Silica exposure is associated with increased risk of developing Rheumatoid Arthritis. Results from the Swedish EIRA-study.

Patrik Stolt, Henrik Källberg, Ingvar Lundberg, Bengt Sjögren, Lars Klareskog, and Lars Alfredsson

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Silica exposure is associated with increased risk of developing Rheumatoid Arthritis. Results from the Swedish EIRA-study.

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Abstract

Objective: To study the association between silica exposure and Rheumatoid Arthritis (RA) and how it is modified by cigarette smoking.

Methods: Data from 276 male cases and 276 male controls aged 18-70 years, collected in a Swedish population based study, during May 1996-June 2001, were analysed. A case was defined as a person in the study base who was recently diagnosed with RA according to the American College of Rheumatology criteria.

Controls were selected from the study base as a stratified random sample considering age, gender and residency. Men with self-reported history of work with rock drilling, stone crushing, or of exposure to stone dust in general were defined as silica exposed. Rheumatoid factor (RF) status among cases was registered.

Results: Silica exposed men had increased risk of RA, with an odds ratio (OR), adjusted for age, residential area, and smoking, of 2.2 (95% confidence interval (95%CI) 1.2-3.9) among men aged 18-70 years and 2.7 (1.2-5.8) among men aged 50-70 years. Men who had worked with rock-drilling or stone crushing (regarded as highly exposed) had a slightly more marked increased risk of RA than silica exposed men in general, with an OR of 3.0 (95%CI 1.2-7.6).

The results regarding the joint effect of silica exposure and smoking was compatible with, but not conclusive for, a synergy between these two exposures in the development of RA.

Conclusion: Silica exposure is associated with increased risk of developing RA and this association is not explained by smoking habits.
Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory disease with a pathogenesis that is likely to be dependent on genetic as well as environmental factors. Smoking has been observed to increase the risk of RA (1-3) but else, there is sparse knowledge about the influence from the environment on the risk of developing the disease (4).

Six previous epidemiological studies have investigated the association between exposure to silica via the respiratory system and the risk of RA (5-10). In these studies, an increased risk of RA was observed among silica exposed persons from certain occupations or work-places (5-7, 9), or among persons with manifest silicosis (5,8). The number of observed cases was, however, small (between 9 and 43) in three of the studies (6,8-9) and only two studies defined cases according to established clinical criteria (5, 10). Furthermore, only two of the studies (one of which with a total of 43 observed cases (6)) adjusted the results for the potential confounding by smoking (6, 10).

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

Material and Methods

This study is a part of the EIRA (Epidemiological Investigation of RA) study, which is an extensive population based case-control study, using incident cases of RA from the population aged 18-70 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 female cases and the 654 female controls gathered during the same period were excluded from the present study, due to small number of silica exposed women.

Case definition and identification

A case was defined as a person from the study base, who was recently diagnosed with RA according to the American College of Rheumatology (ACR) criteria of 1987 (11). 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. There was totally 19 centres that reported cases to the study, of which 15 were “Early Arthritis Clinics” (12). Rheumatoid factor (RF) status was determined via 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 considering age, gender and residential area. The selection of controls was conducted using the national population register, which is continuously updated. If information from one control was lacking, another control was selected by the same principles.
Data collection
Information about environmental exposures was collected using an identical questionnaire given to the cases shortly after they had received information about the diagnosis and 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 contains a wide spectrum of questions regarding heredity, life style factors, health aspects, body height and weight, socio-economic and demographic factors and detailed questions about occupations, occupational tasks and exposures during different periods of time. The classification of exposure was in this study entirely based on the answers by the study subjects to the questions in this questionnaire.

For each case the moment of the first RA symptoms was used to estimate disease onset. The year of that moment was defined as the index-year. The same index-year was used for the corresponding control. Only data on exposures up to the index-year were analysed.

Occupational exposures were asked for using the following question: “Have You ever been in contact with any of the work-tasks, handleings and chemical compounds beneath, 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 and was supposed to be answered with a “no” or a “yes” regarding each of the listed items, with specification of the year in which the exposure started and ended, respectively, and the number of hours per week of exposure. Answers regarding each exposure could be given for up to two different periods of time.

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 have been determined to be associated with substantial levels of silica exposure (13-14), and are also work-tasks 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, socio-economic class, smoking habits and physical work-load were considered as potential confounding factors in the analyses of the association between silica exposure and RA.

Age was categorized into the following ten strata: 18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64 and 65-70 years of age.

The last occupation during the year prior to the index year was used as a marker for socio-economic class which was categorized 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 (i.e. pensioners, students, individuals working from home, and unemployed).
Physical work load was classified according to the frequency of lifting or carrying of heavy items (heavier than 10 kilograms).

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

Statistical analyses
Silica exposed subjects were compared with unexposed subjects with regard to the incidence of seropositive rheumatoid arthritis (RF+RA), seronegative rheumatoid arthritis (RF-RA) and RA overall, respectively, by calculating the odds ratio with 95% confidence interval (95% CI) by means of conditional regression analysis. Odds ratios were adjusted for potential confounding from age, gender, residential area (design variables) and smoking (where appropriate). Adjustment for socio-economic class and physical work-load only marginally changed the estimates and was not retained in the final analyses. Odds ratios were interpreted as relative risks (RR) as the study was population-based and the controls was a random sample from the study base (15).

Similar analyses were also conducted in which persons who had worked with rock-drilling or stone crushing (considered as highly exposed to silica) were compared with unexposed subjects by the same method.

Interaction between silica exposure and smoking habits was evaluated, using departure from additivity of effects as criteria of interaction, as suggested by Rothman (16). Attributable proportion (AP) due to interaction (the proportion of the incidence of RA among the silica exposed ever-smokers that was attributed to interaction between silica exposure and smoking) was calculated together with the 95% confidence interval (17).

All analyses were performed using the Statistical Analysis System (SAS) version 8.2 (18).
Results

Of the 276 male cases in this study, 41 were silica exposed. About two thirds of the silica exposed male cases were found to have experience from occupations associated with the building industry (construction workers, drivers, electricians, sanitary engineers, painters, stonemasons, rock drillers, gardeners, brick-layers and floor-layers). The mean duration of silica exposure among the exposed cases and the exposed controls was 20 and 17 years, respectively.

Thirty seven (90%) of the 41 silica exposed cases and 15 (75%) of the 20 silica exposed controls had ever been cigarette smokers (Table 1).

Table 1

<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

Silica exposed men had an increased risk of developing RA overall when compared with unexposed men, with an odds ratio, adjusted for age, residential area and smoking, of 2.2 (95% CI 1.2-3.9) When older subjects (50-70 years of age) were analysed separately, an odds ratio of 2.7 (95% CI 1.2-5.8) was observed (table 2). The attributable proportion due to silica exposure was about 0.08 when all cases in the study were considered and about 0.55 for the silica exposed cases.

When restricting the analyses to the group assumed to be highly exposed, i.e. men who had worked with rock-drilling or stone crushing, the OR for RA overall was 3.0 (95%CI 1.2-7.6) (table 2).
There was no statistically significant difference between odds ratios regarding RF- RA and RF+ RA, respectively.

An increased risk of RA was only apparent among the silica exposed men who were ever-smokers (table 3).

The attributable proportion due to interaction between silica exposure and smoking was estimated to 0.6 (95% CI 0.1-1.1).
Table 2. Odds Ratio (OR) of RF+ RA, RF- RA and RA overall (Total RA) together with 95% confidence interval (95% CI) among subjects exposed to silica overall and among subjects who have worked with rock-drilling or stone crushing, respectively, compared with unexposed.

<table>
<thead>
<tr>
<th>Age-group (years)</th>
<th>Subjects exposed to silica overall compared with unexposed</th>
<th>Subjects who have worked with rock-drilling or stone crushing compared with unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of exposed cases</td>
<td>OR*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF+ RA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-49</td>
<td>7</td>
<td>1.4</td>
</tr>
<tr>
<td>50-70</td>
<td>20</td>
<td>2.2</td>
</tr>
<tr>
<td>18-70</td>
<td>27</td>
<td>1.9</td>
</tr>
<tr>
<td>RF- RA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-49</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>50-70</td>
<td>11</td>
<td>3.3</td>
</tr>
<tr>
<td>18-70</td>
<td>14</td>
<td>2.1</td>
</tr>
<tr>
<td>Total RA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-49</td>
<td>10</td>
<td>1.6</td>
</tr>
<tr>
<td>50-70</td>
<td>31</td>
<td>2.7</td>
</tr>
<tr>
<td>18-70</td>
<td>41</td>
<td>2.2</td>
</tr>
</tbody>
</table>

* OR were adjusted for the potential confounding from age, residential area and cigarette smoking
Table 3. Odds Ratio (OR) of RF+ RA, RF- RA and RA overall (Total RA) together with 95% confidence interval (95%CI) for different combinations of silica exposure and cigarette smoking compared with never smokers unexposed to silica.

<table>
<thead>
<tr>
<th></th>
<th>Absence of silica exposure</th>
<th>Silica exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of cases</td>
<td>OR*</td>
</tr>
<tr>
<td>RF+ RA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smoking</td>
<td>27</td>
<td>1.0</td>
</tr>
<tr>
<td>Ever-smoking</td>
<td>126</td>
<td>2.8</td>
</tr>
<tr>
<td>RF- RA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smoking</td>
<td>30</td>
<td>1.0</td>
</tr>
<tr>
<td>Ever-smoking</td>
<td>45</td>
<td>0.4</td>
</tr>
<tr>
<td>Total RA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smoking</td>
<td>57</td>
<td>1.0</td>
</tr>
<tr>
<td>Ever-smoking</td>
<td>171</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*OR were adjusted for the potential confounding from age and residential area.
Discussion

Silica exposed men were in this study observed to have a two-fold increased risk of developing RA, compared with unexposed men. When older (50-70 years) and younger (18-49 years) men were analysed separately, a two and a half -fold increased risk of RA was observed among silica exposed men in the older age group, while no significantly increased risk of RA could be 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 three-fold increased risk of RA. The increased risk associated with silica exposure was not explained by differences in smoking habits.

The data about exposure in the present study was retrospectively reported by the cases and the controls. This strategy is connected with a risk of misclassification of exposure because of recall bias that has to be carefully considered when interpreting the results. The risk of misclassification of exposure due to recall bias in this study is most likely limited, however, since significant dust exposure, particularly when related to an occupation or a work-place, has a long duration and commonly occurs within circumstances that are easy to recall. Still, however, there is a risk that some silica exposed were classified as unexposed as silica exposure may occur also in the absence if visible dust. Such a misclassification of exposure, however, would probably be unrelated to disease and consequently bias 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 the 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 hence very limited.

Silica exposure may theoretically be linked to other environmental exposures as well as lifestyle factors and socio-economic circumstances which also may be related to the possibility of an RA to be diagnosed. Adjustments were therefore made for potential differences in smoking habits, age and residential area between individuals that were silica exposed and those that were not. Adjustments for the potential confounding from socio-economic class and physical work load were also made, but affected the results only marginally and were not presented in this report.

If participation is related to silica exposure, this may introduce a selection bias in the estimated odds ratios. The risk of such a bias has been limited in the present study by its high participation rate, 96% among cases and 77% among controls. If the observed increased risk among silica exposed subjects entirely was due to selection bias (i.e. the true odds ratio was 1.0), it can be estimated that the proportion of silica exposed among the non-responding controls would have to be about 30%, 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 substantially differ from those identified with regard to exposure.
Persons with occupational silica exposure generally have physically demanding work-tasks which may increase the probability that they seek help from the health care system compared with persons with physically lighter work-tasks. This potential difference between silica exposed and unexposed in inclination to attend health care facilities could obviously lead to a difference in the rate of identified cases among silica exposed and unexposed, respectively. Adjustment for physical work load 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 RA among subjects exposed to silica is real and not an artefact.

Previous observations on a possible association between silica exposure and development of RA have been reported from different parts of the world such as North-America, South-Africa, Britain and Scandinavia (5-10). As previously mentioned in the introduction, only two of these studies adjusted for the potential confounding from smoking (6,10).

As smoking has been demonstrated as the most evident environmental risk factor for RA (1-3) to date and considering that a correlation between silica exposure and smoking is probable in many contexts, it appears mandatory to take smoking into account when analysing the link between silica exposure and RA.

In the present study silica exposure was observed to be associated with an increased risk of developing RA also after adjustment for smoking. The analyses of the combined effect of silica exposure and smoking revealed results compatible with a synergy between these two factors in the development of RA, but without permitting a firm conclusion, due to small numbers of silica exposed subjects that never had 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 phagocyting inhaled silica particles may activate macrophages-monocytes and lymphocytes systemically as well as in the rheumatoid synovium (19-25). These celltypes also have the potential of increasing the production of matrix metalloproteinases (MMP) that are enzymes involved in the degradation and remodelling of extracellular matrix and also have been shown to be associated with RA as well as with silicosis (26-29).

The production of MMP, as well as of inflammatory mediators such as Tumor Necrosis Factor alpha and Interleukin-1beta, is regulated by the transcription factor Nuclear factor kappaB, the activity of which has been observed to be influenced by silica exposure (30-34).

In summary, the present results, based on data from the general population of a part of Sweden, demonstrate that silica exposure constitutes a risk factor for the development of RA also when smoking habits are taken into account. This observation may have implications for our efforts to understand which types of environmental stimuli that can trigger the onset of the disease process in rheumatoid arthritis.

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References

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