvancy for metal oxides, including silica (85).

Mixed exposures to silica and other chemicals can occur in industries where silica may be only one component of the manufacturing process. If these other chemicals are independently associated with autoimmune diseases, they may confound analyses of the effects of silica. For instance, rubber manufacturing has the potential for both silica and solvent exposure, and some studies suggest that solvents may be associated with SSc (40,41). In addition to silica, uranium miners are also exposed to radon, radon decay products, and heavy metals. The relation between these exposures and autoimmune diseases has not been established, so it is unclear whether they could confound estimated associations between silica and autoimmune diseases. Future studies should consider potential confounding and interaction of silica's effects with other exposures.

Susceptible Subgroups

Disease heterogeneity and differences in genetic susceptibility can make it more difficult to identify associations with environmental agents. The effect of a risk factor may be diluted if evaluated in a heterogeneous population (128). Analyses based on clinical, autoantibody, or genetic subgroups may be one way to illuminate separate causal pathways and identify specific environmental risk factors.

Significant differences in genes of the major histocompatibility complex were found between SSc patients with silica exposure compared to idiopathic cases (99), especially among patients expressing anti-topoisomerase I antibodies. These data suggest that the association of silica and autoimmune diseases may be modified by genetic factors.

Given that women have higher rates of many autoimmune diseases compared to men, it is important to learn if they are more or less vulnerable to environmental exposures. Most documented cases of silica-related autoimmune disease have been male, and some studies have reported lower estimates of the association between silica dust and autoimmune disease in women compared to men (41-43). The discrepancy between the apparent effects of silica in men and women may be explained by two factors: a) Men may be more likely than women be exposed to high levels of silica dust because they comprise the majority of workers in the dusty trades industries. b) Women experience a higher underlying rate of many autoimmune diseases, so the

relative impact of silica dust exposure may be diluted by cases that occur through other causal pathways. An exposure that increases the rate of disease will have a larger impact when measured as a ratio of association (RR or OR) in a group with a low underlying rate compared with a group with a higher underlying rate. For example, suppose that the incidence of a given disease is 1 case per 1,000 men and 10 cases per 1,000 women. If, for a given level of silica dust exposure, 1 additional case appears in 1,000 people, regardless of sex, the relative risk would be 2.0 for men but only 1.1 for women. Thus, exposure would appear to be related to disease in men but not in women.

Limitations and Strengths

Despite the large excess of autoimmune diseases observed in several occupational cohorts, the effects of silica dust exposure are much more difficult to study in the general population where high-level exposures are rare, and moderate- and lower-level exposures are difficult to assess and probably widespread. Rare diseases and rare exposures may result in the lack of power to detect moderate associations or differences among subgroups. The misclassification of silica dust exposure and confounding by other factors may bias the estimated association of silica and autoimmune disease.

Nonetheless, studies with different designs in a variety of exposed occupational groups suggest an association of silica with systemic autoimmune diseases. The adjuvant effect of silica is one mechanism by which silica could be involved in autoimmune disease. These data suggest that silica may act to promote the development of autoimmune diseases, requiring some other factor to break immune tolerance or initiate disease. Unlike known, nonmodifiable risk factors for autoimmune diseases (e.g., age, sex, genetics), silica dust exposure can be reduced through industrial hygiene and engineering measures. For this reason, the association between silica and autoimmune diseases merits further study.

Future research on the association between silica and autoimmune diseases should explore the common threads between the diseases that may be associated with silica exposure. Because autoimmune diseases and high-level silica exposures are rare, both occupational and population-based studies have their limitations. Studies of exposure parameters would be most easily conducted in occupational cohorts with extensive exposure history and monitoring data. Longitudinal research in these cohorts may also be used to examine the predictive value of autoantibodies. Improved exposure assessment in population-based studies will require recognition of the potential for silica exposure in women, including moderate- and lower-level silica exposure. Researchers should also attempt to assess the potential for mixed exposures or confounding by other factors. Finally, experimental models could be used to investigate the mechanisms by which silica may operate in autoimmune diseases and to suggest preventive or treatment strategies.

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