The Classic Pneumoconioses
New Epidemiological and Laboratory Observations

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KEYWORDS

• Coal • Coal workers' pneumoconiosis • Silica • Silicosis • Asbestos • Asbestosis

KEY POINTS

- Digital chest imaging can now be used in the International Labor Office's classification system for the presence and severity of changes of pneumoconiosis with equivalent results to classification of analog film-screen radiographs.
- The role of lung cancer screening of asbestos-exposed individuals with low-dose chest computed tomography scanning is still evolving.
- Coal workers' pneumoconiosis, including severe forms, such as progressive massive fibrosis, is still occurring in the United States and has been seen in relatively young miners.
- Emerging exposure situations include longer work hours, work in small mines, and silica exposure from thin-seam coal mining in Appalachia, construction work, and natural gas extraction by hydraulic fracturing and environmental exposures to asbestos associated with human contamination of the environment or the presence of natural deposits.
- Newly or poorly recognized adverse health effects of exposures include lower-zone, irregular opacities in coal miners; antibodies against citrullinated peptide antigens–positive rheumatoid arthritis and antineutrophil cytoplasmic antibody-positive vasculitis in silicotics; and laryngeal and ovarian cancer in asbestos-exposed individuals.
- Soluble mesothelin-related peptides can be measured in serum to monitor the course of malignant mesothelioma with epithelioid features. The test is not approved in the United States for diagnostic purposes and its diagnostic potential is limited by low sensitivity for malignant mesothelioma at threshold serum values providing good specificity.

INTRODUCTION

The pneumoconioses are a group of lung diseases caused by the inhalation of mineral dust. They have long histories. Classic authorities, such Agricola and Ramazzini, described silicosis and coal workers' pneumoconiosis (CWP) centuries ago.[1,2] Although eliminating causative inhalation exposures can prevent pneumoconioses, they continue to occur. This brief review addresses selected issues of current interest and recent developments related to 3 types of inorganic mineral dust exposures that cause classic forms of pneumoconiosis: coal mine dust, crystalline

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silica, and asbestos. More comprehensive reviews are also available.[3–6] Although this review has a US perspective, mineral dust exposures and the pneumoconioses they cause are an important global issue.[7]

CHEST IMAGING IN PNEUMOCONIOSIS

Recent advances in chest imaging are relevant to all types of pneumoconiosis because imaging technology is critical to identifying these conditions in medical screening and surveillance and in epidemiologic research. Issues discussed in this section include use of digital chest imaging to classify the presence and severity of changes of pneumoconiosis using the International Labor Organization's (ILO) classification system and use of chest computed tomography (CT) for early detection of dust-induced disease.

Use of Digital Chest Imaging for ILO Classification

The ILO classification system is used worldwide to assess the presence and severity of chest radiographic changes of pneumoconiosis.[8] Before 2011, the classification system could only be applied to film-based chest radiographs. However, access to film-based radiography has markedly declined in the United States in recent years because of replacement by modern digital radiographic imaging systems. This replacement has hindered access to ILO classification when it was needed in research and other settings.

To address this issue, in 2009, the National Institute for Occupational Safety and Health (NIOSH), together with partners, including the ILO, established a plan to develop the ILO classification of digital chest images.[9] Since then, several studies have been conducted with the goal of establishing whether and how contemporary digital chest images could be used to perform ILO classifications and yield results equivalent to classifications using film-based images.[10–14] Together, these studies indicate that with appropriate attention to image acquisition and when images are displayed on medical-grade monitors, direct readout digital systems and computed radiography systems provide comparable classification results to traditional film-based radiographs. In addition, a consistent finding across studies is that digital image quality is significantly better than film-screen image quality. The equivalence between digital and film radiography for the classification of pneumoconiosis has also been demonstrated using the Chinese classification system (GBZ 70–2002).[15,16]

Reader variability is an important source of variability in the classification of chest images. Although a variety of measures can be used to reduce within and between reader variation, human subjectivity continues to be an important issue. To address this, efforts have been made to develop computer-assisted classification of chest radiographs for findings of pneumoconiosis. Studies were initially published in the 1970s.[17,18] Although much remains to be done, computer-aided ILO classification of digital chest images may someday be achievable.[19,20]

Medical Screening with Chest CT

High-resolution CT is more sensitive for detecting the earliest stages of pneumoconiosis than conventional chest radiography.[21–26] However, the potential benefits to patients of very early detection of pneumoconiosis, which generally progresses slowly and lacks specific curative treatment, are limited in comparison with the early detection of lung cancer, which can be life saving. A recently published, large, randomized controlled trial, the National Lung Screening Trial (NLST), has documented the effectiveness of early detection of lung cancer in older heavy smokers undergoing annual screening with low-dose chest CT scans (LDCT) as compared with annual screening with plain chest imaging. Its finding of reduced mortality in the group randomized to LDCT has been of great interest to those caring for individuals previously exposed to other carcinogens, including asbestos.[27] LDCT was used for screening instead of conventional CT to limit the potential harmful consequences of radiation exposure.

In the wake of the NLST, 4 medical societies collaborated to conduct a systematic review of the evidence of benefits and harms of lung cancer screening with LDCT.[28] The review found NLST to be the most informative study. Patients included in the NLST were smokers and former smokers aged 55 to 74 years who had smoked for 30 pack-years or more and either continued to smoke or had quit within the past 15 years. After 3 rounds of annual LDCT imaging and appropriate follow-up care for those with abnormal findings, the relative risk of lung cancer mortality was decreased by 20% and absolute risk by 0.33%. Unfortunately, screening does result in false positives. Across studies, nearly 20% of individuals had positive results requiring follow-up, whereas approximately 1% had lung cancer. The review concluded: "For smokers and former smokers aged 55 to 74 years who have smoked for 30 pack-years or more and either continue to smoke or have quit within the past 15 years, we suggest that annual

screening with…LDCT… should be offered over both annual screening with chest radiograph or no screening…"[28] The review categorized this as a weak recommendation based on moderate-quality evidence.

It is unclear how these general screening recommendations for lung cancer might apply to workers at an increased risk from lung cancer caused by exposures, such as asbestos. The American Association for Thoracic Surgery suggested the following group be screened in addition to the one already noted: "Screening may begin at age 50 years with a 20 pack-year history of smoking and additional comorbidity that produces a cumulative risk of developing lung cancer of 5% or greater over the following 5 years."[29] Thus, LDCT screening under this recommendation might target LDCT screening to those with sufficient risk from past asbestos exposure and cigarette smoking.[30]

COAL MINE DUST

Despite marked improvements in the United States relative to several decades ago, several recent studies have documented that CWP, including advanced forms, such as progressive massive fibrosis (PMF), continues to be an important problem. Issues discussed in this section include the persistence of CWP in the United States, underlying factors associated with persistence, respiratory health outcomes among coal dust–exposed workers other than classic CWP, and new technology for personal dust monitoring.

Persistence of CWP in the United States

As a result of the 1969 Federal Coal Mine Health and Safety Act (Coal Act),[31] the United States established and has subsequently maintained an ongoing medical monitoring program for CWP. This monitoring program, called the Coal Workers' X-ray Surveillance Program (CWXSP), provides chest radiographs at about 5-year intervals to underground coal miners at no cost to them. It documented that interventions specified in the Coal Act to track and reduce dust exposures were highly successful. The impact can be seen most markedly in miners of long tenure because CWP typically takes one or more decades to develop after the first exposure. For example, the prevalence of CWP among underground miners with greater than 25 years' tenure who participated in the program in 1970 was 44%. This decreased markedly through the 1990s, reaching a nadir of 2.4% in 1997 (**Fig. 1**).[32–37]

In 1999, NIOSH collaborated with the Mine Safety and Health Administration (MSHA) to

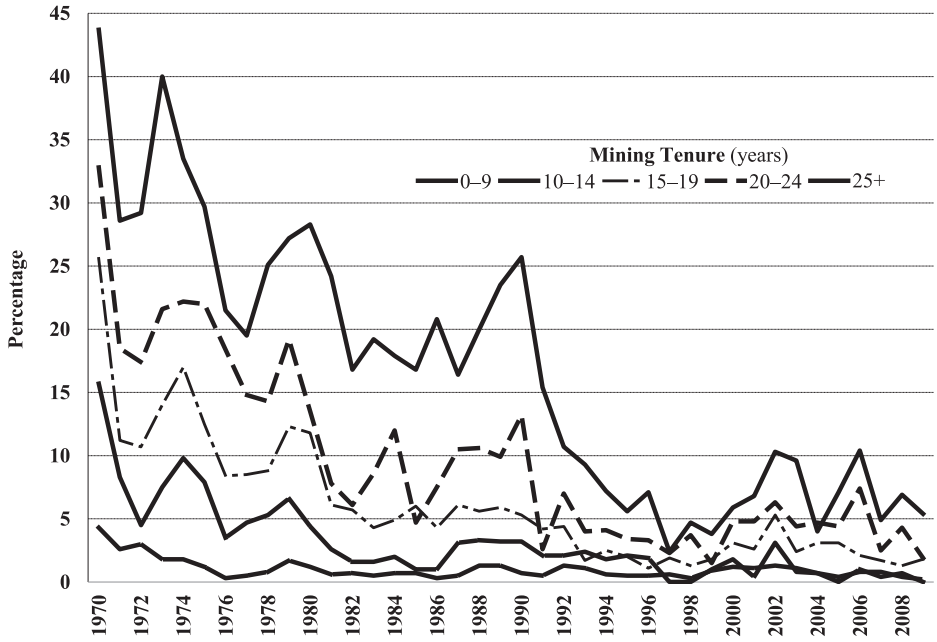

Fig. 1. Percentage of examined underground miners with coal workers' pneumoconiosis (ILO category 1/0+) by tenure in mining, 1970–2009. (*From* CDC/NIOSH. Work-Related Lung Disease Surveillance System (eWoRLD) Coal Workers' Pneumoconiosis and Related Exposures. Available at: http://www2a.cdc.gov/drds/WorldReportData/FigureTableDetails.asp?FigureTableID=2549&GroupRefNumber=F02-05. Accessed August 14, 2012.)

provide chest radiographs to both underground and surface miners through the CWXSP and a supplemental program called Miners' Choice. The effort lasted from October 1, 1999 to September 30, 2002. A total of 35 983 chest films were analyzed. CWP prevalence was 3.2% for underground miners and 1.9% for surface miners.[34] Of concern, advanced CWP, including PMF, was still occurring. Because of concerns about continued occurrence of CWP, including PMF among relatively young coal miners, Antao and colleagues[38] conducted a study that focused on rapidly progressive disease among underground miners from 1996 to 2002. Among the 29 521 miners examined, 886 cases of CWP were identified. Among the miners with CWP who contributed serial radiographs, 35.4% had evidence of rapidly progressive CWP, defined as the development of PMF or an increase in one or more small opacity profusion subcategories within 5 years. The cases of rapidly progressive CWP were clustered in Eastern Kentucky and Western Virginia, with more than 60% of evaluated miners in this region with CWP showing advanced and rapidly progressive CWP. A total of 41 cases of PMF (0.14%) were identified.

In 2005, NIOSH established the Enhanced Coal Workers' Health Surveillance Program (ECWHSP). This program used a mobile examination unit to conduct surveillance outreach. The goals of ECWHSP were to better define the scope and magnitude of the problem of lung disease in coal miners and to identify potentially remediable causes. The mobile unit conducted surveys in March and May of 2006 in the Lee and Wise counties of Virginia.[39] Among the miners surveyed, the prevalence of CWP was 9.0% and the prevalence of PMF was 1.5% (greater than the 1.3% observed in US miners for the period 1968–1972). A subsequent report in 2007 included information from surveys in Southwest Virginia and Eastern Kentucky and found a prevalence of PMF of 1.8%.[40]

Overall national trends of PMF prevalence in underground coal miners with 15 or more years of tenure showed marked decreases from the 1970s to the 1990s. Although prevalence remains far less than in the 1970s, it has trended upward since then.[41] At the state level, West Virginia has reported a similar experience. A large case series of 138 miners with PMF was reported for the 2000–2009 period using data from the West Virginia State Occupational Pneumoconiosis Board (WVSOPB).[42] The average age in this group was 52.6 years (range 40–77 years). The study noted that PMF was more frequent, more aggressive, and occurring at an earlier age among West Virginian miners compensated by the WVSOPB in this period compared with previous years. The rate of premature mortality was significantly elevated in this group.

Years of potential life lost (YPLL) is an important metric for the burden of premature mortality. It is particularly affected by deaths at an early age. At the national level, Mazurek and colleagues[43] reported in 2009 that YPLL before 65 years of age and, to a greater extent, mean YPLL per decedent increased from 2002 to 2006. Recent reports of lung transplantation for severe CWP also document a continued burden of severe cases.[44–46]

Underlying Factors Associated with the Persistence of CWP

A consistent finding among the studies conducted since 2000, which have assessed the effect of mine size (number of employees), is a significant correlation between small mine size and greater levels of CWP.[37,38,47,48] In a large study of US underground miners, miners from small mines (less than 50 employees) had a 3.5-fold greater prevalence of CWP and a 5-fold greater prevalence of PMF compared with miners from larger mines (50 or more employees).[47] The reason CWP risk and severity are highly correlated with mine size is not fully known. However, this finding is similar to injury fatality rates; miner fatalities are highest in the smallest mines.[49–52] It has been observed that smaller mines tend to use younger miners,[47,49] and it is hypothesized that this average inexperience leads to higher rates of injuries. How this would impact respiratory illness is unclear. It is likely that larger mines are more likely to have the resources required to effectively monitor and control dust exposures, whereas smaller mines may lack the capital to upgrade ventilation systems or purchase advanced dust control technologies. In addition, dedicated health and safety officers are less likely to be available in a small workforce.[53]

Another hypothesis for the new epidemiologic observations in CWP is that exposure to crystalline silica has increased in recent years.[47,54,55] Although the available quartz exposure data in coal mining do not provide evidence for an appreciable upward trend, the validity and representativeness of these measures has been questioned.[56–58] One piece of evidence that supports a role for silica exposure as causing pneumoconiosis in at least some miners is that a radiographic abnormality suggestive of silicosis (rounded pneumoconiotic opacities exceeding 3 mm in diameter [designated r-type under the ILO classification system]) has increased among underground coal miners since

2000.[59] Among miners in Kentucky, Virginia, and West Virginia, r-type opacities were 7.6 times more common in the 2000–2008 period compared with the 1980s. However, r-type opacities were found in only a small minority of these Appalachian miners, increasing from approximately 0.2% to about 1.4%. This increase was noted only in Appalachia. Silica exposure in Appalachia might be the result of thin-seam mining (defined as a coal seam less than 43 in). Crystalline silica is most often found in a higher concentration in the rock strata outside of the coal seam than within the coal seam itself, and the practice of breaching the coal/rock interface is more common in thin-seam mines.[60] Often rock is intentionally mined from the floor and roof to provide greater clearance for mining equipment.[37,60] Ninety-six percent of US underground thin-seam mines are located in Kentucky, Virginia, and West Virginia.[61]

Range of Respiratory Outcomes Associated with Coal Mine Dust Exposure

Exposure to coal mine dust can result in pulmonary diseases other than pneumoconiosis with the classical nodular interstitial appearance and upper zone predominance. Several studies have evaluated the zonal distribution of pneumoconiotic small opacities on radiographs of US coal miners.[62–64] Each of these found that the distribution of small opacities was not predominantly in the upper lung zones, despite what is commonly found in textbooks and review articles. In general, the distribution of small pneumoconiotic opacities is associated with the primary shape observed on the radiograph. Irregularly shaped opacities tend to be more common in the lower lung zones, whereas nodular opacities are more presently observed in the upper lung zones. This finding has also been observed among Canadian hard rock miners.[65] Another important adverse health effect of coal mine dust exposure is chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[41,66–68]

Real-time Monitors for Exposure Assessment

An important recent advance has been the development of an essentially real-time personal respirable dust monitor (PDM) that can be worn by coal miners at risk for excessive coal mine dust exposures.[69,70] The PDM uses a tapered-element oscillating microbalance to measure the mass of dust deposited on a filter. It provides continuous measurement of the concentration of respirable coal mine dust in a wearer's breathing zone. Validation testing showed 95% confidence that the individual PDM measurements were within ±25% of the reference measurements obtained using conventional gravimetric samplers. Having immediate information about excessive exposures has great advantages over conventional methods, which do not provide this feedback. If aware of situations causing exposures, coal miners can immediately take steps to correct them. The potential benefits have led to regulatory efforts by MSHA to enable the use of PDM in its proposed rule, "Lowering Miners' Exposure to Respirable Coal Mine Dust Including Continuous Personal Dust Monitors."[71]

CRYSTALLINE SILICA

Exposure to respirable crystalline silica has been associated with several health effects, including silicosis, increased susceptibility to tuberculosis, lung cancer, COPD, autoimmune diseases, and chronic renal disease.[4,72] Issues discussed in this section include the current burden of silica exposure and silicosis in the United States; new occupational settings for respirable crystalline silica exposure and silicosis; and brief updates on selected silica-related health effects, including lymph node involvement and silica-related immune dysfunction and immunologic disease.

Current Burden of Silica Exposure and Silicosis in the United States

Inhalation exposure to crystalline silica is a potential hazard across many occupations and industries. One type of crystalline silica, quartz, is a major component of soil and rocks. Many occupations and industries involve activities that aerosolize quartz-containing dust from soil and/or rocks. Examples include drilling, tunneling, and quarrying or cutting, breaking, or crushing materials, such as stone that contains quartz. Cristobalite and tridymite are types of crystalline silica that can be produced by industrial processes that involve heating quartz or amorphous silica. Examples of such processes include foundry work whereby clay molds are heated by molten metal or in manufacturing brick or ceramics.

Yassin and colleagues[73] analyzed inspection data from the Occupational Safety and Health Administration (OSHA) collected between 1988 and 2003 to assess the level of occupational exposure to respirable crystalline silica in the United States. Although exposures had declined in some industries and occupations, others were still overexposed. It was estimated that about 119 000 employees were potentially exposed in the United States. The industries with the greatest numbers of potentially exposed individuals were automotive repair paint shop; masonry, stonework; testing

laboratories services; and repair shops, not classified elsewhere.

There is no ongoing, organized national surveillance specifically targeted to silicosis in the United States. An especially important gap is information at the national level about silicosis morbidity. A major source of such information in the United States is the Bureau of Labor Statistics' (BLS) *Survey of Occupational Injuries and Illnesses.*[74] It contains information about work-related illnesses provided by employers. However, diseases with long latencies, like silicosis, are undercounted.[75] Silicosis can take decades since first exposure to develop and often manifests long after a worker has left a causative job. Thus, employers will be unaware and not able to enter such cases into BLS' reporting system.

Much of what is known about the burden of silicosis in the United States is gleaned from mortality data. The number of silicosis-related deaths has declined markedly over the past several decades (**Fig. 2**). In the late 1960s, death certificates indicated that in excess of 1000 people died of or with silicosis annually. By 2007, silicosis mortality had declined markedly. In that year, 123 people had death certificates indicating death from or with silicosis, an approximately 10-fold reduction. Rosenman and colleagues[76] have proposed that silicosis mortality can be used to estimate how many of those still living in the population have silicosis. They reported a capture-recapture analysis performed in Michigan that found a ratio of the number of living silicosis cases to deceased confirmed silicosis cases of 6.44. An important metric related to mortality is YPLL. Mazurek and Wood[77] reported that deaths in individuals aged 15 to 44 years accounted for 37% of silicosis-related YPLL in the United States before 65 years of age over the 2000–2005 period.

Emerging Settings of Exposure to Crystalline Silica

Because crystalline silica is present in so many materials, or can be created by heating amorphous silica in a range of industrial processes, new settings for exposure continue to emerge. An important development over the past decade has been increasing recognition of exposures in the construction industry.[78–80] The burden of silicosis in construction (and perhaps other industries) is underestimated when screening is performed using plain chest films, which are less sensitive to early disease than chest CT scans.[81] Another emerging source of exposure is natural gas extraction by hydraulic fracturing.[82] The process involves use of air pumps to transport and drive dry, fine sand into fracture sites to keep them open for gas extraction. Leaks in systems for transporting the sand used in this process can result in substantial overexposures to respirable crystalline silica. Another industry whereby exposures may occur is agriculture, particularly when farming dry, sandy soil.[83] Sand blasting is a well-known source of overexposure and is illegal in many countries. Akgun and colleagues[84] recently reported an outbreak of silicosis among denim sandblasters. This outbreak highlights the

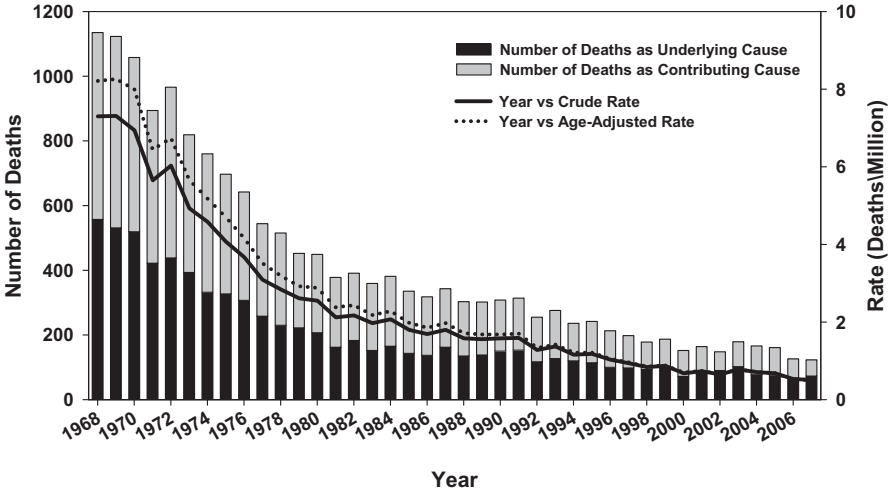

Fig. 2. Silicosis: number of deaths, crude and age-adjusted death rates, US residents aged 15 years and older, 1968–2007. (*From* CDC/NIOSH. Work-Related Lung Disease Surveillance System (eWoRLD) Silicosis and Related Exposures. Available at: http://www2a.cdc.gov/drds/WorldReportData/FigureTableDetails.asp?FigureTableID=2595&GroupRefNumber=F03-01. Accessed August 14. 2012.)

risk when an industry that is unfamiliar with the hazard associated with inhaling crystalline silica, such as the textile industry, implements new processes that create such exposures.

Silica-Related Health Effects

As already described, exposure to respirable crystalline silica can result in a range of adverse health effects. Recent developments in the area of silica-induced adverse health effects described in this section include intrathoracic lymph node involvement, the association between silica exposure and lung cancer, immune dysfunction, and immunologically mediated disease.

Two recent publications have evaluated lung and lymph node histopathology in specimens obtained from an autopsy archive of German uranium miners.[85,86] Occupational history and exposure information were also available to the investigators. Both studies found that lymph node–only silicosis was associated with lower exposures than lung silicosis. In one of the studies, as cumulative exposure to silica increased, lung silicosis increased at the expense of lymph node–only silicosis and no silicosis.[86] Although cross-sectional, these studies' findings suggest that, in at least some individuals, lymph node silicosis precedes lung silicosis.

The International Agency for Research on Cancer (IARC) has classified crystalline silica in group 1, carcinogenic to humans, since 1997. An IARC working group reconfirmed IARC's classification in 2010.[87] The 2010 working group found sufficient evidence in humans for the carcinogenicity of crystalline silica in the form of quartz or cristobalite and remarked that crystalline silica in the form of quartz or cristobalite dust causes lung cancer in humans. It found sufficient evidence in experimental animals for the carcinogenicity of quartz.

An area of controversy has been whether crystalline silica exposure without silicosis is associated with increased risk for lung cancer. Erren and colleagues[88] reported a meta-analysis of epidemiologic studies published from 1979 to 2006. The investigators noted that, in patients with silicosis, lung cancer risks were about double in 38 studies. In 8 studies of patients without silicosis without smoking adjustment, relative risk for lung cancer was smaller at 1.2; this increase was marginal from the standpoint of statistical significance. In 3 studies of patients without silicosis with smoking adjustment, no increased risk was observed. Guha and colleagues[87] discussed the issue of cancer risk in silica-exposed patients without silicosis in their discussion of the IARC classification of crystalline silica as a human carcinogen:

> *The analyses including only patients without silicosis showed no statistically significant association between crystalline silica exposure and lung cancer risk. However, the IARC Working Group noted that studies that restrict their analysis to individuals without silicosis potentially limit their range of silica exposure which would result in reduced power to detect associations and tend to omit individuals with the highest exposures.*[87]

It is likely that this issue will continue to be controversial, especially in view of its important social and economic implications. In 2011, the Italian Society of Occupational Medicine and Industrial Hygiene sought to address issues of liability and compensation. It recommended that, for legal purposes, only lung cancer cases associated with silicosis should be recognized as occupational.[89]

It has long been known that silica exposure, with or without silicosis, is associated with an increased risk for tuberculous and nontuberculous mycobacterial-related diseases.[90] A recent publication documented similarly impaired pulmonary host defense for fungal infections. It showed that patients with silicosis were more likely to die with pulmonary mycosis than those without pneumoconiosis or those with more common pneumoconioses.[91]

The association between silicosis and various connective tissue disorders is well recognized. Makol and colleagues[92] recently published an evaluation of connective tissue disease among 790 patients with silicosis with available medical records identified between 1985 and 2006 by a statewide surveillance system in Michigan. They found that rheumatoid arthritis was the most common classic connective tissue disease in this population of patients with silicosis (33 cases out of 790 patients with silicosis, 4.2%). Scleroderma occurred in 2 of the patients with silicosis (0.3%). A surprising finding was the prevalence of antineutrophilic cytoplasmic antibody (ANCA)–positive vasculitis (6 cases out of 790 patients with silicosis, 0.8%). Prevalence ratios were significantly increased relative to the general population for all of these conditions (rheumatoid arthritis 2.26–6.96, depending on the reference rate used; scleroderma 28.3; ANCA-vasculitis 25.3).

To further characterize rheumatoid arthritis in silica-exposed individuals, Stolt and colleagues[93] evaluated the prevalence of antibodies against citrullinated peptide antigens (ACPA) in rheumatoid

arthritis cases and controls with and without histories of silica exposure. It had previously been demonstrated that increased risk for rheumatoid arthritis associated with cigarette smoking was limited to the ACPA-positive subset of rheumatoid arthritis. There was about a 1.5-fold increased risk for ACPA-positive rheumatoid arthritis among patients exposed to silica. There was no increase in the risk of developing ACPA-negative rheumatoid arthritis, as compared with patients unexposed to silica. There was a strong interaction between silica exposure and smoking, with silica-exposed current smokers having a more than 7-fold increase in the risk of having ACPA-positive rheumatoid arthritis. Thus, ACPA may have some potential as biomarkers for silica-induced rheumatoid arthritis.

ASBESTOS

Asbestos is a commercial name, not a mineralogical definition. It is applied to a group of fibrous minerals with properties such as strength, flexibility, resistance to thermal and chemical degradation, and electrical resistance. These properties resulted in widespread use of asbestos in the last century for a range of purposes, including insulation, construction materials, brake pads, and fireproof woven textiles. Unfortunately, because of long latency, it took decades after the use of asbestos became common for the inhalation of asbestos-containing dust to be recognized as a serious health risk.[5]

There are currently 6 regulated types of asbestos fibers: a serpentine mineral (chrysotile asbestos) and 5 amphibole minerals, including cummingtonite-grunerite asbestos (amosite), riebeckite asbestos (crocidolite), actinolite asbestos, anthophyllite asbestos, and tremolite asbestos. The distinctive constellation of pleural and pulmonary health effects resulting from inhalation of these materials is well recognized, as is the need for preventing exposures. Pleural effects include pleural effusion, parietal pleural plaque, visceral diffuse pleural disease, rounded atelectasis, and mesothelioma. Pulmonary parenchymal effects include asbestosis and lung cancer.[3,5]

This section describes several areas that are controversial or where there have been important new developments. These areas include how asbestos should be defined; recent developments in documenting the nonpleuropulmonary malignancies associated with asbestos; hazards associated with environmental exposures to asbestos, whether from human contamination of the environment or natural deposits; and recent developments in mesothelioma biomarkers.

Definition of Asbestos

Regulated forms of asbestos in the United States are the 6 previously noted asbestos minerals in an asbestiform crystalline morphology or habit. The term *asbestiform* is generally used to describe populations of single-crystal fibrils (the smallest structural unit of a fiber), which occur in bundles and possess certain characteristics, including high aspect ratio, high tensile strength, and flexibility (**Fig. 3**).[94] Several authorities have commented on problems and controversies in how asbestos is defined.[5,94–97] For example, some mineral types other than those named in regulations can occur in asbestiform habit and cause the same diseases. One such mineral is erionite, which is responsible for outbreaks of mesothelioma in residents of some Turkish villages where erionite-containing rock was used to construct homes.[98] Two other such minerals are winchite and richterite. These minerals constitute a major portion of the asbestiform amphibole fibers contaminating vermiculite from Libby, Montana. They also exemplify problems with terminology related to asbestos because winchite and richterite were once included within the definition of tremolite asbestos but have more recently been redefined as separate minerals based on elemental content.[94]

More controversial is whether fibers of asbestos minerals in habits other than asbestiform should be counted as asbestos. Examples include cleavage fragments created by the breakage of mineral in massive crystalline habit or needlelike acicular fibers that grow as single crystals instead of

Fig. 3. Winchite-richterite asbestos, Libby, Montana. (*Courtesy of* the U.S. Geological Survey. Available at: http://usgsprobe.cr.usgs.gov/picts2.html. Accessed August 14, 2012.)

asbestiform bundles. This controversy is a source of a long-standing difference between NIOSH, OSHA, and MSHA, with NIOSH recommending that cleavage fragments of the asbestos minerals be counted as asbestos if they meet the dimensional criteria of a fiber and the permissible exposure limits of OSHA and MSHA not including such elongate mineral particles within their definitions of asbestos. An important source of these differences is imperfect information about the toxicology of such particles.[5]

Certain counting methods are specified in regulatory definitions of asbestos fibers. The most commonly used analytical method to count asbestos fibers in air samples or bulk materials is phase-contrast light microscopy (PCM). The dimensions of asbestos fibers counted using this method are generally defined as a length/width (aspect) ratio of 3:1 and a length of at least 5 μm. Some methods also specify a width no more than 3 μm. An important limitation of PCM is that it does not count thin fibers of less than about 0.25 μm. These fibers can be visualized and counted by electron microscopy, which is used far less frequently than PCM in asbestos exposure assessment. A recent reevaluation of a cohort of chrysotile textile workers documented the important role of thin fibers not visualized by PCM in causing respiratory disease.[99] Fiber dimensions were evaluated in archived samples by transmission electron microscopy. Both lung cancer and asbestosis were most strongly associated with exposure to thin fibers less than 0.25 μm. Long fibers greater than 10 μm were the strongest predictors of lung cancer, but there was not a clear relationship between fiber length and asbestosis.

Nonpleuropulmonary Malignancies Associated with Asbestos

In 2006, the Institute of Medicine (IOM) released the report *Asbestos: Selected Cancers.*[100] The IOM committee writing the report was charged to evaluate evidence for causation of cancers of the pharynx, larynx, esophagus, stomach, and colon and rectum by asbestos. It found sufficient evidence for a causal relationship only for laryngeal cancer. There was suggestive evidence for all the others except esophageal cancer for which there was inadequate evidence. Another extrathoracic malignancy recently recognized as related to asbestos exposure is ovarian cancer. Based on a meta-analysis of available studies, IARC recently concluded that there was sufficient evidence for a causal relationship.[101] The overall pooled standardized mortality ratio estimate for ovarian cancer was 1.77.

Environmental Exposures to Asbestos

Many recent reports have highlighted the potential importance of environmental exposure to asbestos. Human contamination has been an important factor in several outbreaks of asbestos-associated disease. Widespread contamination of Libby, Montana occurred when asbestos-contaminated material from the vermiculite mine there was used across the community as gravel on roads, driveways, playgrounds, and so forth. Even tree bark has been suggested as a contaminated reservoir of asbestos fibers that, if disturbed, could result in exposure.[102] Excess morbidity and mortality has been documented even in those with nonoccupational sources of exposure.[103] A similar environmental disaster with widespread contamination and asbestos-related disease even among those not engaged in mining occurred in the Australian town of Witenoom where riebeckite asbestos (crocidolite) was mined.[104]

Use of asbestos-containing materials to gravel roads is another type of human activity that can result in environmental contamination and disease. Exposure can occur when these materials are disturbed by driving or by road work. Baumann and colleagues[105] investigated malignant mesothelioma in New Caledonia and found that presence of serpentinite on roads was a major environmental risk factor for the disease. Several recent investigations resulted from the realization that roads in Southwestern North Dakota had been graveled with materials contaminated with asbestiform fibrous erionite.[98,106] Two people with histories of road maintenance work were identified with asbestos-related pleuropulmonary disease visualized by chest CT.

Exposure can also occur through disturbance of natural deposits. In 2005, Pan and colleagues[107] reported residential proximity to naturally occurring asbestos in California as an independent risk factor for mesothelioma. Exposure from naturally occurring asbestos has been recognized in California for several years. In 1979, Cooper and colleagues[108] noted that dust fall along roads and trails used recreationally in the Clear Creek area of San Benito County, California was 90% or more chrysotile asbestos. Riding motorcycles on trails was associated with exposures well in excess of occupational exposure limits. A series of studies done since then have confirmed the presence of asbestos and the potential for exposures.[109] Another example of human exposure from natural deposits was in El Dorado Hills, California where the Environmental Protection Agency was petitioned to assess asbestos

exposure after asbestos was found in the soil at a high school.[109] Asbestos was subsequently found in many air and soil samples from across the community. Highest exposures occur when people are engaged in activities that disturb contaminated soil. Both of these situations have been challenging to manage. In such situations, it is often hard to balance desires to preserve land access and property values versus minimizing health risks.

Mesothelioma Biomarkers

An important recent advance has been the development of blood biomarkers for malignant mesothelioma.[110,111] One of these, Mesomark, measures soluble mesothelin-related peptides (SMRP). The US Food and Drug Administration approved it in 2007 for monitoring the course of mesothelioma with epithelioid features. Although not approved for diagnosis of malignant mesothelioma, there has been great interest in this potential application of serum SMRP levels. A recent meta-analysis of available studies found that at a threshold level with 95% specificity, serum mesothelin had a sensitivity of 32%. It was suggested that low sensitivity limited the value of the test for early diagnosis.[112] Osteopontin is another potential blood marker for malignant mesothelioma that has received much attention. A recent study suggests that plasma osteopontin has better performance characteristics for diagnosis than serum osteopontin, but neither performed as well as serum mesothelin. Combining serum mesothelin and plasma osteopontin results did not improve diagnostic performance.[113]

SUMMARY

There is a long history of recognition that coal mine dust, respirable crystalline silica, and asbestos are hazards that can be controlled. However, new settings for exposure continue to emerge and dust-related disease persists. Examples of emerging settings for exposure include thin-seam coal mining in Appalachia, construction work, and natural gas extraction by hydraulic fracturing (all of which can result in exposure to crystalline silica) and environmental exposures to asbestos associated with human contamination of the environment or the presence of natural deposits. New adverse health effects also continue to be recognized, such as ACPA-positive rheumatoid arthritis and ANCA-positive vasculitis in silicotics and laryngeal and ovarian cancer in asbestos-exposed individuals. Important advances continue to be made. Examples include advancements in the application of modern chest imaging and the development of blood markers for malignant mesothelioma. Until they are eliminated, pneumoconioses and related conditions will continue to be an important and dynamic aspect of chest medicine.

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