Silica exposure is associated with increased risk of developing rheumatoid arthritis: results from the Swedish EIRA study

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Objective: To study the association between silica exposure and rheumatoid arthritis and how it is modified by cigarette smoking.

Methods: Data were analysed from 276 male cases and 276 male controls aged 18 to 70 years, included in a Swedish population based study between May 1996 and June 2001. A case was defined as a person recently diagnosed with rheumatoid arthritis according to the ACR criteria. Controls were selected from the study base as a stratified random sample accounting for age, sex, and residency. Men with a self reported history of work with rock drilling, stone crushing, or exposure to stone dust in general were defined as silica exposed. Rheumatoid factor (RF) status among cases was recorded.

Results: Silica exposed men had increased risk of rheumatoid arthritis, with an odds ratio (OR), adjusted for age, residential area, and smoking, of 2.2 (95% confidence interval, 1.2 to 3.9) among men aged 18 to 70 years, and 2.7 (1.2 to 5.8) among those aged 50 to 70 years. Men who had worked with rock drilling or stone crushing (regarded as highly exposed) had a slightly greater increase in risk of rheumatoid arthritis than silica exposed men in general, with an OR of 3.0 (1.2 to 7.6). The joint effects of silica exposure and smoking were compatible with synergy between these two exposures in the development of rheumatoid arthritis but this was not conclusive.

Conclusions: Silica exposure is associated with increased risk of developing rheumatoid arthritis. This association is not explained by smoking habits.

The pathogenesis of rheumatoid arthritis is likely to reflect genetic as well as environmental factors. Smoking has been found to increase the risk but little is known about the influence of other environmental factors.

Six previous epidemiological studies have investigated the association between exposure to silica through the respiratory tract and the risk of rheumatoid arthritis. In these studies, an increased risk for the disease was observed among silica exposed persons from certain occupations or work-studies, an increased risk for the disease was observed among about smoking habits had been collected, and where cases were defined according to established clinical criteria. The number of observed cases was, however, small (between 9 and 43) in three of the studies, and only two studies defined cases according to established clinical criteria. Furthermore, only two of the studies (one of which had a total of 43 observed cases) adjusted the results for the potential confounding by smoking.

To investigate further the association between silica exposure and the risk of developing rheumatoid arthritis, we analysed data from a population based case-control study, in which information about silica exposure as well as smoking habits had been collected, and where cases were defined according to established clinical criteria.

METHODS

This study is a part of the EIRA ("epidemiological investigation of rheumatoid arthritis") study, which is an extensive population based case-control study, using incident cases of rheumatoid arthritis from the population aged 18 to 70 years of a geographically defined area of Sweden. The present report is based on analysis of the 276 male cases and 276 male controls included from May 1996 to June 2001. The 654 male controls included from May 1996 to June 2001. The 654 were defined according to established clinical criteria. Six previous epidemiological studies have investigated the association between silica exposure and rheumatoid arthritis, with an odds ratio (OR), adjusted for age, residential area, and smoking, of 2.2 (95% confidence interval, 1.2 to 3.9) among men aged 18 to 70 years, and 2.7 (1.2 to 5.8) among those aged 50 to 70 years. Men who had worked with rock drilling or stone crushing (regarded as highly exposed) had a slightly greater increase in risk of rheumatoid arthritis than silica exposed men in general, with an OR of 3.0 (1.2 to 7.6). The joint effects of silica exposure and smoking were compatible with synergy between these two exposures in the development of rheumatoid arthritis but this was not conclusive.

Conclusions: Silica exposure is associated with increased risk of developing rheumatoid arthritis. This association is not explained by smoking habits.

Case definition and identification

A case was defined as a person from the study base who was recently diagnosed with rheumatoid arthritis according to the American College of Rheumatology (ACR) 1987 criteria. All potential cases were diagnosed by rheumatologists. All hospital based rheumatology units, as well as most of the very few privately run rheumatology units in the study area, participated in the study. In all, 19 centres reported cases to the study, of which 15 were "early arthritis clinics".

Rheumatoid factor (RF) status was determined by the units entering the cases into the study, and was reported to the study as RF positivity or RF negativity only.

Selection of controls

For each potential case a control was randomly selected from the study base as a stratified random sample accounting for age, sex, and residential area. The selection of the controls involved the use of the national population register, which is continuously updated. If information from one control was lacking, another was selected by the same principles.

Data collection

Information about environmental exposure was collected using an identical questionnaire in cases and controls. This was given to the cases shortly after they had received female cases and the 791 female controls gathered during the same period were excluded from this study because of the small number of silica exposed women.

Abbreviations: ACR, American College of Rheumatology; EIRA, epidemiological investigation of rheumatoid arthritis

* The members of the group are listed at the end of the article
information about the diagnosis, and was sent by mail to the controls. Completed questionnaires were obtained from 96% of the case group and 77% of the controls.

Unanswered or incompletely answered questionnaires were completed by mail or by telephone by trained interviewers.

Exposure
The questionnaire contained a wide spectrum of questions regarding heredity, life style factors, health aspects, body height and weight, and socioeconomic and demographic factors, and detailed questions about occupations, occupational tasks, and exposures during different periods. The classification of exposure in this study was entirely based on the answers by the study subjects to the questions posed in this questionnaire.

For each case the time of the first symptoms of rheumatoid arthritis was used to estimate disease onset. The year in which symptoms first occurred was defined as the index year. The same index year was used for the corresponding control.

We asked about occupational exposure using the following question: “Have you ever been in contact with any of the work tasks, handlings, and chemical compounds below, and if so, during which year/years? (If relevant, you may report more than one period)”. This question was followed by a list of 42 specified items to be answered with a “no” or a “yes” for each of the listed items, with specification of the year in which the exposure started and ended and the number of hours per week of exposure. Answers regarding each exposure could be given for two different time periods but not more.

Study subjects reporting that they had ever worked with rock drilling or stone crushing or that they had ever been exposed to stone dust during the index year or before were classified as silica exposed.

Rock drilling and stone crushing are associated with substantial levels of silica exposure, and are also work tasks that are rather easily recalled, whereas self reported exposure to stone dust in general may be more vague. We therefore considered rock drillers and stone crushers as belonging to a category with higher levels of silica exposure and with more accurate information about silica exposure than those exposed to silica in general.

Potential confounding factors
Age, residential area, socioeconomic class, and smoking habits were considered as potential confounding factors in the analyses of the association between silica exposure and rheumatoid arthritis.

Age was categorised into the following 10 strata: 18–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, and 65–70 years.

The last occupation during the year before the index year was used as a marker for socioeconomic class, which was categorised into the following five strata: 1, workers within the production of goods; 2, workers in the service sector; 3, salaried employees at lower and intermediate levels; 4, salaried employees at higher levels, executives, university graduates; 5, others (pensioners, students, individuals working from home, and unemployed).

Physical workload was classified according to the frequency of lifting or carrying of heavy items (heavier than 10 kg).

Subjects who reported that they were regularly smoking cigarettes during the index year or before were defined as ever smokers, and those who reported that they had never smoked tobacco before or during the index year were defined as never smokers.

Table 1 Categories of silica exposure and smoking habits among silica exposed RA cases and silica exposed controls

<table>
<thead>
<tr>
<th>Category of silica exposure</th>
<th>Number of exposed cases/controls</th>
<th>Number of smokers among exposed cases/controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rock drilling</td>
<td>12/6</td>
<td>10/3</td>
</tr>
<tr>
<td>Stone crushing</td>
<td>9/5</td>
<td>9/4</td>
</tr>
<tr>
<td>Stone dust (unspecified)</td>
<td>33/18</td>
<td>30/14</td>
</tr>
<tr>
<td>Silica exposure overall</td>
<td>41/20</td>
<td>37/15</td>
</tr>
</tbody>
</table>

*Cases and controls may belong to more than one category of silica exposure.
The attributable proportion due to interaction between silica exposure and smoking was estimated to be 0.6 (95% CI, 0.1 to 1.1).

DISCUSSION
Silica exposed men had a twofold increased risk of developing rheumatoid arthritis compared with unexposed men. When older men (50 to 70 years) and younger men (18 to 49 years) were analysed separately, a 2.5-fold increased risk was found among silica exposed men in the older age group, while no increase in risk was seen among the younger men. A somewhat stronger association was observed among persons who had been working with rock drilling or stone crushing, who had a threefold increased risk.

Our data on exposure were reported retrospectively by the cases and controls. This strategy runs the risk of misclassification of exposure because of recall bias, which needs to be considered carefully when interpreting the results. However, the risk of misclassification of exposure because of recall bias was limited in our study because significant dust exposure, particularly when related to an occupation or a work place, has a long duration and commonly occurs in circumstances that are easy to recall. There is still a risk that some silica exposed subjects were classified as unexposed, because silica exposure may occur in the absence if visible dust. Such exposure would probably be unrelated to disease and consequently biases these estimates of relative risks towards the null value.

All potential cases in the present study were examined carefully by a rheumatologist using a structured form to specify concordance with the ACR criteria, and only subjects who fulfilled these criteria were defined as cases. The risk of a substantial misdiagnosis of disease in this study is thus very limited.

Silica exposure may theoretically be linked to other environmental exposures as well as to lifestyle factors and socioeconomic circumstances that may in themselves be related to the possibility of developing rheumatoid arthritis. Adjustments were therefore made for potential differences in smoking habits, age, and residential area between individuals who were silica exposed and those who were not. Adjustment of all results for the potential confounding from socioeconomic class and physical workload were also made, but this affected the results only marginally and is not presented in our report.

If participation is related to silica exposure, this may introduce a selection bias in the estimated odds ratios. The risk of such bias in the present study was limited by the high participation rate (96% among cases and 77% among controls). If the observed increased risk among silica exposed subjects was entirely the result of selection bias (that is, the true odds ratio was 1.0), it can be estimated that 30% of the non-responding controls would have been exposed to silica, which is highly unlikely.

All rheumatology units linked to the general welfare system, as well as privately run rheumatology units within the study area, reported cases to the study. Nevertheless, some cases might have been unidentified. There might, for instance, be cases diagnosed at other health care facilities that were never referred to a participating unit. We consider it unlikely that these unidentified cases would differ

### Table 2 Odors ratios for rheumatoid arthritis (rheumatoid factor positive, rheumatoid factor negative, and overall) among subjects exposed to silica overall and among those who had worked with rock drilling or stone crushing, compared with unexposed subjects

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Subjects exposed to silica overall v unexposed</th>
<th>Subjects who had worked with rock drilling or stone crushing v unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of exposed cases</td>
<td>OR*</td>
</tr>
<tr>
<td>RF+ RA</td>
<td>18 to 49</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>50 to 70</td>
<td>20</td>
</tr>
<tr>
<td>RF - RA</td>
<td>18 to 49</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>50 to 70</td>
<td>11</td>
</tr>
<tr>
<td>Total RA</td>
<td>18 to 49</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>50 to 70</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>18 to 70</td>
<td>41</td>
</tr>
</tbody>
</table>

*Adjusted for the potential confounding from age, residential area, and cigarette smoking.

### Table 3 Odds ratios for rheumatoid arthritis (rheumatoid factor positive, rheumatoid factor negative, and overall) for different combinations of silica exposure and cigarette smoking compared with never smokers unexposed to silica

<table>
<thead>
<tr>
<th>Absence of silica exposure</th>
<th>Silica exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of cases</td>
<td>OR*</td>
</tr>
<tr>
<td>RF+ RA Never smoked</td>
<td>27</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>126</td>
</tr>
<tr>
<td>RF - RA Never smoked</td>
<td>30</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>45</td>
</tr>
<tr>
<td>Total RA Never smoked</td>
<td>57</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>171</td>
</tr>
</tbody>
</table>

*Adjusted for the potential confounding from age and residential area.

CI, confidence interval; OR, odds ratio; RA, rheumatoid arthritis; RF, rheumatoid factor.
substantially with regard to exposure from those who were identified. Persons with occupational silica exposure generally do physically demanding work. This may increase the likelihood that they will seek help from the health care system in comparison with those doing lighter work. This potential difference between silica exposed and non-exposed individuals in attendance at health care facilities could lead to a difference in the rate of identified cases in the two groups. Adjustment for physical workload did not, however, affect the estimates of the relative risk associated with silica exposure.

In summary, we believe that the present observation of an increased risk of developing rheumatoid arthritis among subjects exposed to silica is real and not an artefact. Previous observations of a possible association between silica exposure and development of rheumatoid arthritis have been reported from different parts of the world, such as north America, South Africa, Britain, and Scandinavia. As previously mentioned in the introduction, only two of these studies mentioned in the introduction, only two of these studies found to be associated with an increased risk of developing rheumatoid arthritis even after adjustment for smoking. Our results were compatible with a synergistic effect of smoking and silica exposure, but did not allow a firm conclusion on this to be drawn owing to the small numbers of silica exposed subjects who had never smoked.

The mechanisms behind the biological effects of silica are still not fully understood. It has previously been proposed that increased release of inflammatory mediators from alveolar macrophages phagocytosing inhaled silica particles may activate macrophages/monocytes and lymphocytes systemically as well as in the rheumatoid synovium. These cell types also have the potential to increase the production of matrix metalloproteinases (MMP)—enzymes involved in the degradation and remodelling of extracellular matrix, which have been shown to be associated with rheumatoid arthritis as well as with silicosis.

The production of MMP, as well as of inflammatory mediators such as tumour necrosis factor α and interleukin 1β, is regulated by the transcription factor nuclear factor κB, the activity of which appears to be influenced by silica exposure.

Conclusions

Our results, which are based on data from the general population of a part of Sweden, show that silica exposure is a risk factor for the development of rheumatoid arthritis, even when smoking habits are taken into account. This will affect our understanding of the types of environmental stimuli that can trigger the onset of the disease process in rheumatoid arthritis.

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REFERENCES


