Exploring the role of silica exposure in the aetiology of interstitial lung disorders

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The paper by Iversen and colleagues[1] in this issue of *Occupational and Environmental Medicine* provides interesting insights into the potential contribution of inhaled respirable crystalline silica (RCS) in the development of idiopathic interstitial lung disorders and sarcoidosis. It also interestingly showed an association between low levels of cumulative RCS exposure and the presence of diagnosed silicosis. Importantly, it also reminds us about the uncertainties underlying current diagnostic practices, disease classification and knowledge about the lung's response to inhaled agents. What is certain is that occupational contributions to lung disease are frequently underestimated, and that better information is needed.

The Iversen *et al* study followed more than 5.5 million workers (ie, practically the entire Danish working population) for more than 30 years, tracking their clinical presentation to the Danish healthcare system. Occupational exposure to RCS was estimated using a previously validated job exposure matrix[2 3] (JEM), and cases of idiopathic interstitial pneumonias (IIPs), pulmonary sarcoidosis and silicosis were identified from the Danish National Patient Register (DNPR). The IIPs likely included idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP), the newly emerging genetic disorders and unclassifiable cases. For all studied lung disease outcomes except IPF, elevated incidence rate ratios (IRRs) were found associated with all RCS exposure categories.

This is the first time, to our knowledge, that the IIPs were prospectively studied using a validated JEM to estimate RCS exposure; the JEM was based on a large number of RCS samples collected across many geographies and time periods. Although significantly increased risks from RCS exposure were observed for IIP and sarcoidosis, none were observed when IPF alone was assessed. This lack of a significant association with IPF is intriguing but does not exclude a potential risk from RCS for other IIPs, particularly for NSIP.[4]

The increased IIP and sarcoidosis risks seem unlikely to be related to disease misclassification, given that cases were diagnosed by pulmonologists at one of four national interstitial lung disease (ILD) centres, and previous validation studies on disease classification in the DNPR have been carried out.[5] Adjustment was also made for potential confounding factors such as smoking, connective tissue disease, medication and radiation treatment.

Of those cases identified as sarcoidosis, the vast majority (83%) had no RCS exposure. However, in each of the other RCS exposure categories, monotonic significantly elevated sarcoidosis risks were observed. The authors recognised the possibility of disease misclassification (ie, silicosis misdiagnosed as sarcoidosis). If the clinicians at the ILD centres collected only occupational titles, they may not have recognised that many of their patients had silica exposure, given that many patients had jobs not widely known to be associated with silica exposure (eg, farming jobs). These clinicians would not have diagnosed silicosis in the absence of silica exposure. However, the fact that the IRR for sarcoidosis was significant even in the lowest exposure category (cumulative exposure <43.6 $\mu g/m^3$-years) downplays the possibility of disease misclassification. These findings thus contribute to the increasing evidence base suggesting that exposure to inorganic agents including RCS may be linked to the development of sarcoidosis in susceptible individuals.[6]

The exposure levels for a silicosis diagnosis were significantly lower than those reported in most other studies, with the majority of cases having worked in the construction and farming industries rather than in other industry sectors traditionally related to RCS exposure (eg, mining, iron and steel foundries and manufacturing). Surprisingly, the majority (64%) of silicosis cases were categorised as unexposed to RCS, and estimated cumulative levels of RCS exposure were generally very low; with a cumulative mean of 125 $\mu g/m^3$-years among exposed workers. Even low levels of cumulative RCS dose increments (each additional 50 $\mu g/m^3$-years) were significantly associated with increased silicosis risk. For perspective, a worker with workplace exposure levels of 50 $\mu g/m^3$ (8 hour time-weighted average, which is the RCS exposure standard in the USA[7]) for 10 years of work would have amassed a cumulative exposure of 500 $\mu g/m^3$-years.

Simple silicosis is generally regarded as a disease associated with substantial cumulative RCS exposure over a prolonged time period. The Occupational Safety and Health Administration (OSHA) collated many studies addressing RCS dose and response[8] and developed a summary of cumulative risk estimates for silicosis. Admittedly, these collated studies were performed using chest radiographs for diagnosing silicosis rather than using more sensitive techniques such as CT scanning. OSHA found that the lifetime risks for silicosis were associated with much higher cumulative exposures to RCS compared with those identified by Iversen *et al*.

Important questions still exist in relation to the completeness of the occupational data held by DNPR, the utility of the JEM to accurately assess RCS exposure in all worker groups, how much RCS exposure is required to cause radiological findings consistent with silicosis of any grade and diagnostic accuracy. Although Iversen *et al* reported that detailed occupational histories are obtained at the Danish ILD centres, one wonders if it was comprehensive.

Because this was a population-based registry study, Iversen *et al* were not able to supply further data that could help unravel these diagnostic and exposure complexities. There were no data available on detailed clinical presentation, detailed occupational histories of workplace RCS exposures or peak exposures, differential diagnostic practices, nor detailed radiological findings. These apparent diagnostic anomalies resonate with a wider debate about the accuracy of ILD diagnostic processes and in particular the silicosis versus sarcoidosis diagnostic debate; such cases can be misdiagnosed in both directions.[9–11]

This paper should stimulate efforts to further investigate the population effects of low-dose RCS exposure and to identify diagnostic approaches for better differentiating silicosis from sarcoidosis in RCS-exposed workers. It also highlights the importance of considering an occupational aetiology[12] in patients with interstitial lung disease.

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