CHAPTER 4

Silicosis

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Abstract: Silica refers to the compound SiO_2, which can be found as amorphous or in a variety of crystalline forms. The most common crystalline form is quartz, one of the most abundant minerals in the Earth's crust. Other less common forms found in nature include cristobalite and tridymite. Small particle aerosols, including crystalline silica, can be generated by many activities carried out in industries such as construction, manufacturing, and mining. Respirable crystalline silica (RCS) refers to particles small enough to remain suspended in air and be inhaled into the deep lung. Inhaling sufficient amounts of RCS causes a fibrosing interstitial lung disease called silicosis. It also causes or is a risk factor for a spectrum of diseases, including lung cancer, chronic obstructive pulmonary disease, chronic renal disease, increased susceptibility to tuberculosis, and various autoimmune diseases. These adverse outcomes can be prevented by recognizing potentially hazardous conditions and taking steps to control RCS exposures. Unfortunately, despite being preventable, silicosis continues to occur in many settings, including recent outbreaks in emerging settings. In the USA, recently-promulgated regulations by the Occupational Safety and Health Administration (OSHA) provide a comprehensive set of interventions to control RCS exposures and provide RCS-exposed workers with health surveillance for early detection of silicosis. Current treatment options for those with silicosis are limited and primarily consist of avoiding further exposure and symptomatic management, so primary prevention is extremely important.

Keywords: Acute silicosis, Autoimmune disease, Chest radiograph, Chronic renal disease, Chronic obstructive pulmonary disease, Cristobalite, Epidemiology, Exposure, High-resolution chest computed tomography scan, Lung cancer, Lung transplantation, Occupational Safety and Health Administration, Progressive massive fibrosis, Quartz, Respirable, Silica, Silicosis, Surveillance, Tridymite, Tuberculosis.

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INTRODUCTION

Pulmonary silicosis is an interstitial lung disease caused by inhaling particles of inorganic mineral dust containing crystalline silica into the lungs [1 - 3]. Inhaling sufficient amounts of crystalline silica causes or is a risk factor for a spectrum of diseases, including lung cancer, chronic obstructive pulmonary disease (COPD), chronic renal disease, increased susceptibility to tuberculosis (TB), and various autoimmune diseases [3 - 6]. These adverse outcomes can be prevented by recognizing potentially hazardous conditions and taking steps to control respirable crystalline silica (RCS) exposures. Unfortunately, despite being preventable, silicosis continues to occur in many settings, including recent outbreaks in emerging settings. In the USA, recently-promulgated regulations by the Occupational Safety and Health Administration (OSHA) provide a comprehensive set of interventions to control RCS exposures and to provide RCS exposed workers with health surveillance for early detection of silicosis that can help to identify remediable gaps in prevention [5]. Current treatment options for those with silicosis are limited and primarily consist of avoiding further exposure and symptomatic management, so primary prevention is extremely important.

RESPIRABLE CRYSTALLINE SILICA (RCS)

Silica is a term describing the compound SiO_2. It exists in amorphous and crystalline forms. In amorphous forms, SIO_2 molecules are not arranged in a fixed pattern or structure. In crystalline forms, the SiO_2 molecules are arranged in fixed patterns. Different polymorphs of crystalline silica have molecules of SIO_2 arranged into different structures. There are a number of polymorphs or forms of crystalline silica, but the 3 major ones found in natural settings are quartz, cristobalite, and tridymite. Quartz is found in many types of rocks and is one of the most abundant minerals in the Earth's crust. Cristobalite and tridymite are far less abundant in natural settings but can be found, typically in volcanic rock [4, 7]. However, cristobalite and tridymite can be generated and create hazards in industrial settings where amorphous silica or quartz are exposed to intense heat. An important example occurs in foundries where castings are made by pouring molten metal into amorphous silica-containing clay molds.

The term respirable refers to particle size. Respirable particles are small enough to remain suspended in air and be inhaled into the deep lung. They are conventionally considered to have a diameter of 4 μm or less. OSHA method ID-142, which is used to assess exposure to RCS, uses a sampler that captures about 50% of particles of 3.5 μM and none that are 10 μM or larger [8].

EXPOSURES TO RCS

Because crystalline silica, in particular quartz, is so widely distributed in nature, many types of activities can cause exposure to RCS by aerosolizing dust from natural sources such as rocks or soil or from silica-containing manmade materials such as bricks or concrete. Examples include cutting, drilling, grinding, tunneling, demolition, mining and quarrying. Exposures can also occur from engaging in activities such as abrasive blasting with sand. Because industrial processes that involve heating materials that contain quartz or amorphous silica can generate tridymite and cristobalite, they can also be associated with RCS exposures. For example, cristobalite exposures can occur in foundries when clay molds that have been in contact with molten metal are removed from metal castings.

Worldwide, millions of workers are exposed to RCS. Estimates include 2 million in Brazil exposed at least 30% of the time [9], 3.2 million in the European Union [10], and 10 million at risk in India [9]. OSHA has provided an extensive list of occupations and industries in the USA where exposure to RCS occurs and has estimated that about 2.3 million employees are at risk for exposure and thus are covered by OSHA's RCS standard [5].

A 1998 U.S. publication evaluating RCS air sampling data collected by OSHA during regulatory compliance inspection noted that some of the highest RCS dust concentrations occurred in construction (masonry, heavy construction, and painting), iron and steel foundries (casting), and in metal services (sandblasting, grinding, or buffing of metal parts). The industry that was found to have the highest percentage of workers (6%) exposed to at least the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) was the cut stone and stone products industry [11].

New sources of RCS exposure in work settings continue to emerge [12]. Recent examples include denim sandblasting [13], artificial stone countertop fabrication [14], and natural gas extraction by hydraulic fracturing [15]. In addition, RCS exposure related to contemporary mining methods has played an important role in pneumoconiosis among U.S. coal miners [16].

PATHOGENESIS OF SILICOSIS

RCS-induced toxicity is complex and basic mechanisms of cellular damage have been addressed in recent excellent reviews [17 - 19]. Briefly, cellular targets after intrapulmonary deposition of RCS particles likely include alveolar macrophages and respiratory epithelial cells. RCS can be directly cytotoxic to cells because of its ability to generate free radicals in an aqueous solution, resulting in lipid peroxidation and DNA damage [20]. Freshly-fractured RCS particles with

exposed crystalline silica surfaces are better able to generate oxygen radicals than aged particles with possibly less exposed crystalline silica surface area [21]. RCS particles can also interact with cell-surface scavenger receptors on alveolar macrophages and activate the nucleotide-binding oligomerization domain (NOD-like) receptor (NLR), pyrin domain-containing 3 (NLRP3) inflammasome, a multiprotein complex that activates caspase-1. This leads to conversion of the cytokines such as interleukin (IL)-1β and IL-18 from inactive into active forms and also to the extracellular release of growth factors and alarmins such as basic fibroblast growth factor (bFGF) and high mobility group protein B1 (HMGB1) [22]. In addition to local toxicity induced by RCS, proinflammatory cytokine production and pulmonary inflammation can potentially activate adaptive immunity and break immune tolerance of self-antigen, leading to systemic autoimmunity as an adverse health outcome of RCS exposure [23].

Over time, often many years, toxic effects of RCS exposure evolve pathological changes. These have been described in detail elsewhere [24]. Briefly, an early finding is dust-laden macrophages and loose reticulin fibers. These can be found in peribronchial, perivascular and paraseptal or subpleural locations. Later, silicotic nodules develop. These have a central hyalinized zone with concentrically arranged collagen fibers. The nodule's periphery is a site of ongoing inflammation and enlargement. Nodular growth can involve small airways, pleura, and blood and lymphatic vessels. Coalescence of silicotic nodules together leads to progressive massive fibrosis (PMF). Centers of large PMF lesions can become necrotic and cavitate.

In addition to the chronic nodular fibrotic form of silicosis, inhalation of RCS can also cause the pathology of acute silicosis, which generally presents over a period of a few months to a few years after high levels of exposure [25]. In acute silicosis, there is alveolar filling with proteinaceous material consisting largely of phospholipids or surfactants (or surfactant-like material). Acute silicosis has an appearance that resembles alveolar proteinosis and is sometimes called silicoproteinosis.

EPIDEMIOLOGY OF SILICOSIS

The risk for developing silicosis is related to cumulative RCS exposure [5]. OSHA has published a detailed quantitative risk assessment to determine risks of various adverse outcomes associated with RCS exposure [26]. Based on primarily that analysis, OSHA established a permissible exposure limit (PEL) of 50 μg of RCS per cubic meter of air. At this level of exposure on a daily basis, OSHA estimated that a duration of 45 years' occupational exposure was associated with an estimated silicosis morbidity risk of between 20 and 170 cases per 1,000 for

developing fibrotic pulmonary lesions consistent with an International Labour Office (ILO) category of profusion (density of small opacities) of 1+. The estimated risk from excess lung cancer death was 5–23 excess deaths per 1,000 workers.

Globally, it is estimated that the number of incident silicosis cases increased in 2017 (23,695) compared with 1990 (14,973). However, the age-standardized incidence rate had a decreasing trend [27]. There is only limited information available about incident cases in the USA. This information is typically collected by states. From 2003–2011, Michigan and New Jersey had 292 incident cases. 28 had less than 10 years of potential occupational exposure to RCS, suggesting heavy exposures during those years. 92% of cases were in the manufacturing, construction, and mining industries. The greatest number of cases (63%) were in manufacturing [28].

Silicosis mortality is a lagging indicator of exposure since there is typically an interval of many years between exposure and disease and then another long interval between diagnosis and mortality. However, mortality analysis can provide useful information. In the USA, 333 deaths were identified among adults in 26 states for the years 1999, 2003, 2004, and 2007–2013. Construction, coal mining, and foundries were the major industries that employed decedents. The major occupations were mining machine operators; laborers and freight, stock and material movers; and construction laborers [29].

In addition to causing silicosis, epidemiologic data is consistent with RCS exposure being a cause or risk factor for other adverse health effects [4, 5]. These include COPD [30], lung cancer [31], chronic renal disease [32], susceptibility to tuberculosis [33, 34], and autoimmune diseases including rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis [35]. The International Agency for Research on Cancer (IARC) has formally identified crystalline silica in the form of quartz or cristobalite dust as a Group 1 human lung carcinogen [36]. In the case of chronic renal disease, a recent systematic review and meta-analysis found an increased risk in exposed populations but not a dose-response relationship and suggested that studies involving longitudinal follow-up of exposed cohorts were needed [32]. In the case of susceptibility to tuberculosis, a recent systematic review and meta-analysis found that evidence was robust in the presence of silicosis but was less certain for silica exposure without radiological silicosis [34]. RCS exposure is also associated with an increased risk for idiopathic pulmonary fibrosis and alveolar proteinosis [37]. Associations between RCS exposure and sarcoidosis have also been reported [38], with one study reporting increased risk for sarcoidosis only in RCS-exposed smokers [39].

RADIOGRAPHIC IMAGING OF SILICOSIS

The appearance of silicosis on radiographic imaging can be divided into two broad categories: simple silicosis, usually following relatively long-term exposure, consisting of micronodules and adenopathy; and complicated silicosis, also known as progressive massive fibrosis (PMF) an evolution of simple silicosis in which the nodules aggregate into progressive masses with effects on adjacent lung tissue. In addition, there is the uncommon entity of acute silicosis or silicoproteinosis which can occur within a few weeks but more typically within a months to a few years after high levels of RCS exposure and which resembles pulmonary alveolar proteinosis. An additional uncommon entity is rheumatoid pneumoconiosis or Caplan syndrome, in which pulmonary manifestations of rheumatoid pneumonitis and silicosis are superimposed.

Imaging findings of chronic silicosis will typically appear after at least ten years of RCS exposure. Accelerated changes manifesting after less than ten years can occur with higher levels of RCS exposure. The earliest finding on radiography is nodules approximately 1 mm to 10 mm in diameter, which uncommonly contain calcification, located predominantly in the upper lung zones (Fig. **1**).

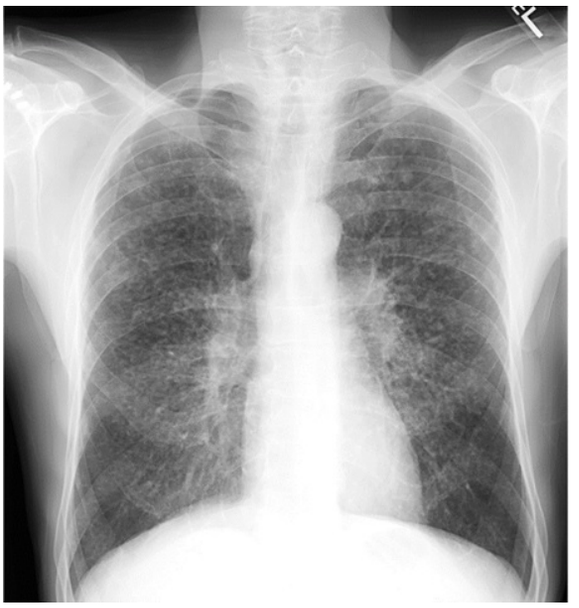

Fig. (1). Note small nodules in the mid and upper zones bilaterally.

Adenopathy in the mediastinum and hila is common and sometimes calcifies peripherally (“egg shell calcification”). On computed tomography, nodules of simple silicosis are distributed in a perilymphatic pattern, along lymphatics in the

bronchovascular bundles, in the interlobular septa, and the subpleural region, and measure from 1 mm to 3 mm (Fig. **2**), similar to the distribution seen in sarcoidosis. A possible mechanism for perilymphatic distribution is the migration of macrophages that have phagocytized RCS-containing particles to the perivascular interstitium, where the ingested silica particles produce an inflammatory response which in turn induces a fibrotic reaction. The resulting pattern of distribution of the nodules is perilymphatic. With the progression of the fibrotic reaction, there is a coalescence of the nodules into masses (Fig. **3**). Interestingly, the distribution of nodules in Coal Workers' Pneumoconiosis (CWP) is somewhat different on high resolution computed tomography (HRCT) scans of the chest, with nodules typically located along respiratory bronchioles in a centrilobular distribution.

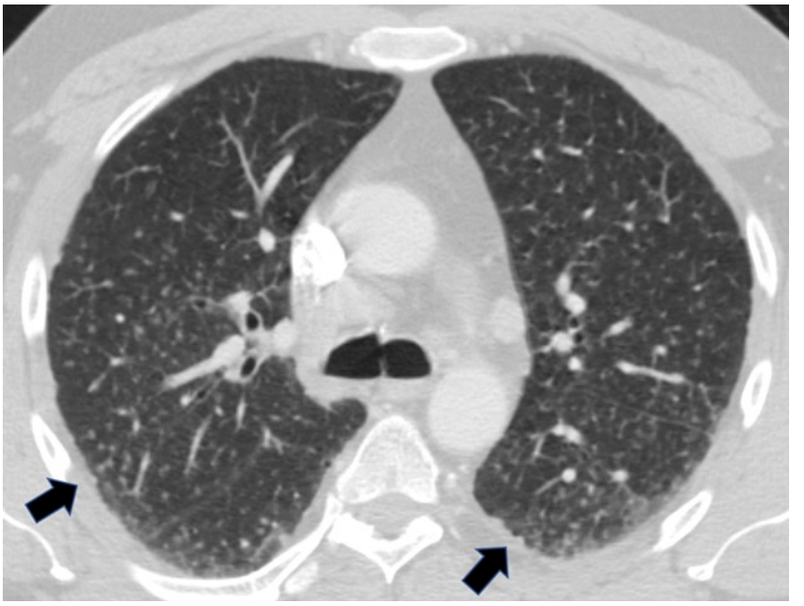

Fig. (2). Perilymphatic distribution; note beaded septa and subpleural nodules (arrows).

As coalescence of nodules continues, the masses of complicated pneumoconiosis develop, predominantly located in the upper lung zones dorsally. They are often symmetrical or nearly so and may have a lenticular shape with a convex lateral border roughly parallel to the chest wall. Hilar elevation is common (Fig. **4**).

Areas of emphysema often occur between the masses and the chest wall (Fig. **5**). As fibrosis progresses, the masses migrate centrally, with increased peripheral emphysema and increased risk of pneumothorax. The masses may contain calcification or may cavitate.

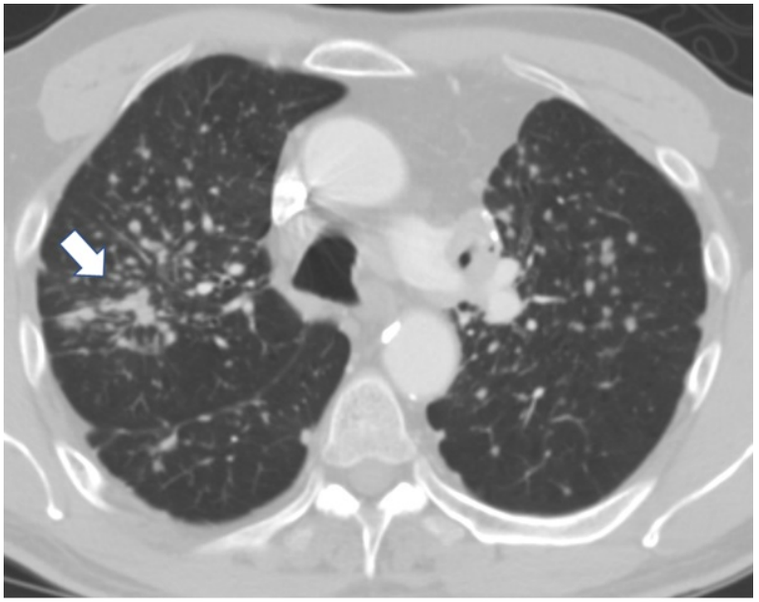

Fig. (3). Note beginning coalescence of nodules into a small mass (arrow).

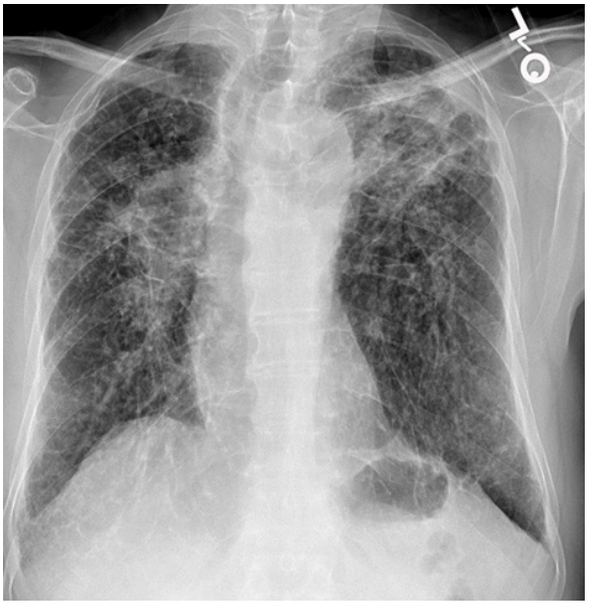

Fig. (4). Note masses in upper lung zone on left, with hilar elevation visible bilaterally.

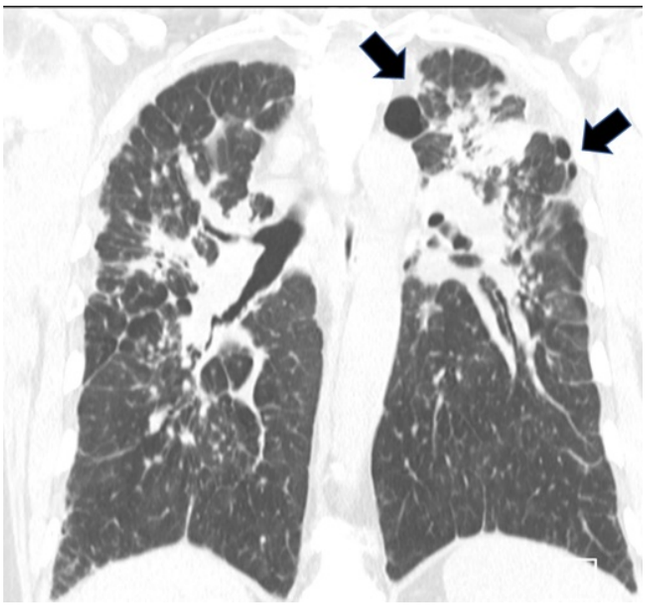

Fig. (5). Same patient as Fig. (**4**); note upper zone mass on left with adjacent emphysema (arrows).

CLINICAL PRESENTATION OF SILICOSIS

Different clinical presentations of silicosis are generally described based on features such as speed of onset and radiographic appearance. The most common presentation, chronic silicosis, develops slowly, manifesting 10 to 30 years after first exposure. Silicosis may not manifest until years after leaving the job that was associated with RCS exposure [40]. Chronic silicosis may have a simple radiographic pattern, PMF, or both. Accelerated silicosis is a presentation that develops less than 10 years after first RCS exposure. It is radiographically identical to chronic silicosis but develops more quickly. Rapid onset of silicosis suggests that there were high levels of RCS exposure. In both chronic and accelerated silicosis, patients may present with respiratory symptoms such as cough and dyspnea. Worsening of radiographic findings is associated with worsening of pulmonary function and PMF is generally associated with the worst symptoms and pulmonary function. Both restrictive and obstructive impairment occurs, and interstitial lung disease can cause impaired diffusing capacity for carbon monoxide.

Acute silicosis is another presentation. It occurs after very high levels of exposure to RCS and can manifest in as little as a few weeks to up to around 5 years after first exposure [41]. As previously noted, acute silicosis is an alveolar filling process resembling alveolar proteinosis. Acute silicosis causes cough, weight loss, fatigue, chest pain and respiratory failure and carries a poor prognosis.

DIAGNOSIS OF SILICOSIS

Considering three main factors helps in making a diagnosis of silicosis. First, evaluate for the history of RCS exposure and assess whether there has been sufficient exposure to cause the disease. It is important to take a detailed occupational history to learn about the patient's jobs and tasks and the types of preventive interventions used on the job. Second, assess whether findings on chest imaging are consistent with silicosis. Findings seen on either plain chest imaging or a chest HRCT may be sufficient for diagnosis. However, if there is any uncertainty, chest HRCT should be obtained because it is more sensitive and allows for superior visualization of findings. Third, rule out alternative diagnoses that might cause similar radiographic findings. These might include miliary mycobacterial or fungal infection, pulmonary malignancy (particularly when masses consistent with PMF are unilateral or asymmetric), rheumatoid nodules (Caplan's Syndrome) or sarcoidosis. In the presence of a history of exposure, typical radiographic findings, and absence of plausible alternative diagnoses, the diagnosis of silicosis can generally be made clinically without resorting to lung biopsy. However, in some cases, lung biopsy may be needed to exclude other diagnoses.

MANAGEMENT OF SILICOSIS

At the current time, conventional treatment of silicosis is primarily supportive. Generally accepted, high-quality evidence does not currently exist showing that any specific treatment alters the long-term course of the disease. Patients should be instructed to avoid further RCS exposure, even though the disease may progress even in the absence of further exposure. Patients should also avoid other exposures such as smoking that can contribute to a decline in lung function over time. Vaccinations to prevent respiratory infection, including influenza, pneumococcal pneumonia, and coronavirus infectious disease 2019 (COVID-19) should be offered consistent with current practice guidelines. It is important to screen silica-exposed patients for latent TB. Latent and active TB should be treated consistent with current guidelines. Additional supportive therapy includes empiric trials of bronchodilators for symptomatic obstructive lung disease, prompt treatment of acute respiratory infections and treatment of chronically hypoxemic patients supplemental oxygen to prevent complications of chronic hypoxemic respiratory failure. Although RCS is a recognized lung carcinogen [36], current lung cancer screening guidelines from the U.S. Preventive Services Task Force do not include the history of RCS exposure as a consideration in initiating periodic lung cancer screening with low-dose computed tomography (LDCT) scans [42]. Another authoritative group, the National Comprehensive Cancer Network, recommends annual screening with LDCT in those 50 years of age or older, with

a history of 20 or more pack-years of smoking, and additional risk factors (other than second-hand smoke exposure), including a history of exposure to occupational carcinogens such as RCS [43].

Patients with end-stage silicosis and without contraindications are candidates for lung transplantation. A recent report that adjusted for covariates such as age, single *vs*. bilateral transplant, ischemic time, serum creatinine, and other factors found that outcomes after lung transplantation for silicosis were similar to outcomes for a lung transplant for non-occupational lung diseases [44].

A number of treatments have been attempted in the past to alter the outcome of Silicosis, such as corticosteroid treatment and whole lung lavage to remove RCS from the lungs [45]. A limited body of literature suggests that there may be beneficial effects of whole lung lavage [46]. Improvements in understanding the pathogenic mechanisms of silicosis may lead to improved therapies [19]. One of these is nintedanib, an intracellular tyrosine kinase inhibitor that interrupts pathways associated with pulmonary fibrosis. Nintedanib was recently demonstrated to slow the rate of forced vital capacity (FVC) decline in patients with progressive fibrosing interstitial lung diseases defined as "a relative decline in the FVC of at least 10% of the predicted value, a relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms or an increased extent of fibrosis on high-resolution CT, or worsening of respiratory symptoms and an increased extent of fibrosis" over the previous 24 months [47]. The trial included exposure-related interstitial lung diseases but did not specify how many (if any) of these were due to silicosis. Also, those with PMF were excluded from the trial. Subsequently, the US Food and Drug Administration approved using nintedanib to treat chronic fibrosing interstitial lung diseases with a progressive phenotype [48]. In view of this, the drug could be used in the USA to treat silicosis with a progressive phenotype. However, there are currently no published randomized controlled clinical trials specific to silicosis or including patients with PMF. A clinical trial is in progress that will hopefully address this gap [49].

PREVENTION OF SILICOSIS

Silicosis is preventable. Primary prevention means preventing the development of disease before it happens. Because silicosis only occurs if sufficient RCS is inhaled, primary prevention of silicosis involves controlling inhalation exposures to at or below occupational exposure limits. Multiple strategies from a hierarchy of controls can be used to prevent exposures. The term hierarchy refers to the effectiveness of controls, with the most effective controls placed highest in the hierarchy.

Elimination is the most effective control and would involve eliminating the use of crystalline silica containing material from the workplace. Substitution involves substituting a less hazardous material in place of crystalline silica in the workplace. Engineering controls such as using wet methods of cutting and grinding for dust suppression, local exhaust ventilation, directional and dilutional ventilation, air filtration, and dust containment are another effective type of intervention in the hierarchy of controls because once implemented, they protect everyone in the workplace without requiring compliance efforts from those in the workplace. In contrast, administrative controls such as posting warnings, limiting those present during hazardous activities, and work practice controls such as avoidance of dry sweeping require ongoing worker compliance and management enforcement to be effective and so are lower on the hierarchy of controls. Although extremely important in many settings, using personal protective equipment such as respirators to control exposures is at the bottom of the hierarchy of controls. The reason for this is that many things can go wrong. For example, workers may not always wear respirators properly or when they are needed and respirators may not always fit or function properly. For this reason, respirators must be used within the context of a rigorous respiratory protection program that involves activities such as respirator selection, training, fit testing, proper storage and maintenance of respirators, and record keeping. In view of these issues, respirators should generally be viewed as the least desirable primary prevention intervention and a last line of defense.

Another form of prevention is secondary prevention. This involves occupational health screening of workers exposed to RCS, including asymptomatic workers, for early detection of disease, ideally before it causes symptoms. This can benefit individual workers by allowing them the opportunity to limit further RCS exposures, thereby limiting cumulative lifetime exposure and the chance for progression to severe disease. This can also benefit co-workers if finding cases of early silicosis identifies unanticipated gaps in workplace prevention efforts that can be corrected. Although plain chest radiographs are usually used for screening asymptomatic workers, in the setting of a silicosis outbreak, more sensitive chest HRCT scans may identify cases not apparent by chest radiographs [50]. It is important to have a standardized approach to evaluating surveillance chest radiographs for the presence and severity of findings of pneumoconiosis. A system from the ILO is widely used for this purpose and, in the USA, NIOSH operates a program to certify physicians as able to apply the system [51]. In addition to evaluating and acting on individual test findings, it is also important for health surveillance results to be reviewed at the population level to identify patterns in results that might be missed at the individual level.

In 2016, OSHA promulgated a comprehensive set of regulations in the USA to prevent silicosis and other adverse health effects caused by inhaling RCS [5]. Requirements in the general industry include assessing employee exposures to RCS if it is anticipated that exposures may be at or above an action level of 25 $\mu g/m^3$, averaged over an 8-hour day. In addition, the regulation establishes a PEL of 50 $\mu g/m^3$, averaged over an 8-hour day. It also mandates engineering controls, administrative controls, and respirators to protect workers from exposures above the PEL. In addition it requires medical exams, including chest X-rays and lung function tests, to be offered every 3 years to workers who are exposed at or above the action level for 30 or more days per year. It also requires worker training on RCS exposure and how to limit it, in addition to other requirements.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

Authors are co-investigators in a planned study of nintedanib for progressive fibrosing coal mine dust-induced interstitial disease that will be funded by Boehringer-Ingelheim.

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Declared none.

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