Editorial

Occupational Exposures and Risk of Rheumatoid Arthritis: Continued Advances and Opportunities for Research

OCCUPATIONAL EXPOSURES AND RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is the most common of the systemic autoimmune diseases, affecting at least 1% of the total population, and 2% to 3% of people over age 60 years[1]. Recent research focusing on the risk of cardiovascular disease in RA and other conditions resulting in chronic systemic inflammation[2] raises new challenges for successful longterm disease management. Is prevention of systemic autoimmune diseases an option? The relatively low contribution of genetic factors in RA compared with some other autoimmune diseases[3], and the declining incidence rates seen in several populations[1], would suggest the answer to that question is yes. Occupational exposures to physical and chemical agents (e.g., noise, asbestos, benzene and other solvents) represent potentially modifiable exposures, and thus potentially constructive avenues for disease prevention. What are the occupations, or occupational exposures, that would be of greatest interest from the standpoint of the systemic autoimmune diseases?

In this issue of *The Journal*, Li, *et al* present an analysis of occupational risk factors for RA using national databases from Sweden[4]. Their study links occupation information collected in the national censuses conducted in 1960, 1970, and 1980 to hospitalization data from 1964 to 2004. The linkage of databases enabled the calculation of relative incidence rates among different occupational groups. This study builds on previous research in RA and other systemic autoimmune diseases, which has largely focused on respirable dusts and solvents[5].

In men, the most striking finding from the Li study is the increased risk seen among miners and quarry workers, with incidence ratios of 1.4 to 1.8 depending on the analysis group. Smaller associations (incidence ratios of 1.2 to 1.4) were seen in some construction-related trades[4]. This is not the first time these occupations have been linked to RA. The occurrence of RA, with a distinctive pattern of small opacities throughout the lung seen on radiography in coal miners with pulmonary fibrosis, was described in the 1950s[6], and several studies reported an increased risk of hospitalizations for RA among people with silicosis[7-10]. Silicosis is not a necessary precondition for RA, however. A prospective study of 1026 quarry workers in Finland reported a 5-fold increased risk of disability due to RA among workers who were free of silicosis at the start of followup[11].

In women, the data from Li, *et al*[4] show more modest relative risks (incidence ratios of 1.1 to 1.3) for a variety of occupations, only some of which (e.g., electrical workers, wood workers) would have been likely to be related a priori to a hypothesized occupational exposure. Given the higher absolute risk of RA in women compared with men, these lower risk ratios should not necessarily be dismissed as being unimportant from an etiological or an attributable risk standpoint. These results may reflect potential difficulties in accurately assessing relevant exposures faced by women in a variety of occupations[12,13]. There are considerable challenges to conducting research on the contribution of occupational exposures to systemic autoimmune diseases that disproportionately affect women.

Registry linkage studies using hospitalization data depend on several specific assumptions. The authors were able to address the validity of some of these assumptions by conducting various sensitivity analyses, but other assumptions would be strengthened by additional research. For example, Li's case ascertainment was based on hospitalization with a primary diagnosis of RA[4]. This definition is clearly not equivalent to the initial occurrence of the disease. Some portion of patients will be missed because they were not hospitalized for their diseases. In addition, for some portion of cases defined on the basis of hospitalization date, the occupation data collected during the preceding census could reflect a job choice that was made because of the illness. It is difficult to imagine a decision-making process that would lead a large number of patients with RA

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to take up quarry work, but other decisions (for example, an interest in social work or healthcare that arises because of experience with a chronic illness) are more conceivable. What proportion of RA patients are hospitalized within a specific period of their initial diagnosis? What is the average duration between disease onset or diagnosis and hospitalization with a primary diagnosis of RA? Does it vary by gender? Information of this type could be used to refine analyses using hospitalization registry data to improve the analysis of work experiences preceding diagnosis.

The Li study[4] is an example of the increasingly complex analyses that have been made possible by the systematic creation of population registers in Sweden and other European countries. This design complements other designs involving more individualized exposure assessment and diagnostic confirmation, including nested case-control studies within occupational cohorts and population-based case-control studies. Each type of design offers a set of strengths and weaknesses, and often tradeoffs, for example, between the completeness of the coverage of a population (via census data) and comprehensiveness of exposure data (via focused individualized interviews or industrial hygiene assessment within a workplace). Totality of evidence is strengthened, as in the case of studies of silica exposure and systemic autoimmune diseases, by observation in a variety of locations, using a variety of designs, and in conjunction with experimental studies.

What are the properties of a respirable dust that could promote an immunogenic response and autoimmune disease? Much recent research has focused on the adjuvant aspect of silica acting along with loss of macrophage activity due to silica-induced apoptosis, in conjunction with silica-enhanced antigen presentation[14]. It is interesting that asbestos, which was also described in one of the early case series of Caplan syndrome[15], has also been the focus of recent research on autoimmune diseases. Relatively strong associations (odds ratio 2.5 or higher) were seen between RA and history of asbestos exposure in men in a population-based case-control study of incident RA in Sweden[16], and in a study of self-reported RA in the Libby, Montana, community (exposed to asbestos through the mining, milling, and processing of asbestos-contaminated vermiculite)[17]. Experimental *in vitro* and *in vivo* studies of asbestos have observed increased autoantibody production and presentation within apoptotic cell-surface blebs and activation of T cells[18,19]. The research pertaining to autoimmune effects of silica and asbestos are examples of the advances that can be made through the communication and collaboration of scientists from a variety of fields, including clinical rheumatology, epidemiology, immunology, and toxicology.

Our understanding of various exposures in relation to cancer or respiratory diseases such as silicosis or asbestosis is in many ways more advanced than our understanding of occupational exposures in relation to RA and other systemic autoimmune diseases. Of particular importance is the relative understanding of the characteristics and timing of exposure, and how these relate to mechanisms of action with respect to different diseases. The risk of cancer from exposures acting through genotoxic or mutagenic properties may be most accurately characterized by a cumulative exposure metric. It is not clear that this same metric is optimal for the characterization of risk of autoimmune diseases. Exposure intensity, and how this relates to clearance mechanisms in the lung and resulting systemic immunogenic effects, may have important implications from the perspective of disease pathogenesis[20]. It may also directly affect the development of effective prevention strategies, since efforts to reduce a cumulative exposure measure may require different types of decisions and controls than efforts to reduce short-term, high-intensity exposures. Thus questions concerning differences in the autoimmune-related effects of varying exposure scenarios are key issues warranting additional research.

In some countries, occupational exposure to these and other agents has declined in the past 50 years as the result of technological improvements and increased regulatory standards. The recent industrialization in other countries, however, has resulted in increased concern about occupational exposures, including silica and asbestos, in mining, manufacturing, and construction settings[21-23]. These changing exposure patterns may have a substantial impact on rheumatologic conditions seen in the 21st century. Continued and expanded research on the effect of potentially modifiable occupational and environmental exposures on RA and other systemic autoimmune diseases, and the translation of this research into effective health protective policies, is needed.

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